A comprehensive investigation into the human smooth pursuit eye movement system

- Kumulative Arbeit -

Inaugural-Dissertation

zur Erlangung der Doktorwürde

der

Philosophischen Fakultät

der

Rheinischen Friedrich-Wilhelms-Universität

zu Bonn

vorgelegt von

Rebekka Schröder

aus

Attendorn

Bonn, 2023

Gedruckt mit der Genehmigung der Philosophischen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

ZUSAMMENSETZUNG DER PRÜFUNGSKOMMISSION:

Prof. Dr. André Beauducel	Vorsitzender
Prof. Dr. Ulrich Ettinger	Betreuer und Gutachter
Prof. Dr. Christoph Klein	Gutachter
Prof. Dr. Gizem Hülür	weiteres prüfungsberechtigtes Mitglied

TAG DER MÜNDLICHEN PRÜFUNG: 17. April 2023

Table of contents

ACKNOWLEDGEMENTS | DANKSAGUNG **5**

ABSTRACT **6**

ZUSAMMENFASSUNG **8**

1 INTRODUCTION **10**

1.1 EYE MOVEMENTS **10**
1.2 BASIC MECHANISMS OF SPEM **11**
1.3 NEURAL MECHANISMS OF SPEM **13**
1.3.1 BOLD and PET correlates of SPEM 14
1.3.2 Other methodological approaches 16
Lesions 16
TMS 16
Non-human primates 17
1.3.3 Interim Summary 18
1.4 EXPERIMENTAL TASK EFFECTS ON SPEM **20**
1.4.1 The background effect 20
1.4.2 Neural correlates of the background effect 22
1.4.3 The target velocity effect 24
1.4.4 Neural correlates of the velocity effect 24
1.5 MOLECULAR MECHANISMS OF SPEM **25**
1.5.1 Nicotine 27
1.5.2 Nicotine effects on SPEM 28
1.5.3 A pharmacogenetic perspective on dopamine-acetylcholine interactions 29
1.6 SPEM AND THE SCHIZOPHRENIA SPECTRUM **31**
1.6.1 Schizophrenia 31
1.6.2 Schizotypy 34
1.6.3 SPEM deficits in schizophrenia and schizotypy 35
1.6.4 BOLD correlates of SPEM deficits along the schizophrenia spectrum 38
1.7 AIMS OF THIS DISSERTATION **40**

2 METHODOLOGY **42**

2.1 ASSESSMENT OF SPEM **42**
2.2 PSYCHOPHARMACOLOGY **44**
2.2.1 Pharmacogenetics with candidate genes 44
2.3 FUNCTIONAL MAGNETIC RESONANCE IMAGING **45**
2.3.1 Pre-processing 47
2.3.2 Data analysis 47
2.3.3 Generalised psychophysiological interaction analyses 48
2.4 MACHINE LEARNING **51**
2.5 ASSESSMENT OF SCHIZOPHRENIA AND SCHIZOTYPY **53**

3 SUMMARIES OF EXPERIMENTAL STUDIES 54

3.1 STUDY I: RELIABILITY OF THE BACKGROUND AND VELOCITY EFFECTS IN SPEM 55
3.2 STUDY II: NICOTINE EFFECTS ON SPEM 58
3.3 STUDY III: FUNCTIONAL CONNECTIVITY DURING SPEM 60
3.4 STUDY IV: NEURAL CORRELATES OF THE BACKGROUND AND VELOCITY SPEM EFFECTS 62
3.5 STUDY V: NEURAL MECHANISMS OF THE SPEM BOLD RESPONSE ALONG THE SCHIZOPHRENIA SPECTRUM 65

4 DISCUSSION 68

4.1 INTEGRATION 68
4.1.1 Basic and neural mechanisms of SPEM 68
4.1.2 The background effect 71
4.1.3 The velocity effect 73
4.1.4 Background and velocity interactions 75
4.1.5 Molecular mechanisms of SPEM 76
4.1.6 SPEM in the schizophrenia spectrum 77
4.2 LIMITATIONS 78
4.3 FUTURE RESEARCH 79
4.4 CONCLUSION 80

REFERENCES 81

LIST OF FIGURES 112

LIST OF TABLES 112

LIST OF ABBREVIATIONS 113

APPENDIX A | STUDY I 115

APPENDIX B | STUDY II 128

APPENDIX C | STUDY III 148

APPENDIX D | STUDY IV 167

APPENDIX E | STUDY V 185

Acknowledgements | Danksagung

Zunächst möchte ich meinem Doktorvater Ulrich Ettinger danken: dafür, dass du mich im Studium für Okulomotorik und Psychopharmakologie begeistert hast, für deine Unterstützung und dein offenes Ohr während der gesamten Promotionszeit und dafür, dass du immer optimistisch warst, wenn ich es nicht war.

Prof. Christoph Klein danke ich dafür, dass er sich bereit erklärt hat, sich die Zeit zu nehmen, mein Zweitgutachter zu sein. Außerdem danke ich Prof. André Beauducel dafür, meiner Prüfungskommission vorzusitzen, und Prof. Gizem Hülür für ihre Bereitschaft, ebenfalls Teil meiner Prüfungskommission zu sein. Prof. Nikolaos Koutsouleris und Prof. Martin Reuter und ihren Teams und allen Mitarbeitenden am Life & Brain danke für ich die angenehme Zusammenarbeit bei unseren gemeinsamen Forschungsprojekten.

Mein besonderer Dank gilt der Studienstiftung des deutschen Volkes für die finanzielle und ideelle Förderung während meiner Studien- und Promotionszeit.

Meinen wundervollen Kolleg:innen in der AP1, Celina, Eli, Kaja, Kristof, Mirko, Philine, Pia und Yaira, danke ich dafür dass ihr eben nicht nur wundervolle Kolleg:innen wart, sondern auch die besten Pausen-Partner:innen und Büro-Interior-Designer:innen. Vor allem danke ich euch für das stets freundschaftliche und lustige Miteinander. Ein ganz besonders fettes Danke geht an Kaja, dafür dass du die beste Büropartnerin warst, die ich mir hätte vorstellen können, dass du dich mit mir durch Matlab und R gekämpft hast, dass du dir immer Zeit genommen hast, mir zuzuhören und mitzudenken, und dass du den gleichen Kaffee-Rhythmus hattest wie ich. Der AP2, besonders Hannah, danke ich für die vielen schönen gemeinsamen Pausen. Judith und Robert, euch danke ich dafür, dass ihr meine Abschlussarbeiten während des Studiums so hervorragend betreut habt, dass ich mich danach in die Wissenschaft gewagt habe.

All meinen wunderbaren Freund:innen, ganz besonders Judith, Luzie, Natti, Sabine, Sara und Vanessa, danke ich dafür, dass ihr in allen Höhen und Tiefen für mich da wart, immer ein offenes Ohr hattet, hervorragend von der Arbeit abgelenkt habt und die besten Cheerleaderinnen wart. Ohne euch wäre das alles viel anstrengender gewesen.

Meinen Eltern und Brüdern danke ich dafür, dass ihr immer an mich geglaubt habt und mich bedingungslos in allem unterstützt. Simon und Daniel, vielen Dank dafür, dass ihr keine Gelegenheit auslasst zu fragen, wann ich endlich fertig bin.

Dir, Chris, danke ich für alles drumherum, besonders für deine Geduld, dein Mitfreuen bei all den kleinen und größeren Erfolgen auf dem Weg und dein Aufmuntern in den schwierigeren Zeiten, dafür dass du der beste Pandemie-Home-Office-Buddy warst und der schönste Grund, Feierabend zu machen.

Abstract

Smooth pursuit eye movements (SPEM) are used to maintain the image of a slowly moving stimulus on the fovea. Previous findings on this major oculomotor system show that SPEM performance is degraded in the presence of a structured vs. blank background (background effect) and at faster vs. slower target velocities (velocity effect). In addition, SPEM is considered an important biomarker in schizophrenia research: patients with schizophrenia often present with impaired SPEM performance. However, the exact psychological, molecular, and neural mechanisms underlying SPEM in healthy individuals and in patients with schizophrenia are not well understood.

This dissertation aimed to investigate these mechanisms in more detail. To this end, data from five experimental studies are reported. Study I focused on the reliability of SPEM performance in general and, additionally, the reproducibility and reliability of the background and velocity effects. In Study II, a pharmacogenetic study design was used to investigate the associations of the dopaminergic and cholinergic systems with SPEM: Nicotine or placebo was administered to participants grouped according to their genotypes on a variable number of tandem repeats (VNTR) polymorphism in the *SLC6A3* gene coding for the dopamine transporter (DAT). The other studies incorporated functional magnetic resonance imaging (fMRI) data to examine the functional connectivity of areas active during SPEM (Studies III–V). In addition, the neural mechanisms underlying the background and velocity effects (Study IV), and differences in the neural correlates of SPEM between patients with schizophrenia and individuals with varying expressions of the personality trait schizotypy were investigated using machine learning methods (Study V).

Across all studies, SPEM task effects were found to be very robust. Their high reliability was demonstrated in Study I. However, neither the drug factor (nicotine, placebo) nor the *SLC6A3* VNTR genotype factor (9R-carriers, 10R-homozygotes), alone or in interaction, had a significant effect on SPEM performance in Study II. The good replicability of the network underlying SPEM, consisting of visual areas in the occipital cortex, parietal and frontal areas (frontal and supplementary eye fields; SEF, FEF), the lateral geniculate nucleus (LGN), and cingulate cortex, was underlined in Studies III–V. Functional connectivity analyses provided evidence of close cooperation between these areas during SPEM (Studies III–V). While the velocity effect was mainly associated with activations in visual areas, the background effect exhibited more widely distributed activations in clusters encompassing visual, frontal, and parietal areas (Study IV). Only very small deficits in SPEM performance were found in patients with schizophrenia spectrum disorders (Study V), contradicting previous findings. However, a combination of functional connectivity and machine learning approaches cautiously suggested that altered functional connectivity from the right FEF may be present in schizophrenia spectrum disorders.

The findings presented here highlight the high replicability of the background and velocity effects and of the activity in the neural network associated with SPEM. The functional connectivity of the components of this network was demonstrated for the first time and showed consistency across studies. SPEM deficits in patients with schizophrenia were more subtle than previously reported. In summary, these findings add considerably to the existing research literature on SPEM, but also leave some questions open for future research.

Zusammenfassung

Glatte Augenfolgebewegungen (smooth pursuit eye movements; SPEM) dienen dazu, das Bild eines sich langsam bewegenden Stimulus auf der Fovea zu halten. Frühere Befunde zu diesem wichtigen okulomotorischen System zeigen, dass die SPEM-Leistung bei einem strukturierten vs. leeren Hintergrund (Hintergrundeffekt) und bei schnelleren vs. langsameren Zielreizgeschwindigkeiten (Geschwindigkeitseffekt) abnimmt. Darüber hinaus gelten SPEM als wichtige Biomarker in der Schizophrenieforschung: Patient:innen mit Schizophrenie weisen häufig eine verminderte SPEM-Leistung auf. Die genauen psychologischen, molekularen und neuronalen Mechanismen, die SPEM bei gesunden Personen und bei Patient:innen mit Schizophrenie zugrunde liegen, werden jedoch noch nicht ausreichend verstanden.

Ziel dieser Dissertation ist es, diese Mechanismen genauer zu untersuchen. Zu diesem Zweck werden Daten aus fünf experimentellen Studien berichtet. Studie I befasste sich mit der Reliabilität der SPEM-Leistung im Allgemeinen und mit der Reproduzierbarkeit und Reliabilität der Hintergrund- und Geschwindigkeitseffekte. In Studie II wurde ein pharmakogenetisches Studiendesign verwendet, um die Zusammenhänge der dopaminergen und cholinergen Systeme mit SPEM zu untersuchen: Teilnehmer:innen, die nach ihrem Genotyp in einem Polymorphismus mit „variable number of tandem repeats“ (VNTR) im *SLC6A3*-Gen, das für den Dopamintransporter (DAT) kodiert, gruppiert waren, bekamen entweder Nikotin oder Placebo. In den anderen Studien wurden Daten der funktionellen Magnetresonanztomographie (fMRT) genutzt, um die funktionelle Konnektivität der während SPEM aktiven Areale (Studien III–V) zu untersuchen. Außerdem wurden die neuronalen Mechanismen, die den Hintergrund- und Geschwindigkeitseffekten zugrunde liegen (Studie IV), sowie Unterschiede in den neuronalen Korrelaten von SPEM zwischen Patient:innen mit Schizophrenie und Personen mit unterschiedlichen Ausprägungen des Persönlichkeitsmerkmals Schizotypie mit Hilfe von Methoden des maschinellen Lernens untersucht (Studie V).

In allen Studien erwiesen sich die SPEM-Aufgabeneffekte als sehr robust. Ihre hohe Reliabilität zeigte sich in Studie I. Allerdings hatte weder die Substanz (Nikotin, Placebo) noch der *SLC6A3* VNTR-Genotyp (9R-Träger, 10R-Homozygote), allein oder Interaktion, einen signifikanten Effekt auf die SPEM-Leistung in Studie II. Die gute Replizierbarkeit des SPEM zugrundeliegenden Netzwerks, bestehend aus visuellen Arealen im okzipitalen Kortex, parietalen und frontalen Arealen (frontale und supplementäre Augenfelder; SEF, FEF), dem Corpus geniculatum laterale (CGL) und dem cingulären Kortex, wurde in den Studien III–V herausgestellt. Funktionelle Konnektivitätsanalysen lieferten Hinweise auf eine enge Zusammenarbeit zwischen diesen Arealen während SPEM (Studien III–V). Während der Geschwindigkeitseffekt hauptsächlich mit Aktivierungen in visuellen Arealen assoziiert war, ging der Hintergrundeffekt mit breiter verteilten Aktivierungen in Clustern einher, die visuelle,

frontale und parietale Areale umfassten (Studie IV). Bei Patient:innen mit Schizophrenie-Spektrum-Störungen wurden nur sehr geringe Defizite in der SPEM-Leistung festgestellt (Studie V), was im Widerspruch zu früheren Ergebnissen steht. Die Kombination von Methoden der funktionellen Konnektivität und des maschinellen Lernens deutete jedoch darauf hin, dass bei Schizophrenie-Spektrum-Störungen eine veränderte funktionelle Konnektivität des rechten FEF vorhanden sein könnte.

Die hier vorgestellten Ergebnisse unterstreichen die hohe Replizierbarkeit der Hintergrund- und Geschwindigkeitseffekte sowie der Aktivität in dem mit SPEM assoziierten neuronalen Netzwerk. Die funktionelle Konnektivität der Komponenten dieses Netzwerks wurde zum ersten Mal gezeigt und war konsistent zwischen den Studien. SPEM-Defizite bei Patient:innen mit Schizophrenie waren weniger deutlich ausgeprägt als in vorherigen Untersuchungen. Insgesamt stellen diese Ergebnisse eine umfassende Ergänzung der bestehenden Forschungsliteratur zu SPEM dar, sie lassen aber auch einige Fragen für künftige Forschung offen.

1 Introduction

1.1 Eye movements

The human visual system is our most important perceptual system. More than a quarter of the human cerebral cortex is devoted to visual function (van Essen, 2004), and 80% of the information received from the outside world is processed by the visual pathway (Haupt, 2008). In the oculomotor system, fundamental aspects of human experience and behaviour, such as perception, cognition, and motor behaviour, are integrated in a very short period of time, making it an ideal platform to study these processes both independently and jointly (Hutton, 2008; Lisberger, 2015; Shaikh & Zee, 2018). Not without reason is the oculomotor system described as a "microcosm of the brain" (Carpenter, 1994, p. 341) and a "window to the brain, mind and more" (Shaikh & Zee, 2018, p. 252). This dissertation aims to peek through this window using different experimental manipulations and methods to contribute to a better understanding of eye movements and their underlying principles.

Advantages of studying eye movements include the rich body of empirical knowledge about the oculomotor system, the availability of animal models, the distinctiveness of eye movement abnormalities which can be easily mapped to anatomical, physiological, or pharmacological dysfunction, the ease and simplicity of assessing and interpreting eye movements – even in patient populations –, a large number of academic disciplines investigating eye movements, enabling a broad and interdisciplinary research program, the ease of combination with other neuroscientific methods such as transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG), and the large number of meaningful and reliably measurable parameters (Klein & Ettinger, 2008; Leigh & Zee, 2015; Shaikh & Zee, 2018).

Eye movements fulfil two fundamental functions: stabilising gaze to keep images steady on the retina and shifting gaze to new objects of interest (Leigh & Zee, 2015). There are seven classes of eye movements to serve these functions in different contexts: vestibular, fixational, vergence, and optokinetic eye movements, as well as saccades, smooth pursuit eye movements (SPEM), and the quick phase of the optokinetic nystagmus (OKN; Leigh & Zee, 2015). This dissertation focuses on SPEM, which is a major oculomotor system. As such, it offers a particularly interesting perspective for studying visuo-motor and cognitive processes (Barnes, 2008; Lisberger, 2015). Furthermore, there is a long history of research on SPEM in psychiatric disorders, highlighting potential clinical applications (Levy, Sereno, Gooding, & O'Driscoll, 2010; see 1.6). However, there are also a number of gaps in the literature, particularly concerning the effects of experimental manipulation, reliability, and the neural

mechanisms behind SPEM at the macroscopic and molecular levels. All of these aspects are addressed in the present dissertation.

1.2 Basic mechanisms of SPEM

SPEM help to keep the image of a slowly moving target on the fovea (Lisberger, 2015). Two distinct phases characterise SPEM: an initial open-loop phase followed by a closed-loop (also: maintenance or steady-state) phase (Wyatt & Pola, 1983). In the open-loop phase at the beginning of SPEM, the eyes begin to accelerate to reach target velocity. In this phase, which lasts for about 100 ms, the SPEM response is driven only by visual motion information without the contribution of internal feedback (Barnes, 2008). In the subsequent closed-loop phase, information is fed back to the SPEM system with negative feedback loops (Barnes, 2008; Lisberger, Morris, & Tychsen, 1987). During closed-loop SPEM, both retinal and extraretinal signals control eye movements (Barnes, 2008). Extraretinal signals encompass all "nonvisual signals related to the ongoing eye movement" (Lisberger, 2015, p. 450), which include recurrent information about the movement of the eye. It has been proposed to add SPEM termination as a third phase, in which eye velocity decreases exponentially (Missal & Heinen, 2017).

SPEM can occur at target velocities up to 100 °/s (C. H. Meyer, Lasker, & Robinson, 1985) but is typically studied at much lower velocities in the range of 15–30 °/s (Lencer & Trillenberg, 2008). The latency to initiate SPEM after motion onset is estimated at 70–130 ms and is caused by delays in visuomotor processing and decision making (Barnes, 2008). Target position, velocity, and acceleration information influence the SPEM command, which is also highly sensitive to extraretinal signals, including prediction, attention, and the use of the so-called efference copy that carries information about the oculomotor command (Barnes, 2008; Holst & Mittelstaedt, 1950; Leigh & Zee, 2015). Critically, SPEM cannot be elicited without a moving stimulus with few and very specific exceptions (Berryhill, Chiu, & Hughes, 2006). The contribution of extraretinal information is reflected in higher SPEM accuracy with predictable compared to non-predictable targets, in the maintenance of SPEM even when the target is briefly blanked, in the occurrence of anticipatory eye movements before motion onset or target direction reversal with predictable targets, and in response to perceptual (e.g., virtual barriers) or abstract cues (Kowler, Rubinstein, Santos, & Wang, 2019).

The SPEM system closely interacts with the saccadic system, and it is even claimed that both are "two outcomes of a single sensorimotor system" (Goettker & Gegenfurtner, 2021; Orban de Xivry & Lefèvre, 2007, p.11). For example, SPEM is usually preceded by an initial saccade, which can be eliminated with so-called step-ramp stimuli, in which the target first jumps in the opposite direction of the movement that is then initiated (Barnes, 2008; Rashbass, 1961). In addition, catch-up and back-

up saccades realign the eye to the target throughout the entire maintenance phase. They occur when the relative motion of the eye with respect to the target is in a non-optimal range, balancing costs related to saccade execution and holding (Orban de Xivry & Lefèvre, 2007). A depiction of the different types of saccades is in Figure 1, and a more detailed description is in 2.1.

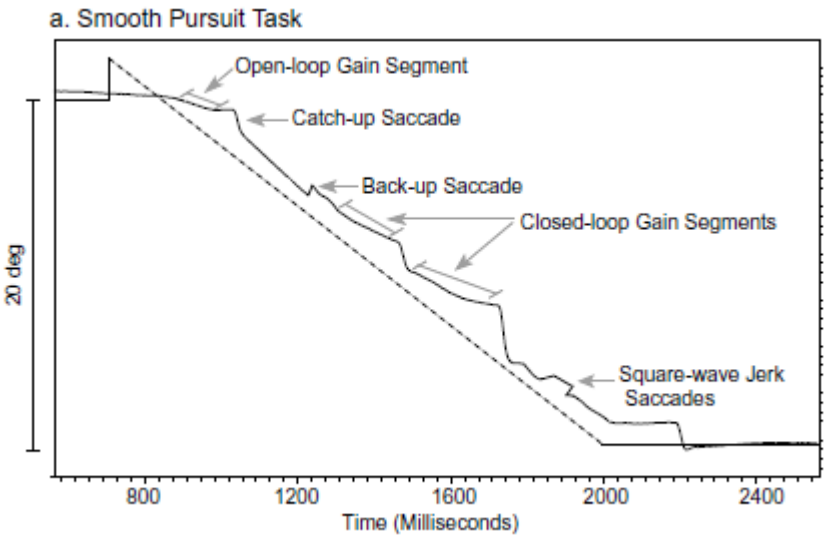

Figure 1: Schematic depiction of SPEM performance with different types of saccades.

Note. The dashed line represents the trajectory of the target, and the solid line represents the trajectory of the eye.

Reprinted from *Brain and Cognition*, *68*(3), Calkins, M. E., Iacono, W. G., & Ones, D. S., "Eye movement dysfunction in first-degree relatives of patients with schizophrenia: A meta-analytic evaluation of candidate endophenotypes", 436–461, Copyright (2008), with permission from Elsevier.

In typical SPEM experiments, SPEM targets are presented on a screen and participants are instructed to follow the targets as accurately as possible with their eyes while keeping their heads still. Targets are presented with fixed, sinusoidal, or pseudorandom velocity patterns (Leigh & Zee, 2015). Target velocity is held constant during the entire SPEM phase with fixed velocity patterns. To study SPEM initiation, single ramps with constant velocity with and without initial steps are typically used (Figure 2). However, to study SPEM maintenance at constant velocity, multiple ramps can also be presented in sequence, resulting in so-called triangular stimuli (Lencer, Sprenger, & Trillenberg, 2019). In contrast, with a sinusoidal pattern, target velocity is never constant but continuously changes over time, accelerating towards and reaching peak velocity at the centre of the screen and then decelerating towards the turning points. Sinusoidal targets are characterised by their frequency[1] (i.e., the number of

[1] All experiments of the studies integrated in this thesis employed horizontal targets following sinusoidal velocity patterns. Following advice from reviewers of some of the manuscripts, I will adopt the term target velocity (instead of target frequency) from now on to avoid confusion with the spatial frequency of targets or distractors.

excursions per second) and amplitude (the horizontal or vertical displacement of the target). They are ideal for studying maintenance SPEM (Lencer et al., 2019). Peak and average velocities of sinusoidal targets increase with increasing target frequency when the target amplitude is held constant. Pseudorandom stimuli consist of multiple superimposed sinusoidal stimuli to separate predictive and non-predictive components of SPEM (Barnes, 2008).

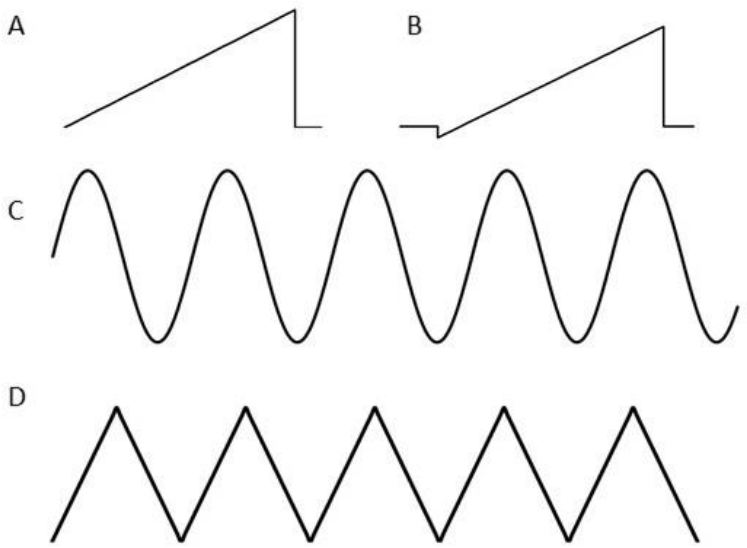

Figure 2: Target velocity patterns to investigate SPEM.

Note. Single ramp with constant velocity (A), single ramp with constant velocity and initial step (B), continuous sinusoidal waveform (C), triangular waveform (D).

SPEM performance can be quantified with different outcome measures, such as SPEM gain (the ratio of eye to target velocity), root mean square error (RMSE; a measure of the spatial position error between eye and target), and the number and quality of saccades during SPEM. More details on these performance outcomes are in 2.1.

1.3 Neural mechanisms of SPEM

Evidence concerning the neural underpinning of SPEM has been accumulated with a variety of different methods, including positron emission tomography (PET), fMRI, TMS, single-cell recordings, microstimulation, induced lesions in non-human primates as well as acquired lesions in humans. Here, I give an overview with emphasis on results from the fMRI literature, but I also draw on evidence from other methodological approaches to provide a comprehensive picture of the neural basis of this complex oculomotor system.

1.3.1 BOLD and PET correlates of SPEM

Early studies to investigate the neural mechanisms of SPEM in vivo used PET with radioactive tracers (O'Driscoll et al., 2000; O'Driscoll, Strakowski, et al., 1998), which was soon replaced by less invasive fMRI (see 2.3). Evidence from both methodological approaches points to a widespread oculomotor network underlying SPEM when contrasted with baseline (e.g., fixation blocks). This network includes areas in visual cortex (including visual areas V1 and V5[2]), parietal cortex (including precuneus, posterior parietal cortex [PPC], and lateral intraparietal sulcus [IPS]), frontal cortex (including frontal and supplementary eye fields [FEF, SEF]), cingulate gyrus, and cerebellum (Berman et al., 1999; Kimmig et al., 2008; Lencer et al., 2004; O'Driscoll et al., 2000; O'Driscoll, Strakowski, et al., 1998; Ohlendorf et al., 2010; Ohlendorf, Kimmig, Glauche, & Haller, 2007; Petit & Haxby, 1999; Tanabe, Tregellas, Miller, Ross, & Freedman, 2002). Subcortical activity during SPEM is found less consistently but has been observed in thalamus (including lateral geniculate nucleus [LGN]; Kasparbauer et al., 2016; Meyhöfer et al., 2015; Tanabe et al., 2002) and basal ganglia (Kimmig et al., 2008; Lencer et al., 2004; Ohlendorf et al., 2010).

The SPEM network partly – but not entirely – overlaps with networks underlying saccades and the OKN. Critically, the SPEM network differs from networks underlying these other types of eye movements in the location of activation peaks and spatial extent of clusters in areas V5, FEF, PPC, cingulate gyrus, and parts of the cerebellum (Berman et al., 1999; Dieterich et al., 2009; Konen & Kastner, 2008; Konen, Kleiser, Seitz, & Bremmer, 2005; O'Driscoll et al., 2000; O'Driscoll, Strakowski, et al., 1998; Petit, Clark, Ingeholm, & Haxby, 1997; Petit & Haxby, 1999; Rosano et al., 2002; Schraa-Tam et al., 2009). The neural mechanisms of the interaction of the SPEM and saccadic systems are not yet well researched. One study did not obtain specific activity related to corrective saccades during SPEM but reported largely – but not completely – overlapping networks of prosaccades and corrective saccades during other types of eye movements and fixation (Haller, Fasler, Ohlendorf, Radue, & Greenlee, 2008).

During continuous target presentation, activity in V5 most likely represents processing of retinal slip velocity and motion processing in general but is also implicated in extraretinal (e.g., predictive) processes and transformation of visual information into motor commands (Barton, Simpson, et al., 1996; Burke & Barnes, 2008; Dukelow et al., 2001; Kimmig et al., 2008; Nagel et al., 2006; Ohlendorf et al., 2010). PPC is also engaged in sensorimotor transformation. Moreover, it has been associated with attentional modulation of SPEM and processing of target velocity relative to a frame of reference

[2] In this dissertation, I will adopt the umbrella term V5 for extrastriate motion processing areas at the occipital-temporal-parietal junction containing the potential human homologues of the middle temporal visual area (MT) and the medial superior temporal visual area (MST) found in non-human primates (e.g., Barton, Simpson, et al., 1996; Chawla et al., 1999; Dukelow et al., 2001).

(Kimmig et al., 2008; Konen & Kastner, 2008; Ohlendorf et al., 2007; Ohlendorf et al., 2010; Trenner et al., 2008).

Frontal areas such as FEF and SEF are more strongly involved in the motor aspect of SPEM (Kawawaki, Shibata, Goda, Doya, & Kawato, 2006; Kimmig et al., 2008). In addition, for SEF, increased activity with predictable (vs. random) targets points to the contribution of this region to the control of timing aspects of SPEM. In FEF, however, the opposite pattern was found (i.e., higher activity with random vs. predictable targets), implying that FEF activity is more strongly related to visual guidance of SPEM (Burke & Barnes, 2008). FEF can be further divided into medial and lateral subregions, but the specific functional roles of these subregions are still not clear (Coiner et al., 2019; Dieterich et al., 2009; Lencer et al., 2004). Activity patterns in cingulate gyrus and pre-supplementary motor area suggest that these regions are associated with motor planning and learning of predictable SPEM targets (Schmid, Rees, Frith, & Barnes, 2001).

Modifications of task characteristics and control conditions can help to further elucidate the specific roles of each component of the oculomotor network in their well-orchestrated and interactive interplay during SPEM. For example, extraretinal processes contributing to SPEM are investigated by briefly blanking the SPEM target and comparing the neural activity during these periods without target presentation with periods of continuous target presentation (Kawawaki et al., 2006; Lencer et al., 2004; Nagel et al., 2006; Nagel, Sprenger, Hohagen, Binkofski, & Lencer, 2008). The blood oxygen level dependent (BOLD; see 2.3) correlates of such blanking paradigms are threefold: Firstly, there is an increase in activity in large parts of the SPEM network, especially in fronto-parietal areas (e.g., FEF, SEF, IPS, PPC) and cerebellum. Secondly, activity is reduced in early visual areas (e.g., V1, but see Nagel et al., 2008). Thirdly, there is additional BOLD activity in areas not found in simple SPEM tasks, including in dorsolateral prefrontal cortex (DLPFC), basal ganglia, and premotor cortex. Activity reductions in visual areas result from the absence of foveal visual information, whereas activity increases during blanking are interpreted as correlates of extraretinal mechanisms. Specifically, activity in frontal (e.g., DLPFC and FEF) and parietal cortex (e.g., IPS) are involved in attentional and motor processes (e.g., use of efference copy) during non-retinal SPEM, whereas lateral occipital cortex adjacent to visual area V5 contributes to target motion prediction (Kawawaki et al., 2006; Lencer et al., 2004; Nagel et al., 2006; Nagel et al., 2008). DLPFC activity has also been associated with attentive monitoring during SPEM (Schmid et al., 2001) and predictive processes closely coupled with working memory (Burke & Barnes, 2008).

1.3.2 Other methodological approaches

Lesions

Deficits in SPEM initiation and maintenance (e.g., lower SPEM gain, increased SPEM latency) after lesions in the temporo-parieto-occipital junction (i.e., V5) are related to impaired retinal image velocity and motion processing in space (Barton, Sharpe, & Raymond, 1996; Heide, Kurzidim, & Kömpf, 1996). In PPC, the effects of lesions are less consistent but have been associated with attentional deficits (Heide et al., 1996; Pierrot-Deseilligny, Gray, & Brunet, 1986). Specific SPEM deficits in patients with FEF lesions (e.g., lower SPEM gain, reduced initial SPEM velocity) highlighted the crucial role of this area for the motor aspects of SPEM initiation and maintenance in a predominantly direction-specific manner in one study (Heide et al., 1996). However, they were found to be essentially direction-independent in another study (Lekwuwa & Barnes, 1996). Lesions in areas surrounding SEF lead to specific deficits at target direction reversal, suggesting their involvement in long-term prediction (Heide et al., 1996). DLPFC lesions, however, apparently do not systematically affect SPEM performance (Heide et al., 1996; Pierrot-Deseilligny et al., 2003). The integral role of the cerebellum for SPEM is made clear by the fact that removal of the cerebellum completely abolishes SPEM (Estanol, Romero, & Corvera, 1979; Sharpe, 2008).

TMS

TMS can be used to temporarily disrupt normal functioning of targeted brain areas (Hallett, 2000). Applying TMS during SPEM has shown the crucial roles of regions in visual cortex and cerebellum for SPEM performance (Haarmeier & Kammer, 2010; Ohtsuka & Enoki, 1998). TMS over parietal cortex reduces SPEM gain (Hutton & Weekes, 2007). More specifically, it helped to establish the role of PPC in controlling attention in a direction and hemisphere-specific manner (Drew & van Donkelaar, 2007b). In addition, the temporoparietal junction (TPJ) was shown to be particularly involved in suppressing OKN (Haarmeier & Kammer, 2010; see also 1.4.2). In frontal cortex, evidence from TMS studies revealed that FEF are crucial for initiating SPEM, allocating attention during SPEM, and controlling the dynamic gain of predictive and retinal signals (Drew & van Donkelaar, 2007a; Gagnon, Paus, Grosbras, Pike, & O'Driscoll, 2006; Jin, Gou, Zhang, & Li, 2021; Nuding et al., 2009). SEF are also engaged in predictive processes during ongoing SPEM, especially at target reversal (Drew & van Donkelaar, 2007a; Gagnon et al., 2006; Nyffeler, Rivaud-Pechoux, Wattiez, & Gaymard, 2008).

Non-human primates

In non-human primates, a broader range of methods can be applied than in humans to gather information about neural systems. For example, single-cell recordings, induced lesions, and microstimulation can help to elucidate the specific neural mechanisms underlying SPEM (Ilg & Thier, 2008).

With these methods, processing in the early visual pathway has been analysed. Visual information from the outside world is propagated from photoreceptors to retinal ganglion cells and on to LGN in thalamus. From there, signals are sent to visual cortex in occipital lobe and on to extrastriate cortex (Nassi & Callaway, 2009). Area MT has been identified as a major hub of visual motion processing based on retinal information. The adjacent lateral MST (lMST) represents motion in world-centred coordinates, suggesting non-retinal input. Its dorsal counterpart (dMST) is engaged in eliminating eye movement-induced optic flow (Ilg & Thier, 2008).

In frontal cortex, evidence from single-cell recordings suggests that FEF neurons represent SPEM movements in three-dimensional space (Fukushima, Yamanobe, Shinmei, Fukushima, et al., 2002). In addition, FEF neurons are considered critical for SPEM initiation (MacAvoy, Gottlieb, & Bruce, 1991) and controlling the gain of retinal signals during ongoing SPEM (Ono, 2015; Tanaka & Lisberger, 2001). They are also involved in extraretinal processes, including prediction and attention (Armstrong & Moore, 2007; Fukushima, Yamanobe, Shinmei, & Fukushima, 2002; Ilg & Thier, 2008; MacAvoy et al., 1991). Similarly, SEF neurons have also been associated with SPEM initiation and prediction with microstimulation methods (Missal & Heinen, 2001, 2004). An additional role of the SEF might lie in controlling the decision to pursue a stimulus (Fukushima, Fukushima, Warabi, & Barnes, 2013; Leigh & Zee, 2015). Neurons in intraparietal cortex code mainly for eye position and are thought to be implicated in perceptual compensation of self-induced image motion as well as in spatial representation (Ilg & Thier, 2008). There is still an ongoing debate about the existence of a cingulate eye field (CEF) in non-human primates and humans and its functional role (Amiez & Petrides, 2009; Gaymard et al., 1998; Wang, Matsuzaka, Shima, & Tanji, 2004).

Specific lesions in oculomotor vermis suggest the importance of this area for adaptively controlling ongoing SPEM (Takagi, Zee, & Tamargo, 2000).

Animal models are also valuable for identifying structural connections. For example, it has been shown that the SPEM network's occipital, frontal, and parietal hubs are highly interlinked via white-matter connections (Abe et al., 2018; Leichnetz, 2001; Maunsell & van Essen, 1983; Stanton, Friedman, Dias, & Bruce, 2005). In addition, connections between cortical and subcortical structures can elucidate the downstream pathway of SPEM signals. Cortical SPEM areas (e.g., V5 and FEF) and superior colliculus (crucial for saccade planning) project to pontine nuclei (the dorsolateral pontine nucleus and the nucleus reticularis tegmenti) that are sensitive to both SPEM and saccadic signals (Ilg & Thier,

2008; Mustari, Ono, & Das, 2009). Projection sites of these pontine nuclei lie in cerebellum. In the flocculus/paraflocculus complex, information is integrated with vestibular signals (Mustari et al., 2009), and posterior vermis is involved in controlling the open-loop phase of SPEM (Ilg & Thier, 2008). From there, signals are sent to the extra-ocular moto-neurons in the brainstem that directly control the eye muscles (Horn & Straka, 2021; Ilg & Thier, 2008).

1.3.3 Interim Summary

Synthesising the evidence from all the methodological approaches described above, the following processing pathway of the SPEM system emerges (Figure 3; Lencer et al., 2019). A SPEM stimulus reaches early visual area V1 via retina and LGN (Nassi & Callaway, 2009), from where the signal is propagated to visual motion processing area V5. V5 is an integral component of the SPEM network implicated with motion processing, but also sensorimotor transformation and extraretinal processes (Barton, Sharpe, & Raymond, 1996; Barton, Simpson, et al., 1996; Chawla et al., 1999; Ilg & Thier, 2008; Kimmig et al., 2008). It closely interacts with parietal and frontal SPEM areas, including FEF and SEF, and cingulate gyrus (Lencer & Trillenberg, 2008). In parietal cortex, SPEM signals are primarily processed in PPC, which is involved in sensorimotor transformation, attention, and integration of velocity relative to a frame of reference (Drew & van Donkelaar, 2007b; Kimmig et al., 2008; Ohlendorf et al., 2007; Ohlendorf et al., 2010; Pierrot-Deseilligny et al., 1986; Trenner et al., 2008). In frontal cortex, FEF are crucial for SPEM initiation, dynamically controlling the gain of retinal and non-retinal signals and attentional processes during ongoing SPEM (Gagnon et al., 2006; Heide et al., 1996; Jin et al., 2021; Tanaka & Lisberger, 2001). SEF support successful SPEM performance by carrying predictive signals, especially at target motion reversal (Gagnon et al., 2006; Heide et al., 1996). In contrast, DLPFC is not believed to be consistently involved in SPEM but may contribute extraretinal information related to attention, monitoring, and prediction when needed (Kawawaki et al., 2006; Lencer et al., 2004; Nagel et al., 2006; Schmid et al., 2001). Cortical SPEM areas propagate information to brain stem nuclei that relay information to cerebellum, from where the final motor command is sent to extra-ocular moto-neurons (Ilg & Thier, 2008; Mustari et al., 2009).

The studies described here all tend to follow a functional segregation approach, in which each brain area is assigned a specific function within the SPEM system. In fact, however, the interaction of the different regions is vital for successful SPEM (Acs & Greenlee, 2008). This interplay (i.e., brain connectivity, see 2.3.3) has been insufficiently investigated so far, which constitutes a critical gap in the literature addressed in this dissertation (**Studies III–V**).

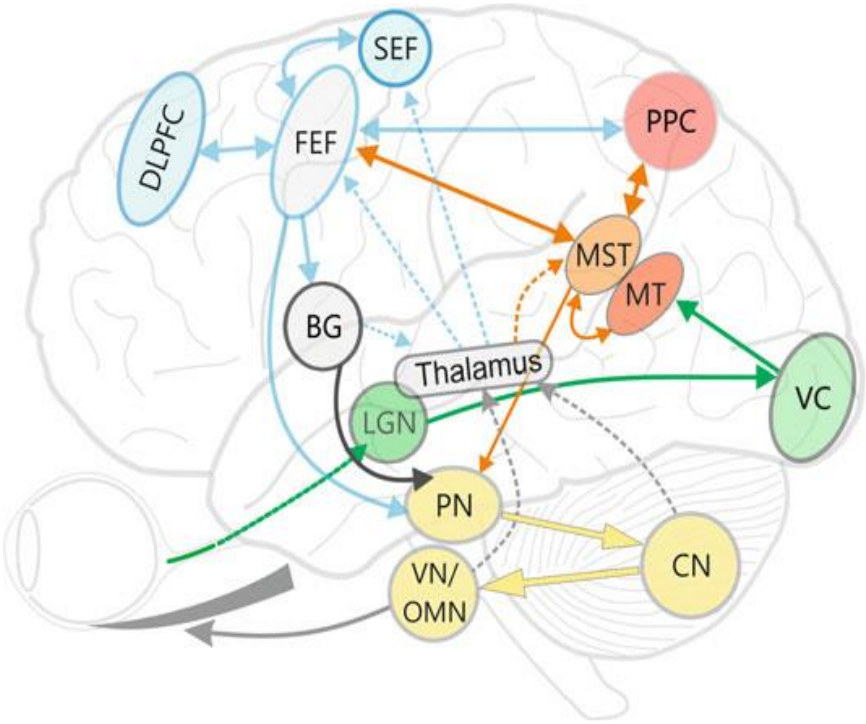

Figure 3: Schematic depiction of the neural network underlying SPEM.

Note. Key components of the SPEM network comprise visual cortex (VC), lateral geniculate nucleus (LGN), middle temporal visual area (MT), medial superior temporal visual area (MST), posterior parietal cortex (PPC), frontal eye field (FEF), supplementary eye field (SEF), dorsolateral prefrontal cortex (DLPFC), basal ganglia (BG), pontine nuclei (PN), cerebellar nuclei (CN), vestibular nuclei (VN), and oculomotor nuclei (OMN).

Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Eye movement research: An introduction to its scientific foundations and applications*, "Smooth eye movements in humans: Smooth pursuit, optokinetic nystagmus and vestibular ocular reflex", Lencer, R., Sprenger, A., & Trillenberg, P., Copyright (2019).

1.4 Experimental task effects on SPEM

SPEM performance is influenced by stimulus features. Specifically, changes in experimental task designs, e.g., concerning the presence and quality of background stimuli or the velocity of the SPEM target, modulate SPEM accuracy (e.g., Barnes, 2008; Lencer & Trillenberg, 2008). Changing these features and investigating the effects on SPEM performance can help to unravel the specific mechanisms involved in SPEM. This dissertation focuses on two experimental task effects: the background and the velocity effect.

1.4.1 The background effect

SPEM in the lab is typically assessed by presenting a target stimulus on a uniform background. Outside the lab, however, SPEM targets move in much more complex and visually rich environments. It is not surprising to find SPEM performance to be influenced by background stimuli. In the last forty years of SPEM research, it has been shown with remarkable consistency that SPEM performance in humans is degraded by background stimuli as indicated by decreased SPEM velocity or velocity gain, increased SPEM latency, increased rates of catch-up saccades, and higher position error (Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton, Crawford, Kennard, Barnes, & Joyce, 2000; Kaufman & Abel, 1986; Kreyenmeier, Fooken, & Spering, 2017; Lindner & Ilg, 2006; Lindner, Schwarz, & Ilg, 2001; Masson, Proteau, & Mestre, 1995; Meyhöfer, Kasparbauer, Steffens, & Ettinger, 2019; Niemann & Hoffmann, 1997; Spering & Gegenfurtner, 2007; Suehiro et al., 1999; Yee, Daniels, Jones, Baloh, & Honrubia, 1983). This pattern of results has also been observed in non-human primates (Keller & Khan, 1986; Kimmig, Miles, & Schwarz, 1992; Mohrmann & Thier, 1995).

Degraded SPEM performance has been shown with a variety of different stationary or dynamic background stimuli (Figure 4), such as patterns of random dots (Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Masson et al., 1995; Suehiro et al., 1999) or vertical stripes (Lindner & Ilg, 2006; Niemann & Hoffmann, 1997; Yee et al., 1983), checkerboards (Collewijn & Tamminga, 1984; Hutton et al., 2000), symmetrically or asymmetrically distributed distractors (such as circles, crosses, lines; Lindner et al., 2001; Meyhöfer et al., 2019), texture (Kreyenmeier et al., 2017), photographs of landscapes (Kaufman & Abel, 1986), and gratings (Collewijn & Tamminga, 1984; Spering & Gegenfurtner, 2007). Of note, the specific structure of the background was shown to be of only marginal importance (Collewijn & Tamminga, 1984). Instead, the relative depth of background and target stimuli in three-dimensional space (i.e., distance along the z-axis) plays a much more crucial

role: background stimuli reduce SPEM performance more when presented in the same depth plane as the target (Howard & Marton, 1992).

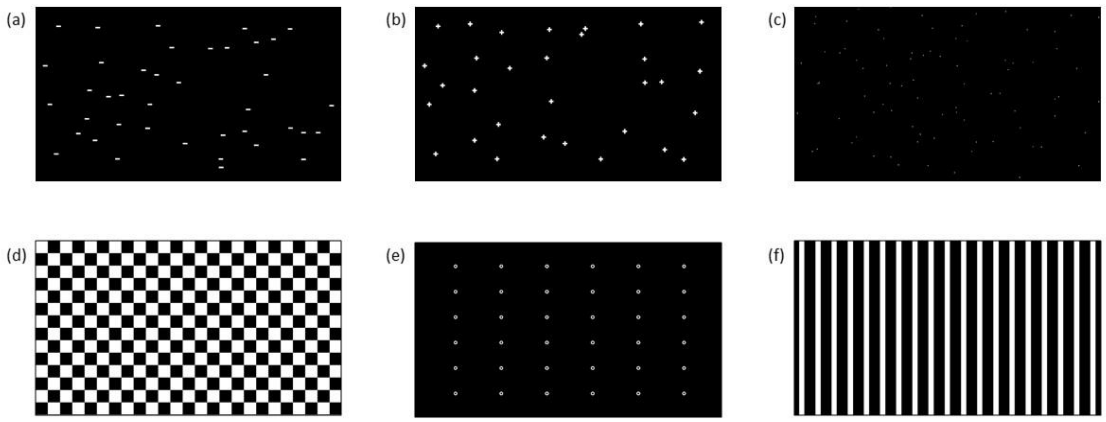

Figure 4: Exemplary depiction of different target displays used as background stimuli for SPEM.

Note. (a) Asymmetrically distributed horizontal lines, (b) asymmetrically distributed crosses, (c) random dots, (d) checkerboards, (e) symmetrically distributed circles, (f) symmetrically distributed vertical lines.

Crucially, however, the presence of a structured background can also enhance SPEM performance, e.g., when target and background move in the same direction (Kreyenmeier et al., 2017; Lindner et al., 2001; Masson et al., 1995; Niemann & Hoffmann, 1997), and when the background stimuli provide crucial information on the target's future movement, e.g., with static barriers and abstract cues, and thus help to guide eye movements based on predictive processes (Eggert, Ladda, & Straube, 2009; Goettker, Agtzidis, Braun, Dorr, & Gegenfurtner, 2020; Ladda, Eggert, Glasauer, & Straube, 2007).

The precise mechanisms underlying the – largely detrimental – background effects on SPEM performance are not yet fully understood. The stationary background induces a optokinetic drive "dragging" the eyes opposite to the direction of target motion, which corresponds to the direction of SPEM-induced image motion (Barnes, 2008; Lindner et al., 2001; Lindner & Ilg, 2006; Suehiro et al., 1999). The control of SPEM with structured backgrounds seems to rely on inhibiting the resulting OKN (Barnes, 2008; Spering & Gegenfurtner, 2008) and simultaneously enhancing the processing of the target (Barnes & Crombie, 1985). For the successful inhibition of the OKN, sensitivity to global motion signals in the opposite direction of the SPEM target is attenuated (Lindner et al., 2001). OKN inhibition does not purely rely on visual signals such as self-induced image motion or relative motion of

background and target but is instead based on the processing of extraretinal signals (Lindner & Ilg, 2006).

Studies I, **II**, and **IV** of the present dissertation focus on the background effect regarding its replicability, reliability, and the neural mechanisms involved at the molecular and neural systems levels, as these matters have not been adequately addressed in research in the past.

1.4.2 Neural correlates of the background effect

While the SPEM background effect is well replicated at the behavioural level, the literature on its neural correlates is scant. Typically, a stable world is perceived when the eyes move on a structured stationary background despite the retinal motion opposite of the target direction caused by the eyes' movement. It is therefore hypothesised that an internal reference signal is used, which codes for the visual action outcome during SPEM with background stimuli. This signal is influenced by two sources of information: an internal representation of the eye movement (e.g., corollary discharge) and the visual context (Lindner, Haarmeier, Erb, Grodd, & Thier, 2006; Tikhonov, Haarmeier, Thier, Braun, & Lutzenberger, 2004). The search for the neural correlates of the reference signal has yielded three candidate regions. Lindner et al. (2006) suggested that the cerebellum is important for the cancellation of self-generated image motion. A MEG study with similar stimuli located correlates of the internal reference signal in medial parieto-occipital cortex (Tikhonov et al., 2004). Findings from another MEG study suggest that area V5 receives extraretinal information during SPEM with background stimuli necessary for perceptual stability (Dunkley, Freeman, Muthukumaraswamy, & Singh, 2013).

Only one fMRI study directly investigated the BOLD correlates of SPEM over a structured background with a whole-brain approach (Ohlendorf et al., 2010). Evidence presented therein points to the pivotal role of the PPC, which was the only area activated in response to differential motion between visual background and target. PPC is thus interpreted as integrating the movement of a frame of reference relative to the target. The same area has also been pinpointed in a previous study with a single background stimulus as critical for dividing attention between target and distractor (Ohlendorf et al., 2007).

An early lesion study identified parts of parietal cortex (especially in supramarginal gyrus and anterior inferior parietal lobe) and white matter connections close to the lateral ventricle as potentially involved in the suppression of background processing (Lawden, Bagelmann, Crawford, Matthews, & Kennard, 1995). Anatomical location of lesions of patients with poorer suppression overlapped in these areas, whereas patients who successfully inhibited the background typically did not have lesions in these areas.

More evidence for the involvement of parietal cortex, especially the TPJ, in background processing or suppression is provided by a TMS study by Haarmeier and Kammer (2010). They demonstrated that – while the presence of a structured background slowed SPEM in general – suppression of OKN during SPEM was impaired after TMS on both TPJs but not on other SPEM-related areas (i.e., V1, V5).

In addition to these studies focusing directly on SPEM, a review of the literature on BOLD correlates of OKN may also help to unravel the neural mechanisms of SPEM against a structured background because of similarities in input stimuli (Bucher, Dieterich, Seelos, & Brandt, 1997; Dieterich, 1998; Dieterich et al., 2009; Dieterich, Bense, Stephan, Yousry, & Brandt, 2003; Konen et al., 2005; Schraa-Tam et al., 2009; Schraa-Tam, van der Lugt, Frens, et al., 2008; Schraa-Tam, van der Lugt, Smits, et al., 2008). Critically, early fMRI studies have pointed to largely overlapping networks underlying both SPEM and OKN (Bucher et al., 1997; Dieterich, 1998; Dieterich et al., 2003; Dieterich et al., 2009; Konen et al., 2005). More recent evidence, however, suggests a more intricate picture by tackling a potential confound in earlier studies. In a series of experiments, Schraa-Tam and colleagues (Schraa-Tam et al., 2009; Schraa-Tam, van der Lugt, Frens, et al., 2008; Schraa-Tam, van der Lugt, Smits, et al., 2008) used limited lifetime dots (as opposed to vertical stripes) as OKN stimuli. As the dots' lifetimes were too short to trigger the SPEM system, OKN and SPEM-related processes could be separated. OKN BOLD correlates were found to be less widespread than in previous investigations. Specifically, the overlap of SPEM and OKN was mainly restricted to early visual areas. In contrast, other cortical areas, such as FEF, parietal cortex, V5, and cerebellar area VI, were involved in SPEM but less consistently in OKN with limited lifetime dots. These findings on the comparison of SPEM and OKN highlight that – despite similar visual input – BOLD correlates of OKN and SPEM over structured backgrounds are clearly distinguishable, suggesting that differences are potentially due to higher-order processes.

Evidence from literature on response inhibition additionally suggests that frontal areas are involved in successfully inhibiting the processing of background stimuli (Wager et al., 2005).

To recapitulate, it is evident that the literature on the neural mechanisms underlying the robust behavioural background effect is heterogenous and sparse. However, there is emerging evidence for significant contributions of parietal cortex to the processing or suppression of background stimuli during SPEM, as activity in this part of the cortex was found across different task designs and methodological approaches. The specific location in the parietal subregions and the cognitive mechanisms involved are, however, still unclear. Moreover, the contribution of other areas, such as FEF, cerebellum, and V5, has not been addressed in depth. Therefore, **Study IV** of the present dissertation compares BOLD response to SPEM in conditions with and without structured background stimuli to tackle these open questions.

1.4.3 The target velocity effect

The evidence for negative effects of increasing target velocity on SPEM performance is arguably even more robust than the findings of decreased performance in the presence of a structured background. Specifically, increasing target velocity reduces velocity gain (Barnes, 1993; Collewijn & Tamminga, 1984; Ettinger et al., 2004; Ettinger, Kumari, Crawford, et al., 2003; Fransson et al., 2008; Haraldsson et al., 2008; Hutton et al., 1998; Hutton et al., 2000; Hutton et al., 2001; Hutton & Tegally, 2005; Lekwuwa & Barnes, 1996; Lisberger, Evinger, Johanson, & Fuchs, 1981; Waterson, Barnes, & Grealy, 1992; Wyatt & Pola, 1983), increases rates (Ettinger et al., 2004; Ettinger, Kumari, Crawford, et al., 2003; Meyhöfer et al., 2017; Meyhöfer et al., 2019) and amplitudes of catch-up saccades (Meyhöfer et al., 2017) as well as rates of all types of saccades (Haraldsson et al., 2008), increases RMSE (Hutton & Tegally, 2005; Meyhöfer et al., 2017), decreases overall eye velocity (Buizza & Schmid, 1986), and increases temporal or phase-lag between eye and target (Hutton et al., 2001; Wyatt & Pola, 1983). These effects have been shown consistently for constant (e.g., Fransson et al., 2008; Haraldsson et al., 2008; Hutton et al., 2000) and sinusoidal (e.g., Barnes, 1993; Lisberger et al., 1981; Meyhöfer et al., 2017; Waterson et al., 1992) target velocity patterns (Figure 2). Based on these results, it can be concluded that the SPEM system works excellently at low velocities, but – as target velocity increases – it is gradually supported by the saccadic system to realign eye and target (Barnes, 2008). The decay in SPEM accuracy at increasing target velocities is thought to result from non-linearities in the SPEM system based on eye velocity and acceleration saturation (Barnes, 2008; Buizza & Schmid, 1986).

Target velocity processing may also depend on the presentation of background stimuli. The negative effect of background on SPEM performance has been shown to increase with increasing target velocity, suggesting that the two processes may draw on overlapping cognitive resources (Meyhöfer et al., 2019).

In all studies employed in this dissertation (**Studies I–V**), targets are presented at different velocities, enabling a broad outlook on the specific mechanisms involved in guiding SPEM in these contexts.

1.4.4 Neural correlates of the velocity effect

Given the large and well-replicated effects of target velocity on SPEM performance, there is surprisingly little literature on the nature of these effects at the neural level.

The importance of FEF for processing target velocity is highlighted by single-cell recordings that revealed increased firing rates of neurons in these areas with faster targets (Gottlieb, MacAvoy, & Bruce, 1994). Evidence from fMRI approaches in humans comes from Nagel et al. (2008), who reported

increased activity in primary visual cortex, angular gyrus, cerebellum, and subcortical structures, including thalamus and putamen, with increasing target velocity. A more intricate regression analysis additionally pointed to increased activity with higher target velocity in V5, lateral parietal cortex, FEF, and SEF. A subsequent study largely replicated these results in a control group of healthy participants (Nagel, Sprenger, Steinlechner, Binkofski, & Lencer, 2012). However, in patients with schizophrenia, when compared to healthy controls, target velocity was less strongly related to neural activity in V5 and IPS and not correlated with activity in SEF, putamen, and cerebellum (for a detailed summary of SPEM and their neural correlates in schizophrenia see 1.6.3 and 1.6.4). Crucially, these results were obtained with short target ramps and constant target velocity, which might be better suited to reflect SPEM initiation but is suboptimal to study SPEM maintenance. More recent findings with continuous sinusoidal SPEM targets provide evidence for robust effects of increased activity with higher target velocity in visual cortex but not in other brain areas in medicated participants and participants with varying levels of schizotypy (Kasparbauer et al., 2016; Meyhöfer et al., 2015; Steffens et al., 2016). Data of control or placebo participants of these three studies are re-analysed in **Study III** of the present thesis to examine the velocity effect in a homogeneous sample, with greater power, and with more sophisticated methods of analysis. Additional insights into the specific neural mechanisms are also expected from **Studies IV** and **V**.

1.5 Molecular mechanisms of SPEM

In the previous sections, the macroscopic neural mechanisms of SPEM were shown to be relatively well understood, even though there are still significant research gaps, especially concerning the nature of the background and velocity effects. The literature regarding the molecular mechanisms of SPEM, in particular the underlying neurotransmitter systems, on the other hand, is still insufficient. In recent years, however, progress has been made in this area with pharmacological, clinical, genetic, and nuclear imaging (PET and single photon emission computed tomography [SPECT]) approaches.

A particular focus in the search for the molecular basis of SPEM has been on the dopamine and acetylcholine neurotransmitter systems (e.g., Naicker, Anoopkumar-Dukie, Grant, & Kavanagh, 2017; Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008; Figure 5). There are several reasons to presume that these systems may be associated with SPEM. First, both dopamine and acetylcholine are involved in cognitive function in general, particularly in attention (Hahn, 2015; Heishman, Kleykamp, & Singleton, 2010; Nieoullon, 2002; Poorthuis & Mansvelder, 2013), which is also essential for SPEM (Souto & Kerzel, 2021). Second, SPEM performance is disturbed in patients with known dysfunction in these neurotransmitter systems, e.g., in schizophrenia (Levy et al., 2010; see 1.6.1), Parkinson's disease (Frei, 2020; Waterston, Barnes, Grealy, & Collins, 1996; White, Saint-Cyr, Tomlinson, & Sharpe, 1983), and

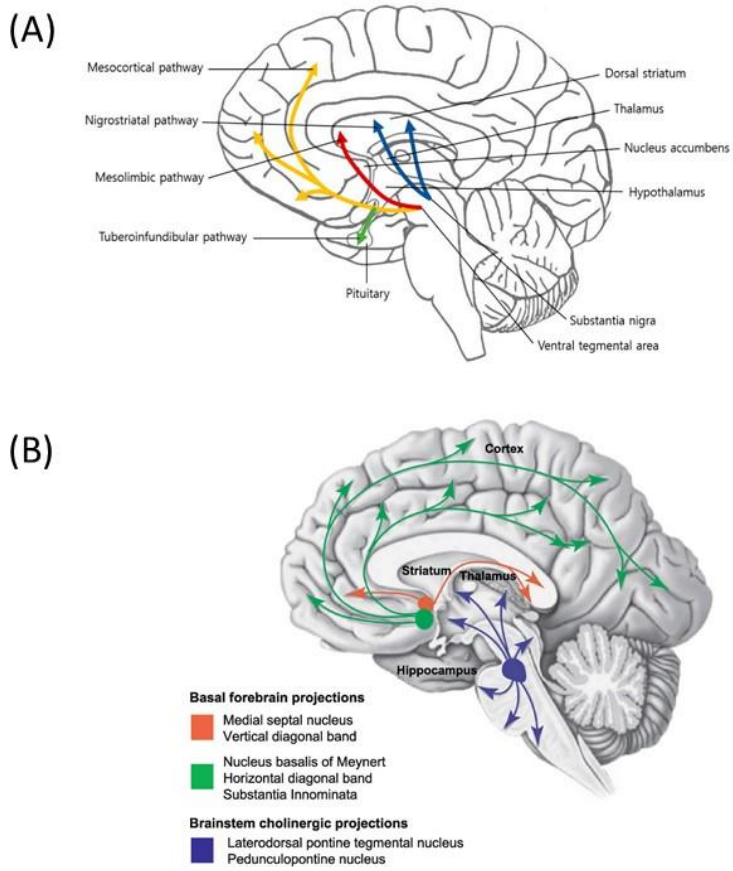

Figure 5: The dopaminergic and cholinergic systems.

Note. Panel (A) shows the major dopaminergic pathways, and panel (B) shows the major cholinergic pathways.

Panel (A) is reprinted from "Association between chronic pain and alterations in the mesolimbic dopaminergic system" by Yang, S., Boudier-Revéret, M., Choo, Y. J., & Chang, M. C., 2020, *Brain Sciences*, *10*(10), p. 3. Licensed under CC BY 4.0. Panel (B) is reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Behavioral Pharmacology of the Cholinergic System*, "A review of the cholinergic system and therapeutic approaches to treat brain disorders", Bertrand, D., & Wallace, T. L., Copyright (2020).

Alzheimer's disease (Molitor, Ko, & Ally, 2015). Third, drugs that modulate dopaminergic and cholinergic function have been found to influence SPEM performance in some but not all investigations (Allman, Ettinger, Joober, & O'Driscoll, 2012; Bareš et al., 2003; Ettinger, Kumari, Zachariah, et al., 2003; Kasparbauer et al., 2016; Naicker et al., 2017; Penetar, Haegerstrom-Portnoy, & Jones, 1988; Schmechtig et al., 2013; for nicotine, see 1.5.2). In addition, the cholinergic and dopaminergic systems closely interact at the cellular level. For example, the balance of acetylcholine and dopamine in striatum is important for general movement control (Aosaki, Miura, Suzuki, Nishimura, & Masuda, 2010) and might thus also be relevant for SPEM.

One study integrated in this dissertation (**Study II**) aims to study the molecular mechanisms involved in SPEM by targeting the dopaminergic and cholinergic systems with a pharmacological

approach through nicotine administration whilst also taking into account individual differences in dopamine function at the molecular genetic level.

1.5.1 Nicotine

Nicotine is a nonselective agonist of the nicotinic acetylcholine receptor (nAChR) with extensive effects in the nervous system (Dani & Bertrand, 2007; Kloet, Mansvelder, & Vries, 2015). These receptors can be found in cortical and subcortical brain areas, including in thalamus, striatum, hippocampus, substantia nigra, ventral tegmental area (VTA), locus coeruleus, and the raphe nuclei, and in the peripheral nervous system (J. S. Meyer & Quenzer, 2013). In the central nervous system, nicotine triggers dopamine release in striatum, especially in nucleus accumbens (Ferrari, Le Novère, Picciotto, Changeux, & Zoli, 2002; Nisell, Nomikos, & Svensson, 1994). Cholinergic neurons are regarded as a major modulatory input of dopamine neuron activity in the VTA (Kloet et al., 2015), and cholinergic interneurons play an important role in dopamine release in striatum (Cachope et al., 2012; Threlfell et al., 2012). In addition to these direct influences, nicotine also has an indirect modulatory effect on the dopamine system via activation of γ-aminobutyric acid (GABA) and glutamate (Bonci, Bernardi, Grillner, & Mercuri, 2003; Kloet et al., 2015).

Nicotine has been studied extensively for its addictive potential and adverse effects on global health (Benowitz, 2010). In clinical settings, it has received particular attention due to the high prevalence of self-administration in patients with schizophrenia and attention deficit hyperactivity disorder (ADHD; N. M. Lambert & Hartsough, 1998; Leon & Diaz, 2005). High rates of nicotine self-administration may be due to positive effects on cognitive symptoms and alleviation of adverse side effects of antipsychotic medication in schizophrenia, referred to as the self-medication hypothesis (Kumari & Postma, 2005; McClernon & Kollins, 2008). Indeed, beneficial effects of nicotine on cognitive task performance have been found in groups of patients with schizophrenia and ADHD (Barr et al., 2008; D'Souza & Markou, 2012; Levin et al., 1996; Rezvani & Levin, 2001).

Crucially, however, pro-cognitive effects of nicotine were also reported in healthy participants. Specifically, positive influences of nicotine on motor abilities, attention, and memory were obtained in a comprehensive meta-analysis in non-smokers and satiated or minimally deprived smokers (Heishman et al., 2010). Similarly, in deprived smokers, nicotine improves cognitive function in various domains (Evans & Drobes, 2009). There is a relatively consistent pattern of nicotine effects for oculomotor control with evidence pointing to improvement of antisaccade performance under nicotine influence (Ettinger & Kumari, 2019), but inconclusive findings regarding SPEM performance.

1.5.2 Nicotine effects on SPEM

Early investigations on nicotine effects on SPEM performance found SPEM accuracy decreased and rates of intrusive or compensatory saccades increased after nicotine administration (Sibony, Evinger, & Manning, 1988; Thaker, Ellsberry, Moran, Lahti, & Tamminga, 1991). In contrast, later studies mainly yielded positive results, as shown by increased SPEM gain and SPEM velocity and decreased rates of catch-up and leading saccades after nicotine administration (Avila, Sherr, Hong, Myers, & Thaker, 2003; Dépatie et al., 2002; Domino, Ni, & Zhang, 1997; Meyhöfer et al., 2019; Olincy, Ross, Young, Roath, & Freedman, 1998; Sherr et al., 2002). Other studies could not establish any effect of nicotine on SPEM performance (Kasparbauer et al., 2016; Schmechtig et al., 2013).

Several different factors may be considered as potential moderators of these heterogeneous results. First, between-group differences have to be considered: positive results were primarily obtained in samples of deprived smokers (Avila et al., 2003; Dépatie et al., 2002; Domino et al., 1997) or patients with schizophrenia (Avila et al., 2003; Dépatie et al., 2002; Olincy et al., 1998; Sherr et al., 2002; Tregellas, Tanabe, Martin, & Freedman, 2005). Evidence for nicotine effects on SPEM in healthy non-smokers, on the other hand, is mixed, including positive (Meyhöfer et al., 2019), negative (Thaker et al., 1991), and null results (Avila et al., 2003; Domino et al., 1997; Kasparbauer et al., 2016; Schmechtig et al., 2013; Sherr et al., 2002). Second, methodological shortcomings might have caused this heterogeneity and call into question the validity of some of the results. Specifically, not all studies had an adequate placebo control (Avila et al., 2003; Domino et al., 1997; Olincy et al., 1998; Sherr et al., 2002; Sibony et al., 1988; Thaker et al., 1991). Some studies were not double-blinded or did not provide information on blinding (Avila et al., 2003; Tanabe, Tregellas, Martin, & Freedman, 2006; Tregellas et al., 2005) or were ill-powered (Sibony et al., 1988) and one study reported clinical results but did not have a healthy control group (Tregellas et al., 2005). In addition, studies differed in the method of nicotine administration, e.g., using gum (Meyhöfer et al., 2019; Tanabe et al., 2006), patches (Dépatie et al., 2002; Kasparbauer et al., 2016; Schmechtig et al., 2013), cigarette smoking (Domino et al., 1997; Olincy et al., 1998; Sibony et al., 1988; Thaker et al., 1991), or nasal spray (Avila et al., 2003; Sherr et al., 2002), study design, e.g., within-subject (Meyhöfer et al., 2019) vs. between-subject design (Domino et al., 1997; Kasparbauer et al., 2016; Schmechtig et al., 2013), and nicotine dosage, e.g., 2 mg (Meyhöfer et al., 2019) vs. 4 mg or 6 mg gum (Tanabe et al., 2006), ad libitum smoking (Olincy et al., 1998) vs. smoking of one cigarette (Domino et al., 1997), and 7 mg (Kasparbauer et al., 2016; Schmechtig et al., 2013) vs. 14 mg patches (Dépatie et al., 2002).

Thus, despite the rich body of research on the effects of nicotine on SPEM, there is still no clear overall picture. More recent, well-controlled evidence tentatively points to enhancing effects on SPEM performance even in non-smokers, especially in the presence of a structured background (Meyhöfer et al., 2019). However, given the generally inconsistent literature on nicotine effects on SPEM and the

large number of possible moderators, the effect of nicotine on SPEM is further explored in the present work (**Study II**).

1.5.3 A pharmacogenetic perspective on dopamine-acetylcholine interactions

As noted above (see 1.5), the dopamine system is associated with SPEM, warranting a more detailed investigation into the specific molecular mechanisms. **Study II** of this dissertation focuses on genetic variation in the gene coding for the dopamine transporter (DAT). The sodium- and chloride-dependent DAT is a crucial component of the human dopamine system. It is essential for dopamine neurotransmission by controlling the active re-uptake of dopamine in the presynaptic neuron, where it is re-packed into new vesicles for re-release (Figure 6; McHugh & Buckley, 2015; Piccini, 2003; Salatino-Oliveira, Rohde, & Hutz, 2018). DAT-mediated re-uptake is – along with enzymatic degradation – one of two mechanisms to terminate DAT neurotransmission (McHugh & Buckley, 2015) and thus directly regulates extracellular dopamine availability.

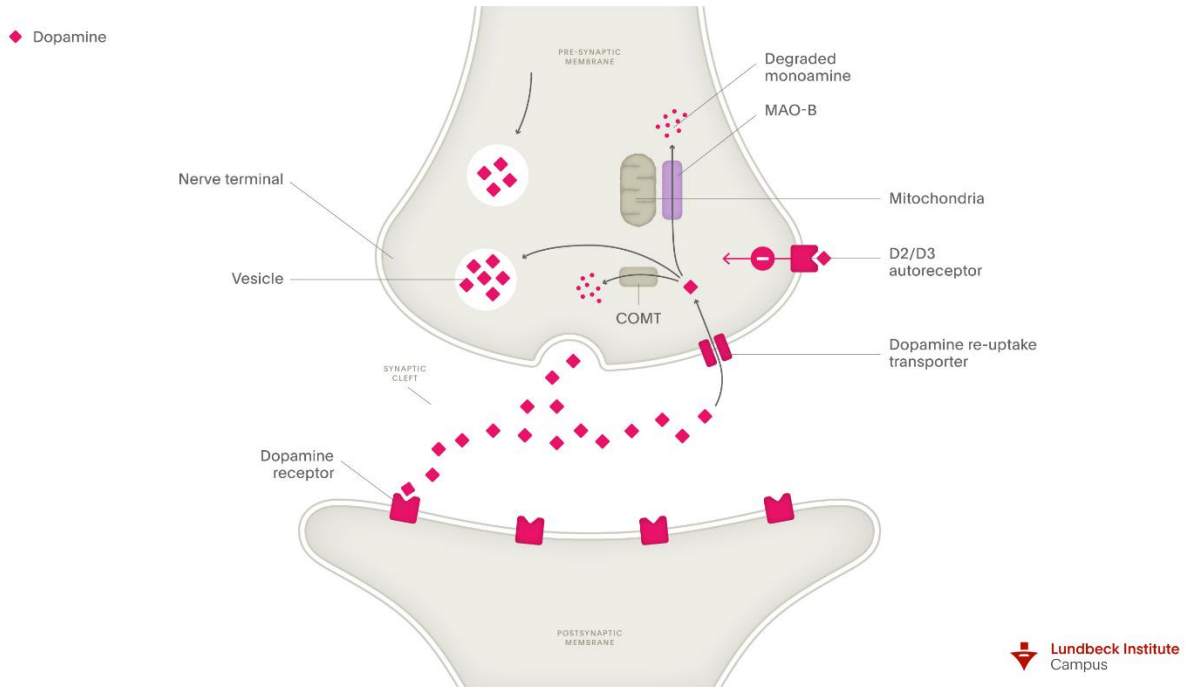

Figure 6: Synaptic dopamine reuptake and degradation.

Note. From "Synaptic Dopamine reuptake and degradation", The Lundbeck Institute, Copyright (2016), (institute.progress.im).

The specificity of DAT occurrence in dopaminergic neurons has been exploited to study the dopaminergic system in vivo with radioactive tracers (Piccini, 2003). DAT density is highest in striatum (putamen, caudate nucleus, and nucleus accumbens) and olfactory tubercle but can also be found in other cortical and subcortical structures (including amygdala, hypothalamus, hippocampus, substantia nigra, VTA, parts of the thalamus, and neocortex; Piccini, 2003; Salatino-Oliveira et al., 2018).

DAT is the site of action of many drugs, such as cocaine, amphetamine, methamphetamine, and methylphenidate. Therefore, it is widely studied to understand mechanisms of drug action as well as substance abuse and addiction (Salatino-Oliveira et al., 2018).

Apart from substance-related disorders, DAT is also investigated in other physiological and psychiatric disorders associated with dopaminergic dysfunction, including Parkinson's disease, ADHD, and schizophrenia (McHugh & Buckley, 2015; Salatino-Oliveira et al., 2018). In addition, considerable interindividual differences in dopamine function exist in the non-clinical range (Cools et al., 2009; Cools & D'Esposito, 2011; Costa et al., 2013).

Some of these dopamine-related interindividual differences may be attributed to variation at the genetic level (Bogdan, Carré, & Hariri, 2012; Hariri, 2009; Siebner, Callicott, Sommer, & Mattay, 2009). The DAT gene (*SLC6A3*) is located in chromosome 5p15.3 and has 15 exons, separated by 14 introns, spanning over more than 60 kb (Bannon, Michelhaugh, Wang, & Sacchetti, 2001; Giros et al., 1992; Vandenbergh et al., 1992). One of the most widely studied polymorphisms in the DAT gene is a 40-base pair variable number of tandem repeats (VNTR) polymorphism (rs28363170) in the 3' untranslated region of the gene. The number of repeats of the VNTR ranges from 3 to 12 (Kang, Palmatier, & Kidd, 1999; Vandenbergh et al., 1992), but the most common alleles are the 9- (9R) and 10-repeat (10R) forms with substantial variability between ethnic groups (Kang et al., 1999). Typically, 9R-carriers (i.e., 9R-homozygotes and 9R/10R-heterozygotes) are compared to 10R-homozygotes to investigate potential differences between groups. The localisation of the rs28363170 VNTR in the untranslated region precludes a direct influence on DAT structure or function. Instead, DAT genotype may affect messenger ribonucleic acid (mRNA) localisation, transcript stability or regulation of protein synthesis (Bannon et al., 2001; Kang et al., 1999).

At the molecular level, meta-analyses of the association of DAT availability and the VNTR have shown that 9R-carriers have higher DAT availability than 10R-homozygotes (Costa, Riedel, Müller, Möller, & Ettinger, 2011; Faraone, Spencer, Madras, Zhang-James, & Biederman, 2014). The same pattern of results was also found in three subsequent studies at the descriptive level (Jakobson Mo et al., 2022; Kasparbauer et al., 2015; Wagner et al., 2014). These findings corroborate the emerging pattern from meta-analyses but also emphasise the importance of well-powered studies and meta-analyses to detect significant associations between genotype and phenotype.

On the behavioural level, however, despite extensive research, there is no consistent association between genotypes and cognitive functioning (Ettinger, Merten, & Kambeitz, 2016; Rincón-Pérez,

Sánchez-Carmona, Albert, & Hinojosa, 2018). Crucially, evidence is more consistent when looking at subjective experience and brain function in pharmacological studies. Here, 9R-carriers were found to react more strongly to pro-dopaminergic interventions (Brewer et al., 2015; Franklin et al., 2009; Franklin et al., 2011; Gelernter, Kranzler, Satel, & Rao, 1994; Kambeitz, Romanos, & Ettinger, 2014; Lott, Kim, Cook, & Wit, 2005; Millar et al., 2011). For example, Franklin et al. showed in two independent samples of smokers that 9R-carriers, compared to 10R-homozygotes, had stronger fMRI activations to videos containing smoking cues (vs. neutral cues) in ventral striatal, pallidal, and orbitofrontal regions (Franklin et al., 2009; Franklin et al., 2011). In another study, 9R-carriers displayed reduced P50-gating following nicotine administration, while no such effect was found for 10R-homozygotes (Millar et al., 2011). Concerning subjective experience, 9R cocaine users reacted more strongly to intravenously administered cocaine than 10R-homozygote users (Brewer et al., 2015). Furthermore, paranoia was found more often in cocaine users with 9R-alleles than with 10R-alleles (Gelernter et al., 1994). For *d*-amphetamine, however, the results are more heterogeneous. While 9R/10R-heterozygotes and 10R-homozygotes showed enhanced subjective experience following *d*-amphetamine administration, results for 9R-homozygotes did not differ from placebo (Lott et al., 2005). Response to methylphenidate treatment in ADHD is not consistently associated with DAT genotype, although the response was poorer in 10R-homozygotes than in other genotype groups in studies using naturalistic designs (Kambeitz et al., 2014). Overall, most studies point to higher responsivity to pro-dopaminergic challenges in 9R-carriers.

As outlined in 1.5.2, nicotine effects on SPEM are inconsistent across studies. Some of these discrepancies might be explained by variability between individuals at the genetic level. As nicotine interacts with the dopamine system and the DAT is an essential component of that system, here, focus is placed on variability in the *SLC6A3* gene coding for the DAT. Specifically, in **Study II** of the present dissertation, participants are grouped according to their *SLC6A3* VNTR genotype to investigate if 9R-carriers differ from 10R-homozygotes in how nicotine influences their SPEM performance.

1.6 SPEM and the schizophrenia spectrum

1.6.1 Schizophrenia

Schizophrenia is a psychiatric disorder characterised by disturbed thinking and perception, cognitive and motor impairments, avolition, apathy, abnormal affective expression, and communication difficulties (Tandon, Nasrallah, & Keshavan, 2009). Schizophrenia phenomenology is often described in terms of symptoms on different dimensions or categories. There is disagreement on

the specific number and quality of these dimensions (Peralta & Cuesta, 2001). The most simplistic approaches entail three dimensions (positive symptoms/reality distortion, negative symptoms/psychomotor poverty, and disorganisation; Liddle, 1987). Other approaches additionally include cognitive (e.g., impaired executive function) and affective (depression and mania) features (van Os & Kapur, 2009) or even more specific facets (e.g., Peralta & Cuesta, 2001). Critically, the clinical expression of schizophrenia is very heterogeneous, with some overlap with other psychiatric conditions (Tandon et al., 2009; van Os & Kapur, 2009). Schizophrenia is only one of several psychotic – or schizophrenia spectrum – disorders (American Psychiatric Association, 2000; Heckers et al., 2013). Critically, it is the most frequent one (Bogren, Mattisson, Isberg, & Nettelbladt, 2009; Chang et al., 2017; Perälä et al., 2007) and arguably the one that is studied the most, which is why studies involving patients with schizophrenia are emphasised here.

Lifetime prevalence of schizophrenia averages at approximately 0.4% across different studies and is about 2- to 3-fold higher for any psychotic disorder (Bogren et al., 2009; Chang et al., 2017; Perälä et al., 2007; Saha, Chant, Welham, & McGrath, 2005). Importantly, schizophrenia is considered one of the most severe psychiatric disorders associated with increased suicidality (Hawton, Sutton, Haw, Sinclair, & Deeks, 2005; Hor & Taylor, 2010; Siris, 2001) and mortality (Laursen, Nordentoft, & Mortensen, 2014; Saha, Chant, & McGrath, 2007), high rates of physiological and psychiatric comorbidity (esp. depression and substance abuse; Buckley, Miller, Lehrer, & Castle, 2009; Carney, Jones, & Woolson, 2006; T. J. R. Lambert, Velakoulis, & Pantelis, 2003; W. Li et al., 2020; Tsai & Rosenheck, 2013), and low quality of life (Huppert, Weiss, Lim, Pratt, & Smith, 2001; Reine, Lançon, Di Tucci, Sapin, & Auquier, 2003; Sim, Mahendran, Siris, Heckers, & Chong, 2004) compared to healthy individuals. In addition, it leads to substantial direct and indirect economic burdens (Chong et al., 2016; Knapp, Mangalore, & Simon, 2004).

At the level of brain structure, patients with schizophrenia show substantial reductions in total brain volume and grey matter (Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Glahn et al., 2008; Haijma et al., 2013; Steen, Mull, McClure, Hamer, & Lieberman, 2006). Similarly, BOLD activity is decreased across widespread brain networks in patients with schizophrenia compared to healthy controls in different tasks (Glahn et al., 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; S. F. Taylor et al., 2012; see 1.6.4 for SPEM). However, increased activity in some areas might point to compensatory mechanisms (Glahn et al., 2005; Minzenberg et al., 2009; S. F. Taylor et al., 2012).

In addition to these regional brain abnormalities, patients with schizophrenia also show abnormal brain connectivity, which has been found at the structural and functional levels (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). These findings led to the formulation of the influential dysconnection hypothesis of schizophrenia (Friston, Brown, Siemerkus, & Stephan, 2016; Friston & Frith, 1995; Stephan, Friston, & Frith, 2009), which states that "the core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, leading to abnormal functional integration of

neural systems, ie, dysconnectivity" (Stephan et al., 2009, p. 510). Importantly, dysconnectivity in this context does not necessarily refer to decreased connectivity but describes abnormal connectivity per se (Pettersson-Yeo et al., 2011; Stephan et al., 2009).

To date, the aetiology of schizophrenia is insufficiently understood (Tandon, Keshavan, & Nasrallah, 2008). Although it has been shown that schizophrenia is highly heritable (>80% heritability; Sullivan, Kendler, & Neale, 2003) and modern approaches to genetic research with genome-wide association studies have identified more than a hundred candidate genes that are associated with vulnerability to schizophrenia (Pardiñas et al., 2018; Ripke et al., 2014), it has also become clear that it is not a single or a few genes that cause the development of the disorder, but that its origin is complex and multifactorial. In addition to genetic factors, environmental factors and gene-environment interactions contribute significantly to schizophrenia aetiology (Fusar-Poli et al., 2017; Radua et al., 2018; Tandon et al., 2008).

Importantly, schizophrenia cannot be regarded as a diagnostic category that has clear boundaries with other conditions and that falls into a dichotomy of disease and health. Instead, it is often viewed as the extreme pole of a continuum covering a range of psychosis-like phenomena with normal experience at the other end of the spectrum (Allardyce, Suppes, & van Os, 2007; DeRosse & Karlsgodt, 2015; Haslam, McGrath, Viechtbauer, & Kuppens, 2020; Stefanis et al., 2002; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). This view implies that subclinical manifestations of psychosis can also be observed in the general population and that there is a gradual unfolding from psychotic experiences over psychotic symptoms to psychotic disorders with increasing levels of severity (Figure 7; van Os et al., 2009).[3]

[3] In what follows, I will refer to this continuum as the schizophrenia spectrum.

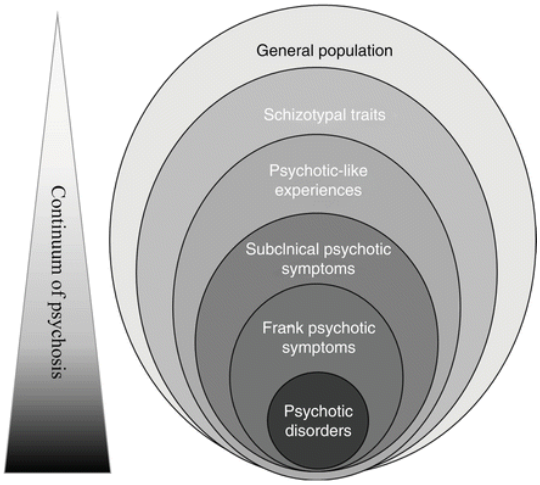

Figure 7: Schematic depiction of the schizophrenia (or psychosis) spectrum.

Note. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Encyclopedia of Adolescence*, "Psychotic-like experiences", Fonseca-Pedrero, E., Lemos-Giráldez, S., Paino, M., Sierra-Baigrie, S., & Muñiz, J., Copyright (2011).

1.6.2 Schizotypy

An influential approach to quantifying variance along the schizophrenia spectrum is schizotypy, a multidimensional personality trait that is stable over time and reflects a general tendency towards psychosis-like experiences (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014; Kwapil & Barrantes-Vidal, 2015).

There are two distinct theoretical conceptualisations of schizotypy: a fully- and a quasi-dimensional approach (Nelson, Seal, Pantelis, & Phillips, 2013). The quasi-dimensional approach proposed by Meehl sees schizotypy as a manifestation of schizotaxia, which is defined as a "genetically determined integrative defect, predisposing to schizophrenia" (Meehl, 1990, p. 35). This approach maintains a certain degree of binarity as only a distinct subgroup of the population is considered genetically vulnerable, i.e., at risk of developing psychosis, while the larger part of the population is not (Lenzenweger, 2006; Meehl, 1990; Nelson et al., 2013). The fully-dimensional approach, on the other hand, is based on the work of Claridge (e.g., Claridge, 1997) and focuses on interindividual differences from a psychological point of view. In this framework, schizotypy is understood as a normally-distributed trait that is present and measurably to a varying degree across the entire population (Kwapil & Barrantes-Vidal, 2015; Nelson et al., 2013). As such, schizotypy spans a broad spectrum from the lowest level of normal psychological experience and health, through schizotypal personality disorder, to the extreme of manifest psychosis or schizophrenia (Figure 7; Claridge, 1997).

There is evidence for both perspectives on schizotypy, but the fully-dimensional approach has recently found better support in the literature (Nelson et al., 2013).

Resembling the factor structure in schizophrenia (Lenzenweger & Dworkin, 1996; Liddle, 1987), three dimensions can be distinguished in schizotypy, namely the cognitive-perceptual (or positive), interpersonal (or negative), and disorganised dimensions (Bentall, Claridge, & Slade, 1989; Fonseca-Pedrero, Paino, Lemos-Giráldez, Sierra-Baigrie, & Muñiz, 2011; Raine et al., 1994; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000; Wuthrich & Bates, 2006).

1.6.3 SPEM deficits in schizophrenia and schizotypy

Over the past years, several potential biomarkers of schizophrenia have been identified and investigated, with SPEM emerging as one of the most promising candidates (Allen, Griss, Folley, Hawkins, & Pearlson, 2009; Braff, Freedman, Schork, & Gottesman, 2007; Calkins et al., 2008; Calkins, Iacono, & Curtis, 2003; Lencer et al., 2015). The term biomarker refers to "objectively measured biological antecedents or consequences of normal or pathogenic processes or a physiologic response to a therapeutic intervention" (Lenzenweger, 2013, p. 1347). Biomarkers are useful in clinical settings as they promise improvement in diagnosis, prognosis, and prediction of treatment response (Singh & Rose, 2009; Weickert, Weickert, Pillai, & Buckley, 2013).

The study of SPEM deficits in schizophrenia has a long history, with the first evidence dating back to the seminal studies of Diefendorf and Dodge in the early 20th century (Diefendorf & Dodge, 1908). Almost 70 years later, Holzman and colleagues independently rediscovered these results (Holzman, Proctor, & Hughes, 1973), prompting a remarkably rich body of research with more than 80 replications of SPEM deficits in schizophrenia until the publication of a comprehensive literature review in 2010 (Levy et al., 2010) and more replications until now (e.g., Lencer et al., 2015; Sami et al., 2021; Shiino et al., 2020).

A meta-analysis integrating data from more than 2000 patients and 1900 controls based on the SPEM literature from 1994 to 2008 (O'Driscoll & Callahan, 2008) points to large effect sizes of all global SPEM measures, such as RMSE, qualitative ratings, signal to noise ratio, and total saccade rate. Effect sizes of similar magnitude were also found for some specific measures, including maintenance gain and leading saccade rate. Other specific measures of SPEM performance, such as open-loop gain, catch-up saccade rate, and SPEM latency, yielded smaller but still significant effect sizes in the medium to small range. In contrast, rates of back-up saccades and square wave jerks were not significantly different between patients and controls. Exemplary data on SPEM performance in a patient with schizophrenia and a healthy control individual is in Figure 8.

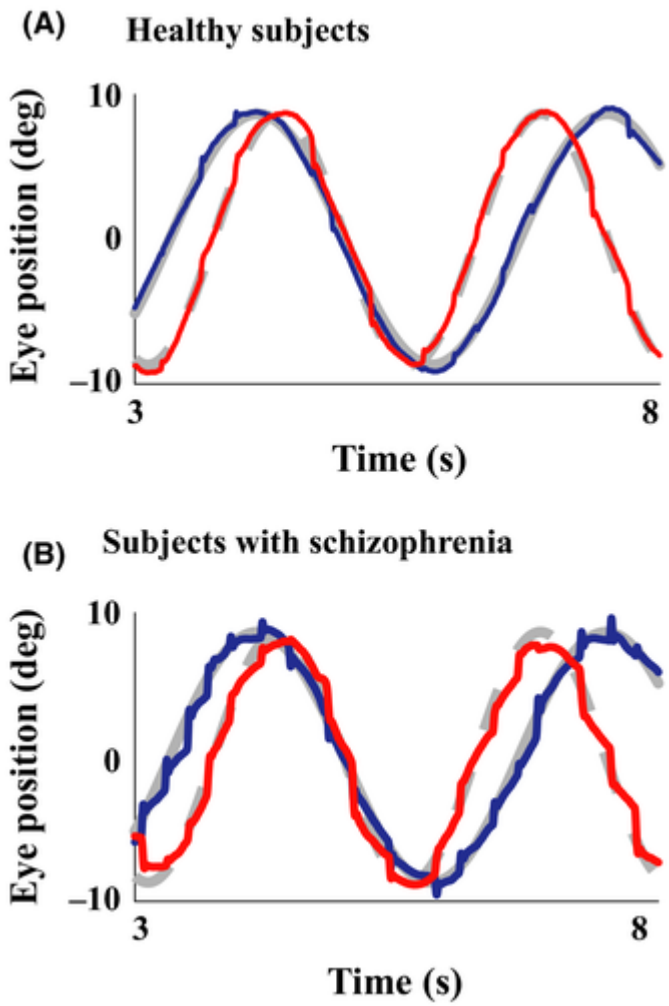

Figure 8: Exemplary SPEM performance in a healthy individual and a patient with schizophrenia.

Note. Target and eye position for the horizontal (eye position in blue, target position in grey [solid line]) and vertical (eye position in red, target position in grey [dashed line]) directions. The upper panel (A) shows data of a healthy individual. The lower panel (B) shows data of a patient with schizophrenia.

Reprinted from "Eye movement characteristics in schizophrenia: A recent update with clinical implications" by Morita, K., Miura, K., Kasai, K., & Hashimoto, R., 2020, *Neuropsychopharmacology Reports, 40*(1), p. 3. Licensed under CC BY 4.0.

Analyses of potential moderators of these effects showed that results were largely unaffected by task (such as target velocity or velocity pattern) and patient characteristics (including duration of illness, symptom ratings, and number of patients receiving atypical medication).

The effect sizes obtained in this meta-analysis are among the largest reported for any neurocognitive measure for direct comparisons of patients with schizophrenia and controls (Heinrichs, 2004; O'Driscoll & Callahan, 2008), highlighting the particular importance of this biomarker for schizophrenia research.

SPEM deficits show high temporal stability (Benson et al., 2012; Calkins et al., 2003; Gooding, Iacono, & Beiser, 1994) and can be found across patient groups in different stages of the disease, including in patients with first-episode, residual, and chronic schizophrenia (Arolt, Teichert, Steege, Lencer, & Heide, 1998; Campion et al., 1992; Hutton et al., 1998; Hutton et al., 2001; Katsanis & Iacono, 1991; Lencer et al., 2010; Sweeney, Haas, & Li, 1992; Thaker, Ross, Buchanan, Adami, & Medoff, 1999). Considering that deficits are also found in drug-naïve and unmedicated patients (Campion et al., 1992; Hutton et al., 1998; Hutton et al., 2001; Lencer et al., 2008; Thaker et al., 1999) and that medication was not a significant moderator of effect size when sex-matching was controlled for in the meta-analysis (O'Driscoll & Callahan, 2008), it is unlikely that differences between patients and controls are due to antipsychotic medication. Instead, they represent a highly robust time-stable trait directly associated with the underlying disorder (Levy et al., 2010).

Poorer SPEM performance has also been observed in patients with schizoaffective, delusional, and bipolar disorders (Campana, Gambini, & Scarone, 1998; Lencer et al., 2010; Lencer et al., 2015; Yee et al., 1987), individuals at high risk of psychosis (van Tricht et al., 2010), and relatives of patients with schizophrenia (Calkins et al., 2003; Calkins et al., 2008; Lencer et al., 2015). The findings of impaired SPEM performance in relatives are particularly relevant as they led to the consideration of SPEM deficits as potential endophenotypes of schizophrenia (Allen et al., 2009; Calkins et al., 2003; Calkins et al., 2008; Lencer et al., 2015). Endophenotypes are measurable and heritable state-independent traits associated with a certain illness in the population that show co-segregation with the illness within families and can be found in unaffected family members to a greater extent than in the general population (Glahn et al., 2014; Gottesman & Gould, 2003). The definition of endophenotypes thus goes beyond that of biomarkers by including a genetic dimension (Glahn et al., 2014; Gottesman & Gould, 2003; Lenzenweger, 2013). Intriguingly, deficits in SPEM performance can also be found in persons scoring high on schizotypy (Gooding, Miller, & Kwapil, 2000; Holahan & O'Driscoll, 2005; Kendler et al., 1991; Koychev et al., 2016; Meyhöfer et al., 2017; O'Driscoll, Lenzenweger, & Holzman, 1998; Smyrnis et al., 2007), supporting the dimensional quality of the schizophrenia spectrum (Smyrnis, Amado, Krebs, & Sweeney, 2019).

Although multiple approaches to explaining SPEM deficits along the schizophrenia spectrum have been developed and investigated, these remain poorly understood. There is evidence that impaired motion processing (Chen, 2003; Chen, Levy, et al., 1999; Chen, Nakayama, Levy, Matthysse, & Holzman, 1999), faulty sensorimotor transformation (Lencer et al., 2010; Trillenberg et al., 2017), defective extraretinal (e.g., predictive or efference copy) processes (Hong et al., 2008; Hooker & Park, 2000; Spering, Dias, Sanchez, Schütz, & Javitt, 2013; Thaker et al., 1999; Thakkar, Diwadkar, & Rolfs, 2017), or a combination of these factors underlie SPEM deficits in schizophrenia (Levy et al., 2010). For

schizotypy, however, there is no conclusive evidence to explain SPEM dysfunction (Faiola, Meyhöfer, & Ettinger, 2020).

The multiplicity of possible mechanisms and the sometimes heterogeneous findings demonstrate – along with the finding that global measures are generally more impaired than specific measures (O'Driscoll & Callahan, 2008) – that SPEM deficits along the schizophrenia spectrum are complex and multifactorial and that more research is needed to understand them better. One possible approach to address this heterogeneity is to additionally consult neural data, as detailed in the following section.

1.6.4 BOLD correlates of SPEM deficits along the schizophrenia spectrum

Abnormalities of BOLD response during SPEM have been observed in almost all components of the SPEM network in patients with schizophrenia compared to healthy controls (Hong et al., 2005; Keedy, Ebens, Keshavan, & Sweeney, 2006; Lencer et al., 2011; Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005; Nagel et al., 2007; Nagel et al., 2012; Tregellas et al., 2004). However, there are substantial differences between studies.

For example, in one study, decreased BOLD response in patients compared to healthy controls was obtained across almost the entire SPEM network (Keedy et al., 2006), suggesting a global oculomotor – but not cortical or general motor – deficit underlying abnormal SPEM in patients. Other results, however, point to more nuanced differences. Specifically, some authors suggest a deficit in visual motion processing based on reduced activations in area V5 and its immediate projection sites (Lencer et al., 2005; Lencer et al., 2011; Nagel et al., 2012). They further argue that this deficit is partially compensated for by extraretinal mechanisms as indicated by increased BOLD response in patients in areas such as cerebellum, DLPFC, anterior cingulate gyrus, and FEF (Lencer et al., 2011; Nagel et al., 2007; Nagel et al., 2012).

An alternative line of arguments hints at deficits in areas related to extraretinal processing based on findings of reduced activity in FEF and SEF, medial superior temporal cortex, and anterior cingulate gyrus but increased BOLD response in areas associated with the processing of retinal information in middle temporal cortex in patients vs. controls (Hong et al., 2005). Lastly, it has been proposed that hippocampal hyperactivity related to dysfunctional inhibitory interneurons in the hippocampus may underlie SPEM deficits in schizophrenia (Tregellas et al., 2004; Tregellas et al., 2005; Tregellas et al., 2010).

Paralleling the results in schizophrenia, reduced BOLD activity in occipital regions has been observed during SPEM in individuals scoring high on schizotypy (Meyhöfer et al., 2015). These results suggest that impaired motion processing or attentional dysfunction may be at the root of SPEM deficits

in schizotypy, again pointing to an overlap between schizophrenia and schizotypy at the neural and behavioural levels (Lencer et al., 2011; Meyhöfer et al., 2015).

In summary, the findings on neural mechanisms of SPEM deficits are heterogeneous, similar to the findings on cognitive mechanisms, with evidence for deficits in motion or extraretinal processing, so that no clear picture emerges as to what causes SPEM deficits in individuals with schizophrenia and high schizotypy. Partly, this inconsistency is due to the fact that many of the studies presented were ill-powered or operationalised and measured SPEM differently, strongly calling for more well-conducted research in this area. Apart from the need to increase sample sizes and correct BOLD data appropriately for multiple testing, studying the brain from an integrative perspective can also help to gain a better understanding of SPEM deficits. In this context, particular attention should be paid to (dys)connectivity approaches which represent a time-honoured perspective on explaining schizophrenia pathophysiology (Friston et al., 2016; Friston & Frith, 1995; Pettersson-Yeo et al., 2011; Stephan et al., 2009; see also 1.6.1). Only two studies have focused on studying functional dysconnectivity during eye movements in schizophrenia (Krishna, O'Neill, Sanchez-Morla, & Thaker, 2014; Tu et al., 2010), despite the highly robust finding of eye-tracking dysfunction in schizophrenia (see 1.6.3). By combining eye-tracking and electroencephalography (EEG), impaired connectivity between frontal and posterior cortical regions was observed during SPEM in patients with schizophrenia compared to controls (Krishna et al., 2014). In addition, evidence for aberrant functional connectivity of the CEF in patients with schizophrenia was obtained with fMRI data during saccades (Tu et al., 2010). While these findings are essential first steps towards understanding abnormal oculomotor control in schizophrenia, the scarcity of studies also points to a significant gap in the literature. Critically, task-based BOLD functional connectivity during SPEM has not yet been investigated in schizophrenia or schizotypy. Additionally, no direct comparison of BOLD response during SPEM between patients with schizophrenia and individuals with different levels of schizotypy is available. These open questions are addressed in **Study V** of this dissertation.

1.7 Aims of this dissertation

The overall aim of this dissertation is to expand our understanding of the mechanisms underlying SPEM. To accomplish this, I will adopt a framework proposed by Siebner et al. (2009) that illustrates the different levels of analysis linking genome to phenome (Figure 9) and how they are connected. This dissertation integrates data from multiple levels of measurement to provide a broad and comprehensive view of the SPEM system. These levels encompass clinical syndromes and symptoms, behavioural traits, neural systems, more specifically both macroscopic and cellular pathways, and the genome. I address different sets of open questions in the SPEM literature in five studies. In each study, data on SPEM performance located at the behavioural level are analysed and complemented as appropriate with data from one or multiple additional levels.

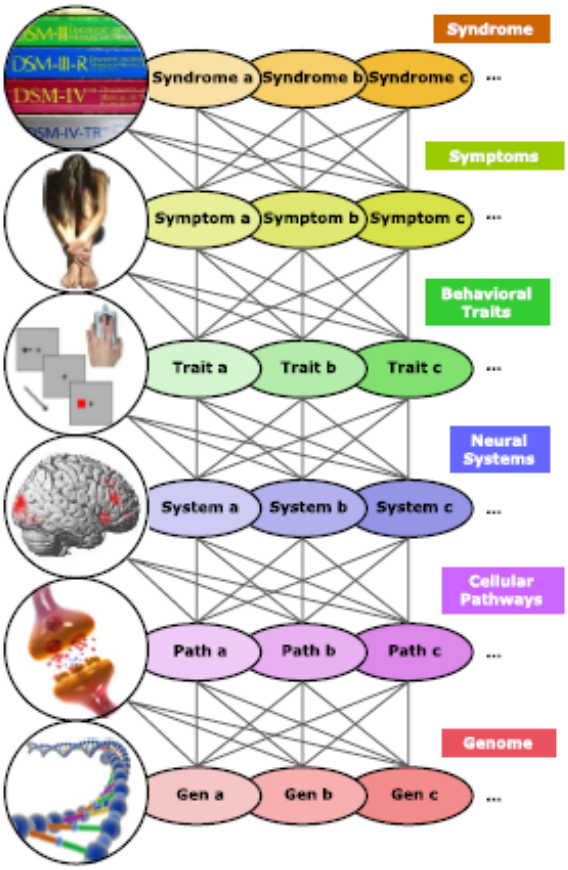

Figure 9: Schematic depiction of the neurobiological levels tapped in this dissertation.

Note. Reprinted from *Neuroscience*, *164(*1), Siebner, H. R., Callicott, J. H., Sommer, T., & Mattay, V. S., "From the genome to the phenome and back: linking genes with human brain function and structure using genetically informed neuroimaging using genetically informed neuroimaging", 1–6, Copyright (2009), with permission from Elsevier.

In the first study (**Study I**), the replicability and reliability of background and target velocity effects, two highly robust findings in the SPEM literature, are probed to provide an important methodological foundation for all subsequent studies.

The second study (**Study II**) integrates data from the lowest levels of analysis, namely those of cellular pathways and their genetic basis. Specifically, in this study, the heterogeneity in SPEM response to nicotine, a substance known for its pro-dopaminergic effects, is addressed with a pharmacogenetic study design that aims to advance our comprehension of how the dopaminergic and cholinergic systems are associated with SPEM.

Studies III, **IV**, and **V** additionally draw on data from neural systems, specifically BOLD fMRI data collected during the execution of SPEM. Critically, **Study III** helps to close an important gap in the SPEM literature, namely the question of how different brain areas work together temporally to accomplish SPEM in healthy participants, and it thus incorporates functional connectivity analyses.

The fourth study (**Study IV**) also adopts an fMRI approach, yet with a more refined experimental design. In particular, SPEM performance is investigated both at different target velocities and in the presence and absence of a structured background. The neural mechanisms underlying the behavioural response to these stimuli are explored using methodological approaches to address local brain activations and functional connectivity reflecting the velocity and background effects.

Finally, the fifth study (**Study V**) includes data from the highest and arguable most complex levels of the model tapping clinical symptoms and syndromes. Specifically, this study explores the neural mechanisms underlying SPEM deficits along the schizophrenia spectrum by directly comparing healthy controls with individuals scoring high on schizotypy and patients with schizophrenia spectrum disorders. Again, both functional segregation and integration methods, and additionally complex machine learning algorithms, are used to investigate differences in patients and controls and to examine similarities and dissimilarities of schizotypy with the two extremes of the spectrum.

2 Methodology

2.1 Assessment of SPEM

Several different methods can be employed to assess eye movements, ranging from subjective evaluation by experts (bedside assessment) via electrooculography (EOG), scleral contact lenses or search coil techniques, infrared-limbus tracking, dual-Purkinje tracking, to video-based combined pupil and corneal reflection techniques (VCPCR; Duchowski, 2017; Holmqvist et al., 2011; Holmqvist et al., 2022; Hutton, 2019). Each of these methods comes with advantages and disadvantages.

The most highly used approach today is VCPCR (Holmqvist et al., 2022; Hutton, 2019) which offers low invasiveness, high temporal, and high spatial resolution (although somewhat lower than with search coil or dual-Purkinje techniques). In VCPCR, infrared light is shone at the eye, and a video camera is used for data collection (Holmqvist et al., 2011). Eye position is obtained by identifying the centres of corneal reflection (first Purkinje image) and pupil and calculating their position relative to each other (Holmqvist et al., 2011; Hutton, 2019). Complex computer algorithms perform this calculation following a three-step procedure from image acquisition via image analysis to gaze estimation (Holmqvist et al., 2011; Hutton, 2019). To compute the point of regard (or gaze), the system exploits the fact that the relative position of corneal reflection and pupil changes when the eyes move. The pupil moves as the eye moves, whereas the corneal reflection remains relatively stable with the infrared light source at a fixed location (Duchowski, 2017). Typically, point of regard is determined in the pixel coordinate system of the target display (Holmqvist et al., 2022). Before data collection, calibration and validation procedures are performed. These are crucial steps to guarantee the spatial accuracy of the collected data as they establish a mapping function linking eye position to predefined locations on the screen (Hutton, 2019). Critically, specific VCPCR eye-trackers can also be used in magnetic resonance imaging (MRI) scanners with the help of mirror techniques to allow concurrent assessment of eye movements and BOLD images.

The quality of SPEM performance can be assessed with a variety of different parameters. Velocity gain is usually considered the key and primary outcome of the SPEM system (Smyrnis, 2008). It is defined as the ratio of eye to target velocity and thus provides a direct measure of the success of the SPEM system in aligning the eye with the slowly moving target. SPEM typically occurs in combination with saccades (Goettker & Gegenfurtner, 2021; Orban de Xivry & Lefèvre, 2007), which is why the number of saccades, as well as their timing, direction, velocity, and amplitude provide important additional information on SPEM performance. Saccades are detected using velocity (e.g., > 30 °/s), amplitude (e.g., > 1 °) and acceleration (e.g., > 3800 °/s^2) criteria. Saccades during SPEM can be further classified into different categories for more detailed analysis (Smyrnis, 2008), although the total

number of saccades is already a well-established, valid and useful performance outcome measure (O'Driscoll & Callahan, 2008; Smyrnis, 2008). A valuable element of differentiation relates to the interaction of saccades with the SPEM system: specifically, saccades can be regarded as either intrusive (i.e., disrupt SPEM) or compensatory (i.e., relocate the eyes on the target after a phase of low SPEM gain; Orban de Xivry & Lefèvre, 2007; Smyrnis, 2008). While researchers largely agree on this basic distinction, there is less consensus on the specific criteria used to further define the different types of SPEM-related saccades (Smyrnis, 2008). The most frequent type of compensatory saccades is catch-up saccades, which occur in the same direction as the moving target and reduce eye position error when the eye lags behind the target (Smyrnis, 2008). Back-up saccades occur in the opposite direction of the moving target, reducing eye position error when the eye is ahead of the target (Levy et al., 2000). Intrusive saccades comprise anticipatory and leading saccades as well as square wave jerks (Levy et al., 2000; Ross, Olincy, Zerbe, & Radant, 2001; Smyrnis, 2008). Depending on the research question, sample, and task setup, all or only some types of saccades are analysed.

RMSE is a global measure that describes the spatial deviation between eye and target (O'Driscoll & Callahan, 2008; Smyrnis, 2008). Segments of SPEM and saccades are included in the calculation of RMSE, and blinks are excluded. The angular distance between eye and target position is calculated for each time point. The resulting values are then squared, added across time points and divided by the number of time points. Finally, the square root of this mean value is calculated to obtain the RMSE measure.

Specific task setups such as target blanking or step-ramp paradigms allow the measurement of additional SPEM outcomes (Barnes, 2008; O'Driscoll & Callahan, 2008; Smyrnis, 2008) that go beyond the scope of this dissertation. **Studies I–V** each report at least one of the following outcomes to quantify SPEM performance: SPEM gain, RMSE, catch-up, and total saccade rate.

These SPEM performance outcomes have been studied regarding their reliability in the past. Importantly, interpreting reliability indices is not straightforward, as different interpretation guidelines exist (Hedge, Powell, & Sumner, 2018). In this dissertation, the guidelines proposed by Cicchetti (1994) are adopted, which indicate poor reliability for scores less than 0.40, fair reliability for scores between 0.40 and 0.59, good reliability for scores between 0.60 and 0.74, and excellent reliability for scores between 0.75 and 1.00. Following these guidelines, studies investigating the reliability of different SPEM performance outcomes point to largely good test-retest and internal consistency reliability scores of SPEM gain, RMSE, and catch-up saccade rate (Bargary et al., 2017; Calkins et al., 2003; Ettinger, Kumari, Crawford, et al., 2003; Roy-Byrne, Radant, Wingerson, & Cowley, 1995; Versino et al., 1993). **Study I** seeks to complement these earlier results by reporting test-retest and split-half reliability for the SPEM task effects, e.g., the difference measures between conditions with and without a structured background and between conditions with higher and lower target velocity.

2.2 Psychopharmacology

Psychopharmacology studies the interaction of drugs, the nervous system, experience, and behaviour. More precisely, drugs or other chemical compounds are used "to understand neural function, to prevent and treat mental illness and drug abuse, and to understand how nontherapeutic psychoactive drugs and natural substances alter human mood, memory, motor activity, endocrine, and other centrally mediated functions" (Stolerman & Price, 2015b, p. 1389). Psychopharmacology thus incorporates two directions: pharmacodynamics which entails the "processes through which drugs bring about their actions on living organisms" (Stolerman & Price, 2015a, p. 1275) and pharmacokinetics, which relates to "what the body does to a drug and hence concerns itself with the quantitation of drug absorption, distribution, metabolism, and excretion" (Wolff, 2015, p. 1280).

When designing psychopharmacological studies, it is recommended to follow what constitutes the gold standard of pharmacological research comprising (double-)blinding, placebo control, and randomisation (Karpouzian, Petrovsky, Ettinger, & Reilly, 2019). Substances can be administered within or between participants. Within-subjects designs have higher statistical power as variance due to individual differences can be better controlled. Between-subjects designs, on the other hand, are better suited to control for potential order or practice effects but require a larger sample size (Karpouzian et al., 2019).

Other important aspects to consider in psychopharmacological studies are how, when, and in which doses substances are administered. For example, with nicotine, administration mode (e.g., cigarette, nasal spray, patch, lozenge, chewing gum) affects the magnitude and timing of maximum blood concentration and half-life (Hansson, Rasmussen, & Kraiczi, 2017; Shiffman, Fant, Buchhalter, Gitchell, & Henningfield, 2005). With nicotine gum administration, nicotine reaches maximum blood concentration after approximately 15–90 minutes (median 30 minutes; Nyberg et al., 1982). Dosage should be chosen depending on the specific sample and task. For example, the same nicotine dose might affect smokers and non-smokers differently (Kalman & Smith, 2005; Logemann, Böcker, Deschamps, Kemner, & Kenemans, 2014). While nicotine blood concentration parametrically increases with increasing dose (Hansson et al., 2017; Kraiczi, Hansson, & Perfekt, 2011), nicotine can affect behavioural reactions in a linear (Myers, Taylor, Moolchan, & Heishman, 2008) or non-linear way (Almeida et al., 2020).

2.2.1 Pharmacogenetics with candidate genes

„Pharmacogenetics (PGx) deals with genetically determined variation in how individuals respond to drugs" (U. A. Meyer, 2004, p. 669). Research in this area is considered paramount as it offers

hope for developing personalised medicine, which could dramatically improve treatment response (U. A. Meyer, 2004). In addition, pharmacogenetic studies can help to explain heterogeneity in response to pharmacological compounds and thus provide insights into the mechanisms underlying interindividual differences at the behavioural level (Bogdan et al., 2012).

There are two distinct approaches to studying the genetic basis of complex traits such as drug response. The candidate gene approach aims to identify correlations between specific genetic variants and specific phenotypes such as a disease, human mental operation, or neural process based on prior knowledge (Frank & Fossella, 2011; Tabor, Risch, & Myers, 2002). In contrast, genome-wide association studies use mass-univariate testing to assess genetic associations between a large number of independent genetic variants and a specific phenotype without prior hypotheses (Montag, Ebstein, Jawinski, & Markett, 2020). Both approaches have advantages and disadvantages (Frank & Fossella, 2011). Candidate gene approaches are particularly promising when genes with a strong biochemical functionality are studied, e.g., genes coding for neurotransmitter receptors (Bogdan et al., 2012; Frank & Fossella, 2011).

In **Study II**, a VNTR polymorphism in the *SLC6A3* gene coding for the DAT is investigated (see 1.5.3). More specifically, the two most common allele groups (10R-homozygotes and 9R-carriers) are compared concerning how their SPEM performance is affected by nicotine, a drug with downstream effects on the dopaminergic system (see 1.5.1). The participants (non-smokers) are given 2 mg nicotine gum or placebo in a randomised, double-blind, between-subjects study design.

2.3 Functional magnetic resonance imaging

MRI is a powerful and widely-used non-invasive brain imaging technique to indirectly measure properties of the brain, including structure, blood flow, and neural activity (Logothetis & Wandell, 2004). The MR signal is obtained in a strong static magnetic field in which hydrogen nuclei align in parallel or antiparallel (Huettel, Song, & McCarthy, 2014; Logothetis & Wandell, 2004). Radiofrequency coils produce brief electromagnetic fields (excitation pulses) and receive information about the realignment (i.e., relaxation) of hydrogen nuclei in the static field in the longitudinal and transverse dimensions (Huettel et al., 2014; Logothetis & Wandell, 2004). Additional gradient fields are used for localising MR signals in three-dimensional space, and shimming coils assure the homogeneity of the magnetic fields. Crucially, relaxation times of hydrogen nuclei differ depending on tissue types and thus help to generate contrast images of the brain (Huettel et al., 2014). Relaxation times are characterised by time constants, e.g., T1 for longitudinal relaxation, T2 and T2* for transversal relaxation. T2*-weighted images additionally factor in inhomogeneities in the static magnetic field. To generate images sensitive to one form of contrast or another, the interval between successive excitation

pulses (repetition time; TR) and the interval between excitation pulses and data collection (echo time; TE) are varied (Huettel et al., 2014).

Studies III–V use fMRI which relies on BOLD contrasts and is based on the fact that the magnetic properties of haemoglobin molecules change depending on whether oxygen is bound to them or not (Ogawa & Lee, 1990; Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990). Critically, oxygen consumption increases when an area in the brain is activated, resulting in an increased flow of oxygen-rich blood to that region. A positive BOLD signal is elicited by a subsequent increase in the proportion of oxygenated blood compared to deoxygenated blood in the vicinity of the activated area of the brain. BOLD contrasts thus reflect the difference in signal on T2*-weighted images as a function of the amount of deoxygenated haemoglobin (Huettel et al., 2014).

The so-called haemodynamic response to a brief stimulus, i.e., the change in MR signal triggered by neuronal activity, is characterised by distinct phases (Figure 10; Huettel et al., 2014). After an initial dip (1–2 seconds), the BOLD signal increases above baseline and reaches its peak after about 4–6 seconds. The BOLD signal then decreases below baseline (undershoot; Logothetis & Wandell, 2004). When stimuli are presented in rapid sequence or continuously over a more extended period of time, the haemodynamic response reaches a plateau slightly below its peak value (Huettel et al., 2014).

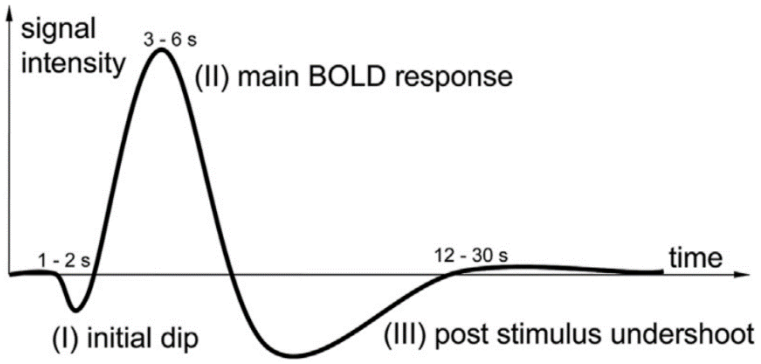

Figure 10: Depiction of a typical BOLD haemodynamic response function.

Note. Reprinted from *PET Clinics*, *8*(3), Siero, J. C. W., Bhogal, A., & Jansma, J. M., "Blood Oxygenation Level-dependent/Functional Magnetic Resonance Imaging: Underpinnings, Practice, and Perspectives", 329–344, Copyright (2013), with permission from Elsevier.

Despite disadvantages such as the indirectness of measuring neuronal activity and relatively low temporal resolution, MRI has many advantages that make it one of the most widely used neuroimaging techniques today. Notably, MRI is widely available, non-invasive, has relatively high spatiotemporal resolution, and can be used to delineate the entire network of brain areas involved in a specific task (Logothetis, 2008).

2.3.1 Pre-processing

MR images are pre-processed to reduce the variance of systematic non-task-related sources and thus increase power, and to prepare data for subsequent statistical analyses (Ashby, 2019; Huettel et al., 2014). The crucial steps employed in all papers presented in this thesis are briefly introduced here (Figure 11). First, data are realigned to correct for head motion, using a least square approach and six-parameter rigid-body transformation. Next, anatomical and functional images are aligned by co-registration. This step is crucial to improve the spatial localisation of the low-resolution functional data. Then, images are normalised with affine linear transformation to map the individual images to standard brain space (e.g., Montreal Neurological Institute [MNI]) and thus increase comparability between studies and facilitate anatomical interpretation. Lastly, smoothing with a Gaussian filter is applied to reduce non-systematic spatial noise (Ashby, 2019; Huettel et al., 2014).

2.3.2 Data analysis

Statistical analysis of BOLD fMRI data (Figure 11) is typically based on a voxel-wise mass-univariate general linear model (GLM) approach (Friston et al., 1994; Friston et al., 1995; Worsley & Friston, 1995). Briefly summarised, time courses of specific events (e.g., the task) are convolved with the haemodynamic response function (HRF) and modelled as regressors along with a constant to predict signal intensity in a given voxel. A high-pass filter is applied to account for slow signal drifts. At the individual level (first level), contrasts are formed to compare specific task conditions with each other or with baseline (Friston et al., 1994; Friston et al., 1995; Worsley & Friston, 1995). The resulting contrast maps are then taken to the second level for group-level analyses, where data have to be appropriately corrected for multiple comparisons.

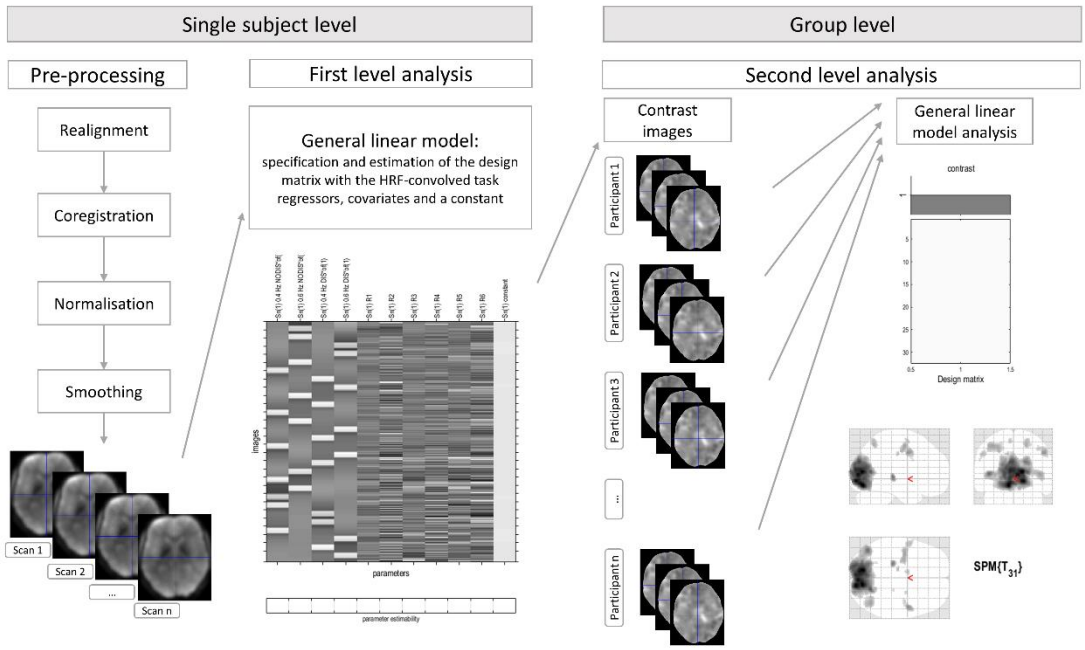

Figure 11: Schematic depiction of the fMRI data analysis flow.

Note. After data acquisition and reconstruction, fMRI scans are pre-processed. The pre-processed scans are then fed into a first level analysis where contrast images for each participant are generated. These contrast images are then taken to the second level to analyse effects across groups. HRF = haemodynamic response function.

2.3.3 Generalised psychophysiological interaction analyses

The investigation of the interplay of distributed components of large-scale brain networks has become increasingly important in recent years and has complemented the previously dominant approach of studying functional segregation or specialisation to understand brain function (Friston, 2011; Rogers, Morgan, Newton, & Gore, 2007). As the number of available analytical approaches to study brain integration (as opposed to segregation) increased, so did the number of publications in this area (Friston, 2011; K. Li, Guo, Nie, Li, & Liu, 2009; Rogers et al., 2007). Methods for analysing functional integration can be grouped based on different criteria. An important distinction is between functional and effective connectivity. The former reflects "statistical dependencies among remote neurophysiological events", whereas the latter "refers to the influence that one neural system exerts over another, either at a synaptic or population level" and thus integrates the notion of causal influence (Friston, 2011, p. 14). Another – albeit related – distinction concerns data-driven vs. model-based approaches (K. Li et al., 2009; Rogers et al., 2007). And lastly, connectivity analysis methods can be divided into task-based and resting-state approaches (K. Li et al., 2009).

In this thesis, I was interested in the functional network underlying the execution of SPEM and therefore I focus on task-based connectivity analyses here, in particular the psychophysiological interaction (PPI) analysis approach adopted in Studies **III–V.**

PPI analyses[4] were initially introduced by Friston et al. (1997) as seed-based connectivity analyses following a GLM approach. The underlying principle of PPI can already be inferred from its name. It is based on the statistical interaction of a psychological ("psycho") and a physiological variable ("-physiological"), where the psychological variable corresponds to a specific task (or context), while the physiological variable refers to the neural activity in a specific brain region. The results of PPI analyses can be interpreted from two perspectives: (1) they allow us to understand how the contribution of one brain area to another changes with the psychological context (e.g., the task), and (2) they help to elucidate how the response of specific brain regions to the psychological context depends on the activity in the influencing region (Friston et al., 1997; Rogers et al., 2007). Generally, PPI analyses adopt a whole-brain approach to identify those voxels in the brain that show significant association with the interaction term. Critically, they require the a priori definition of seed regions derived from anatomical or functional hypotheses or task activation peaks in the conventional BOLD analysis (O'Reilly et al., 2012).

After their introduction, PPI analyses were significantly improved by addressing two potential pitfalls. First, as these interactions occur at the neural level and not at the haemodynamic level, Gitelman et al. (2003) introduced a deconvolution step of the seed region to ensure that the task and seed voxel time course and their interaction are captured at the same level of measurement. Second, the traditional PPI approach allowed the investigation of only two task conditions, which prevented more complex study designs from being investigated using these methods. This limitation was overcome with the introduction of the generalised PPI (gPPI) by McLaren et al. (2012), which proved to be compelling tools, especially in tasks with block designs (Cisler, Bush, & Steele, 2014; McLaren et al., 2012). In this new approach, it is now possible to implement a hypothetically unlimited number of task conditions and concurrently increase sensitivity and specificity compared to the original version.

[4] PPI might be regarded as models of effective connectivity as they not merely rely on statistical covariation but define a clear linear model to explain the activity in a given voxel. As these models are very simple, the direction of influence is uncertain, and alternative explanations such as common input or indirect effects cannot be ruled out, it is the subject of ongoing debate whether PPI analyses truly reflect effective connectivity (Friston, 2011; Friston et al., 1997; Gerchen, Bernal-Casas, & Kirsch, 2014; Rogers, Morgan, Newton, & Gore, 2007; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). Therefore, they were also described as models of "directed functional connectivity" (Gerchen et al., 2014, p. 5072). In this thesis, I will refer to them simply as a method to study functional connectivity, as this is a widely accepted umbrella term.

In gPPI, to form the interaction term, the first eigenvariate of the time course in the seed region is extracted after removing the effects of covariates of no interest and then de-convolved from the HRF to obtain an estimate of neural activity. Then, the element-by-element product of this seed region vector and the task vector (e.g., boxcar function of the task) is calculated to form the PPI term (Figure 12), which is then re-convolved with the HRF (Gitelman et al., 2003; O'Reilly et al., 2012). Crucially, in gPPI analyses, multiple PPI terms are formed in the case of multiple task vectors (i.e., one PPI term per vector; McLaren et al., 2012). Finally, a GLM is built including all PPI terms, but – critically – also the seed region time course and all task vectors along with nuisance covariates of no interest (e.g., the motion vectors extracted from the realignment pre-processing step) and a constant. This procedure ensures that significant results from a PPI term reflect only the variance beyond what is modelled by the task and seed region vectors alone (i.e., in statistical terms: the main effects of task and seed region; O'Reilly et al., 2012). As in the standard BOLD GLM analyses, contrast images are calculated at the first level (i.e., intra-individually) and then taken to the second level to analyse effects across multiple participants or between groups of participants.

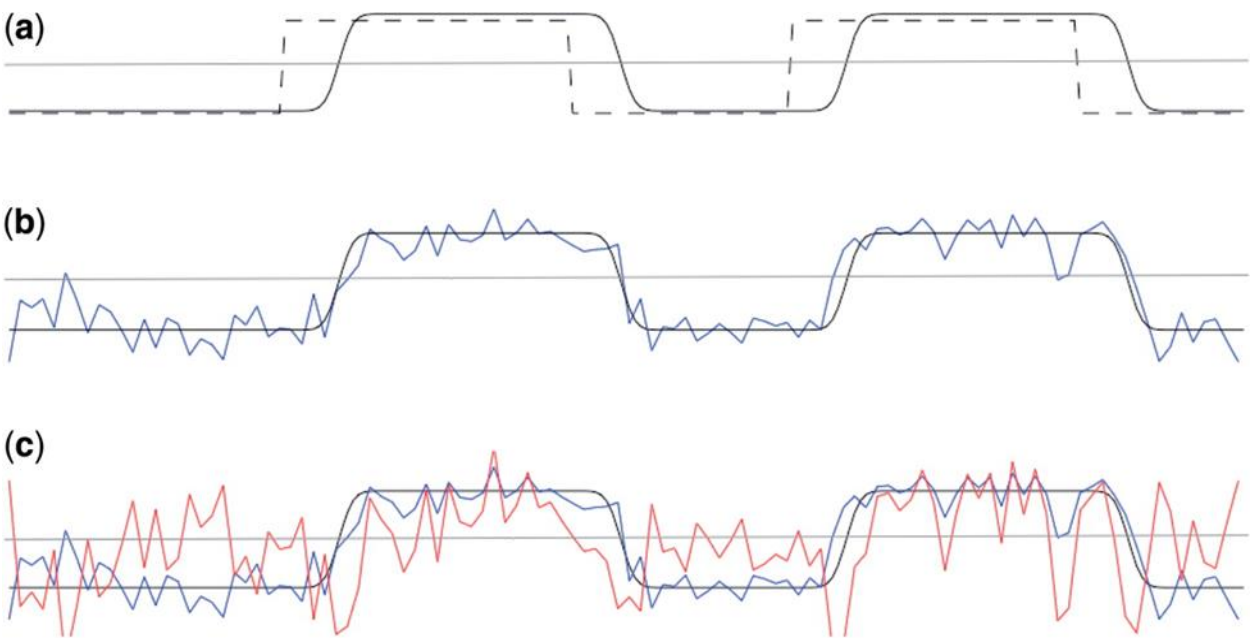

Figure 12: Generation of the psychophysiological interaction (PPI) term.

Note. Panel (a) shows the time course of the main effect of the blocked task regressor before (dashed line) and after convolution with the haemodynamic response function (solid black line). The grey line is zero. Panel (b) additionally shows the time course of the extracted activity from a seed region of interest (blue line). In panel (c), the red line represents the time course of the psychophysiological interaction term, i.e., the element-by-element product of the seed region (red line) and the convolved task regressors (black line).

Reprinted from O'Reilly, J. X., Woolrich, M. W., Behrens, T. E. J., Smith, S. M., & Johansen-Berg, H., "Tools of the trade: psychophysiological interactions and functional connectivity", *Social Cognitive and Affective Neuroscience*, 2012, *7*(5), 604–609, by permission of Oxford University Press.

2.4 Machine Learning

Machine learning helps to "uncover general principles underlying a series of observations without explicit instructions" (Bzdok & Meyer-Lindenberg, 2018, p. 223). It employs an automatic computational procedure to find an optimal solution for a given problem without prior definition of an algorithm to find a fixed solution (Dwyer, Falkai, & Koutsouleris, 2018). With machine learning methods, classifiers can be trained to determine whether a person belongs to one of two groups, e.g., patients or healthy controls. Machine learning has been employed in clinical settings for diagnosis, prognosis, and treatment prediction of psychiatric disorders and to find and evaluate potential biomarkers (Bzdok & Meyer-Lindenberg, 2018; Dwyer et al., 2018).

Two important goals of machine learning are high accuracy and generalisability of the newly-determined classifier (Dwyer et al., 2018). Accuracy can be assessed with parameters such as sensitivity, specificity, and balanced accuracy (mean of sensitivity and specificity; Dwyer et al., 2018). Generalisability is the "extent to which a statistical model generated in one group performs accurately in new groups or individuals" (Dwyer et al., 2018, p. 96). It can be estimated and optimised with cross-validation (CV) procedures in which models are trained in one set of examples and then applied to another. The gold standard of CV is nested CV, a two-stage procedure in which the sample is divided into multiple partitions at the so-called outer CV (or CV2). One set of participants is completely left out, and models are trained and selected based on the remaining participants (i.e., in the inner CV, CV1). The models are then applied to the left-out participants for validation. This process is repeated in an iterative procedure with a predefined number of permutations and sets (also: folds, partitions) of individuals, and the best-performing model is selected.

Machine learning involves two necessary analysis steps: pre-processing and training of the example data (Figure 13 A). Pre-processing encompasses data preparation for the subsequent training pipeline and includes steps such as pruning, correction for nuisance covariates, and dimensionality reduction (Dwyer et al., 2018). Pre-processing is performed inside the CV framework to prevent information leakage and overfitting (Dwyer et al., 2018; Madsen, Krohne, Cai, Wang, & Chan, 2018). In both pre-processing and training, hyperparameters can be optimised to find the best models (Dwyer et al., 2018). Significance of classification is assessed by permutation testing with random-label allocation (Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012).

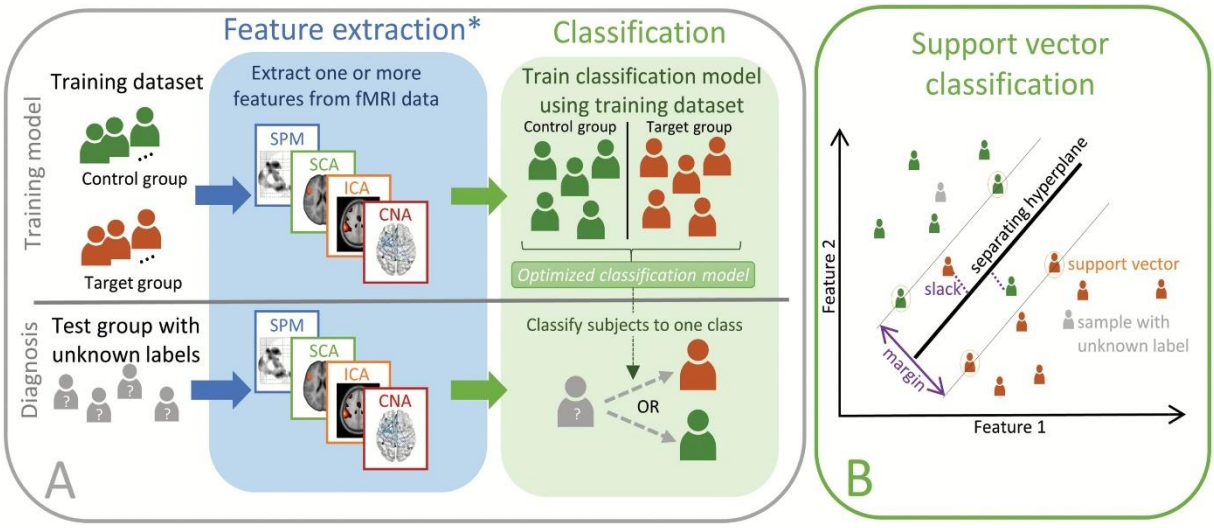

Figure 13: Illustration of the pattern classification procedure with support vector machines.

Note. Panel A shows the feature extraction and classification steps, and panel B is a schematic depiction of support vector classification.

Reprinted from Madsen, K. H., Krohne, L. G., Cai, X., Wang, Y., & Chan, R. C. K., "Perspectives on machine learning for classification of schizotypy using fMRI data", *Schizophrenia Bulletin*, 2018, *44*(suppl 2), S480–S490, by permission of Oxford University Press.

There are several approaches to determine the group-separating classifiers (Schmah et al., 2010). One of these is support-vector machine (SVM) learning, a widely-used method of supervised machine learning with neuroimaging data (Figure 13 B; Dwyer et al., 2018; Madsen et al., 2018; Orrù et al., 2012; Schmah et al., 2010). Supervised approaches rely on labelled data for pattern classification (Madsen et al., 2018). More specifically, SVM is a multivariate pattern classification technique which aims to find a decision function to categorise individual observations into distinct classes based on data in high-dimensional space (Orrù et al., 2012). With this method, the margin between two a priori defined (i.e., labelled) groups (e.g., diagnostic categories) is maximised by relying on so-called support vectors, i.e., those examples lying closest to the group-separating plane (Madsen et al., 2018; Orrù et al., 2012). The algorithm is thus based on those examples that are hardest to categorise. With a soft margin, misclassification is allowed to ensure the generalisability of the classifier (Dwyer et al., 2018; Madsen et al., 2018). The trade-off between maximal margin and misclassification can be optimised within the machine learning framework to find the best solution for the data and research question (Dwyer et al., 2018; Madsen et al., 2018). Complementing previous univariate analysis methods, **Study V** uses an SVM-based machine learning approach to separate individuals on the schizophrenia spectrum and healthy controls and to examine how individuals with high levels of schizotypy are classified.

2.5 Assessment of schizophrenia and schizotypy

The schizophrenia spectrum covers a broad range of symptoms and experiences that can be assessed with various different methods. In clinical settings, strict classification criteria guide experts to determine which – if any – diagnostic category a patient is assigned to, e.g., using the International Classification of Diseases (ICD; World Health Organization, 1993) or Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2000) manuals and criteria that were also employed in **Study V**. Symptom ratings can further inform classification and are useful in clinical and research contexts. For example, the positive and negative syndrome scale (PANSS) for schizophrenia (Kay, Fiszbein, & Opler, 1987) is used by clinicians to rate the absence or presence and severity of positive, negative, and general psychopathological symptoms.

In the subclinical domain, a wide range of methods have been developed to assess schizotypy, including self-report questionnaires and interviews (see Mason, 2015, for a comprehensive review). In **Study V** of the present dissertation, the German version of the short Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) questionnaire (Grant et al., 2013; Mason, Claridge, & Jackson, 1995; Mason, Linney, & Claridge, 2005) is used to assess the schizotypy dimensions unusual experiences, cognitive disorganisation, introvertive anhedonia, and impulsive nonconformity. Exemplary items for each scale are in Table 1. The O-LIFE is based on the fully-dimensional conceptualisation of schizotypy (see 1.6.2; Grant et al., 2013; Mason & Claridge, 2006). Its short version consists of 43 items. Each item is a question, and participants are asked to indicate whether it applies to them or not (yes/no). Cut-off thresholds can be used to assign participants to high and low scorers, e.g., on the overall score or positive (unusual experience) and negative schizotypy (introvertive anhedonia; Meyhöfer et al., 2017; Morgan, Bedford, O'Regan, & Rossell, 2009; Park, Lim, Kirk, & Waldie, 2015). The O-LIFE questionnaire is widely used and has good test-retest reliability, internal consistency (Grant et al., 2013; Mason et al., 1995), and construct validity (Mason, 2015).

Table 1: Exemplary items for each scale of the O-LIFE questionnaire

Item	Scale
Have you ever thought that you had special, almost magical powers?	Unusual experiences
Are you easily distracted when you read or talk to someone?	Cognitive disorganisation
Do you like mixing with people? *(reverse)*	Introvertive anhedonia
Do you often feel the impulse to spend money which you know you can't afford?	Impulsive nonconformity

3 Summaries of experimental studies

The five experimental studies included in this dissertation are listed in Table 2.

Table 2: Overview of the experimental studies integrated in this dissertation.

Number	Reference
I	Schröder, R., Baumert, P. M., & Ettinger, U. (2021). Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements. *Acta Psychologica*, *219*, 103364. https://doi.org/10.1016/j.actpsy.2021.103364
II	Schröder, R., Reuter, M., Faßbender, K., Plieger, T., Poulsen, J., Lui, S. S., Chan, R. C. K., & Ettinger, U. (2021). The role of the *SLC6A3* 3'UTR VNTR in nicotine effects on cognitive, affective, and motor function. *Psychopharmacology*, *239*(2), 489–507. https://doi.org/10.1007/s00213-021-06028-x
III	Schröder, R., Kasparbauer, A. M., Meyhöfer, I., Steffens, M., Trautner, P., & Ettinger, U. (2020). Functional connectivity during smooth pursuit eye movements. *Journal of Neurophysiology*, *124*(6), 1839–1856. https://doi.org/10.1152/jn.00317.2020
IV	Schröder R., Keidel, K., Trautner, P., Radbruch, A., & Ettinger, U. (2022). Neural mechanisms of background and velocity effects in smooth pursuit eye movements. *Human Brain Mapping, 44*(3), 1002–1018. https://doi.org/10.1002/hbm.26127
V	Schröder, R., Faiola, E., Urquijo, M. F., Bey, K., Meyhöfer, I., Steffens, M., Kasparbauer, A. M., Ruef, A., Högenauer, H., Hurlemann, R., Kambeitz, J., Philipsen, A., Wagner, M., Koutsouleris, N., & Ettinger, U. (2022). Neural correlates of smooth pursuit eye movements in schizotypy and recent onset psychosis: A multivariate pattern classification approach. *Schizophrenia Bulletin Open*, *3*(1), 1–13. https://doi.org/10.1093/schizbullopen/sgac034

3.1 Study I: Reliability of the background and velocity effects in SPEM

Detrimental effects of structured backgrounds on SPEM accuracy belong to the most robust observations in SPEM research (e.g., Barnes & Crombie, 1985; Hutton et al., 2000; see section 1.4.1). Similarly, increasing target velocity impairs SPEM with large effect sizes (e.g., Collewijn & Tamminga, 1984; Ettinger et al., 2004; see also section 1.4.3).

In previous investigations on SPEM reliability, mostly moderate to good reliability indices were found for direct SPEM outcomes (Bargary et al., 2017; Calkins et al., 2003; Ettinger, Kumari, Crawford, et al., 2003; Roy-Byrne et al., 1995; Versino et al., 1993), and reliability was higher for faster compared to slower target velocities (Ettinger, Kumari, Crawford, et al., 2003). Critically, however, the background and velocity effects (i.e., the difference measures of SPEM performance) have not yet been studied systematically regarding their reliability. This lack of research is critical as it has recently been demonstrated that robust task effects at group level often do not translate into reliable individual difference measures, a phenomenon termed the reliability paradox (Hedge et al., 2018). Notably, if these SPEM task effects prove to be reliable, they might be applied in the future, e.g., concerning their correlation with schizotypy.

Therefore, this study aimed at (1) replicating the background and target velocity effects and (2) investigating the reliability of both these effects and the direct performance outcomes. Additional aims were to explore task length and repetition effects on SPEM performance and on performance reliability.

A sample of $N = 45$ healthy participants performed a SPEM task employing three sinusoidal target velocities (0.2 Hz, 0.4 Hz, 0.6 Hz) in the presence and absence of a structured background consisting of a grid of white circles (Figure 14). The task was presented at the same time of day at two time points approximately one week apart. Short and long versions of the task were compared where each task

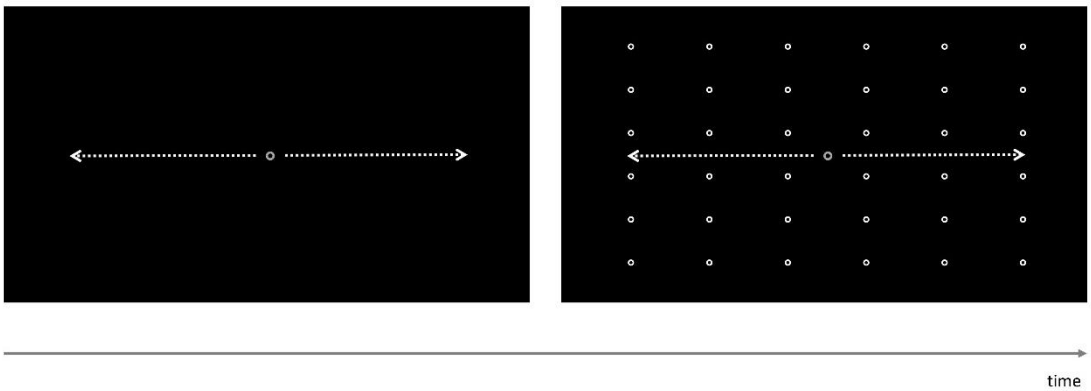

Figure 14: Schematic depiction of the target display.

Note. The target moved at 0.2 Hz, 0.4 Hz, and 0.6 Hz in the absence (left) and presence (right) of the stationary background stimuli. Each target velocity was presented once with and once without background stimuli for 30 s. Order of the conditions was randomised.

condition (i.e., each velocity × background pairing) was presented once (block A) or twice (blocks A and B) for 30 s in randomised order. Eye movements were assessed using VCPCR, and SPEM gain was analysed as the primary performance outcome. Reliability was calculated with split-half and test-retest methods using intraclass (ICC) and Pearson correlations. The individual background effect was calculated as the difference in SPEM gain between the conditions without and with backgrounds. The individual velocity effect was calculated as the differences in SPEM gain between the 0.2 Hz and 0.6 Hz velocity conditions.

In line with previous investigations large velocity and background effects were observed for SPEM gain (Figure 15, panel A). In addition, task performance was significantly better in the second compared to the first assessment. There were significant interactions between the background and

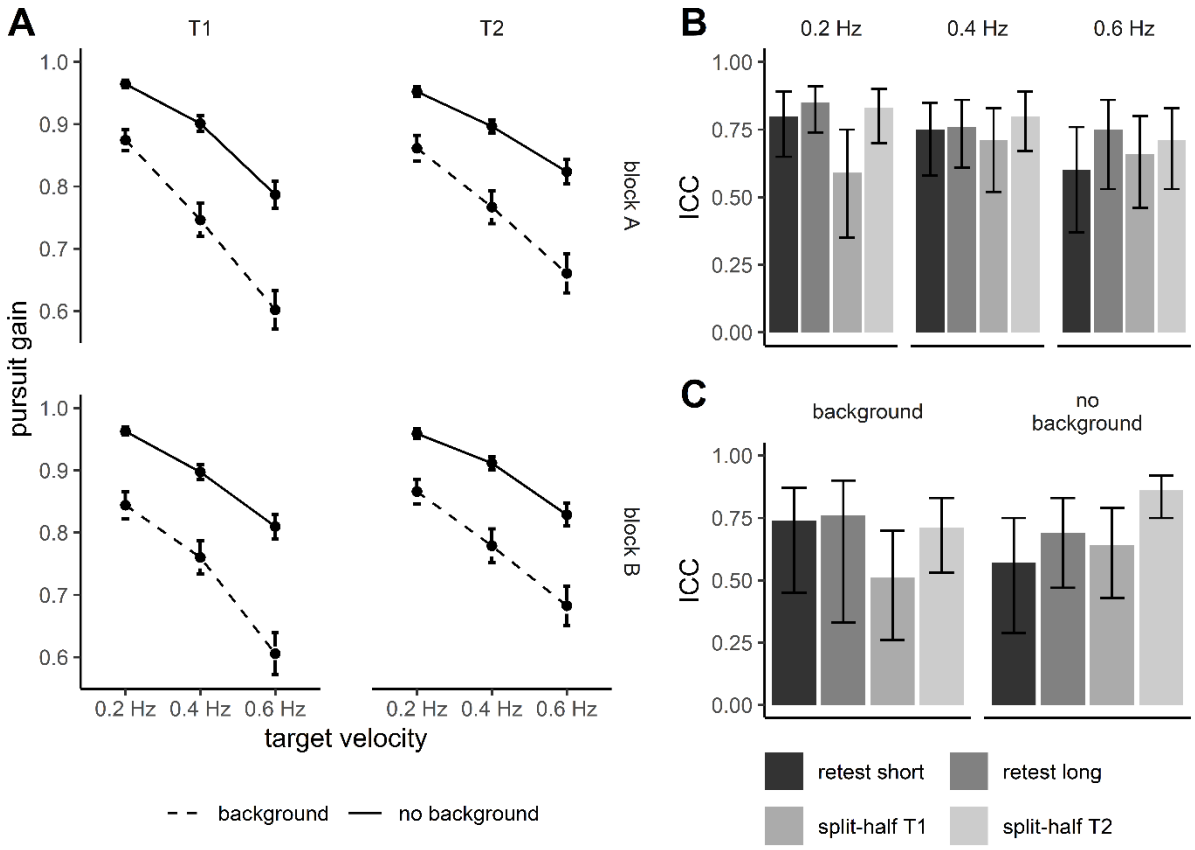

Figure 15: Key findings from Study I.

Note. Mean SPEM gain (panel A) at the first and second assessment day (T1, T2) in blocks A and B as a function of the target velocity and background conditions. Error bars in panel A represent standard errors. Intraclass correlation (ICC) reliabilities for the SPEM gain background effect (panel B; no background condition minus background condition) and SPEM gain velocity effect (panel C; 0.2 Hz condition minus 0.6 Hz condition). Error bars in panels B and C represent the upper and lower limit of the 95% confidence interval.

Adapted from "Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements" by Schröder, R., Baumert, P. M., & Ettinger, U., 2021, *Acta Psychologica*, *219*, p. 6, and Appendix A. Supplementary data, p. 5. Material has been modified (rearrangement of the panels). Licensed under CC BY-NC-ND 4.0.

velocity factors (indicating larger background effects with increasing target velocity), the background and time factors (indicating that gain increased from T1 to T2 only in the background condition) as well as the velocity and time factors (indicating that gain increased from T1 to T2 only in the 0.6 Hz velocity condition), but no further interactions and no main effect of block. Hence, performance was relatively stable from the first to the second half of the long version of the task.

Analyses of reliability showed similar results for the ICC and Pearson correlations. Reliability scores of the velocity and background effects were largely good to excellent (Figure 15, panels B and C). Reliability scores of the direct performance outcomes were fair to good at lower target velocity without background but good to excellent at higher target velocity and in the background conditions. The longer version of the task achieved higher retest reliability scores than the shorter version in nearly all conditions, and split-half reliability was consistently higher on the second than the first assessment day. However, confidence intervals overlapped, suggesting that these differences were not significant.

The results of this study complement a long series of earlier findings and thus confirm the robustness of the background (e.g., Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Kaufman & Abel, 1986; Lindner et al., 2001; Meyhöfer et al., 2019) and velocity effects (e.g., Collewijn & Tamminga, 1984; Lisberger et al., 1981; Meyhöfer et al., 2019; Nagel et al., 2008) in SPEM. Intriguingly, these results also demonstrate that velocity and background effects are reliable, suggesting that the so-called reliability paradox found for standard cognitive tasks cannot simply be extended to SPEM performance outcomes (Hedge et al., 2018). Reasons for this discrepancy might be higher ecological validity in oculomotor tasks (Burgess et al., 2006), lower task impurity, and fewer biases such as speed-accuracy trade-offs (Draheim, Mashburn, Martin, & Engle, 2019; Miller & Ulrich, 2013). These findings are well in line with evidence from other forms of oculomotor behaviour, such as saccades and fixation (Castelhano & Henderson, 2008; de Haas, Iakovidis, Schwarzkopf, & Gegenfurtner, 2019; Linka & de Haas, 2020; Meyhöfer, Bertsch, Esser, & Ettinger, 2016). Employing a longer task version improved reliability at a descriptive level. As this improvement was not significant, no clear recommendations for task length in future studies can be drawn. Similarly, the difference in split-half reliabilities between sessions (T1 < T2) was not significant, but the pattern of results hints at a possible reduction in error variance at T2. Relatively low reliability scores for SPEM gain in the condition with slow targets and no background might be due to a ceiling effect of performance and resulting low between-subject variance. Performance was reasonably stable within each session, as the factor task block had no significant effect. Crucially, however, SPEM gain improved when the task was repeated after one week, consistent with a practice effect between sessions. Interactions with the background and velocity factors suggest that this effect might be due to learning effects (Eibenberger, Ring, & Haslwanter, 2012; Kerkhoff et al., 2013) in the more challenging task conditions, i.e., in the background conditions and at higher target velocity.

Taken together, the findings from this study demonstrate that the SPEM background and velocity effects are not only highly replicable but also reliable, demonstrating that they also lend themselves to the study of individual differences.

3.2 Study II: Nicotine effects on SPEM

The effect of nicotine on SPEM has been extensively researched, with largely positive (e.g., Dépatie et al., 2002; Meyhöfer et al., 2019) but also negative (e.g., Sibony et al., 1988; Thaker et al., 1991) and null (e.g., Kasparbauer et al., 2016; Schmechtig et al., 2013) effects on SPEM performance. Some of these discrepancies might be explained by differences in study design, such as dosage (Almeida et al., 2020) and participants' smoking (Avila et al., 2003; Domino et al., 1997) and psychiatric status (Olincy et al., 1998; Sherr et al., 2002), or should be interpreted with caution due to methodological deficits, such as poor or no control conditions and lack of blinding (Avila et al., 2003; Domino et al., 1997; Olincy et al., 1998; Olincy, Johnson, & Ross, 2003; Sherr et al., 2002; Sibony et al., 1988; Thaker et al., 1991). Importantly, another line of argument points to interindividual differences at the genetic level contributing to these heterogeneous results (Bogdan et al., 2012; Hariri, 2009; Siebner et al., 2009).

The dopaminergic and cholinergic systems have been identified as important neurotransmitter systems underlying SPEM (Allman et al., 2012; Heishman et al., 2010; see also 1.5). A key element of the dopamine system is the DAT which regulates synaptic dopamine availability by controlling the re-uptake of dopamine into the presynaptic neuron (McHugh & Buckley, 2015; see also 1.5.3). The striatum is the area of the highest DAT density (Piccini, 2003). Strikingly, it also has a pivotal role in dopamine response to nicotine (Cachope et al., 2012; Threlfell et al., 2012). The *SLC6A3* VNTR polymorphism is investigated as a potential moderator of heterogeneous results in response to pharmacological challenges. 9R-carriers typically react more strongly to the administration of substances that act on the dopaminergic system (e.g., Brewer et al., 2015; Franklin et al., 2011; see also 1.5.3) and have higher DAT-availability than 10R-homozygotes (e.g., Faraone et al., 2014; see also 1.5.3).

It was therefore hypothesised that the differences between genotype groups in response to pro-dopaminergic challenges are a result of differences in baseline DAT availability (9R>10R) and ensuing synaptic dopamine levels (9R<10R). Specifically, we expected 9R-carriers to respond more strongly (i.e., show higher SPEM performance increases) to nicotine than 10R-homozygotes and that this effect is mediated by spontaneous blink rate (SBR), which was assessed as a non-invasive and indirect measure of dopamine function in striatum (Jongkees & Colzato, 2016).

To test these hypotheses, N = 194 participants, stratified for their *SLC6A3* genotype, were given 2 mg nicotine or placebo in a between-subjects design. In addition, SBR was obtained in an initial fixation paradigm. Then, participants performed a SPEM task with sinusoidal targets moving at three different velocities (0.2 Hz, 0.4 Hz, 0.6 Hz) in the presence or absence of a structured background consisting of a 6-by-6-grid of white circles (as in **Study I**, Figure 14). SPEM gain was computed as the primary performance outcome. Additional tasks were administered that are not relevant to the present dissertation, which is why no further details are reported here.

Substantial SPEM task effects were observed, replicating previous findings of performance decreases in the presence of a structured background and with faster target velocity (Figure 16). However, no significant drug or genotype effects on SPEM gain and no interaction of the two factors could be observed. Bayesian analyses confirmed these null results. The proposed conditional process

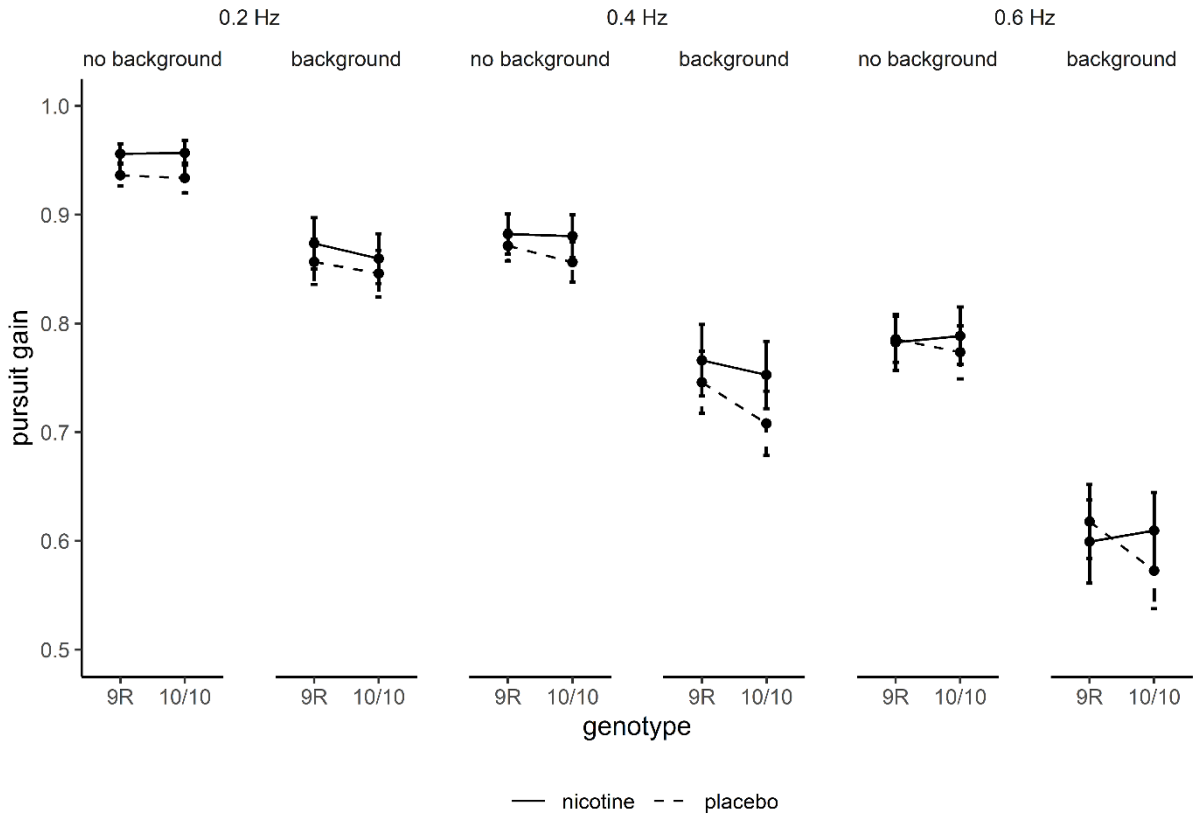

Figure 16: Key findings from Study II.

Note. Effects of the between-group factors substance and *SLC6A3* VNTR genotype and the within-group factors background (present, absent) and target velocity (0.2 Hz, 0.4 Hz, 0.6 Hz) on SPEM gain. Data are presented as mean ± standard errors.

Reprinted from "The role of the *SLC6A3* 3' UTR VNTR in nicotine effects on cognitive, affective, and motor function", by Schröder, R., Reuter, M., Faßbender, K., Plieger, T., Poulsen, J., Lui, S. S. Y., Chan, R. C. K., & Ettinger, U., 2022, *Psychopharmacology, 239*(2), p. 497. Licensed under CC BY 4.0.

model testing the mediating effect of SBR on the drug effect on SPEM gain and its moderation by genotype yielded no significant results.

The absence of a nicotine effect is surprising given the substantial overlap in study and task design with a previous study (Meyhöfer et al., 2019) that reported enhancing effects of nicotine on SPEM performance with large effect sizes. The only major methodological deviation was the use of a between-subjects design in our study compared to a within-subjects design in the previous study. Between-subjects designs have lower statistical power than within-subjects designs due to the lower controllability of within-subjects effects (Karpouzian et al., 2019). Importantly, however, we tried to overcome this constraint by choosing a much larger sample size with 90% power to detect a medium effect. It is, therefore, unlikely that our results were due to low statistical power. This notion was also supported by Bayesian analyses, which provided strong evidence not to include the drug and genotype factors in the models. Our results are consistent with some prior null findings (Kasparbauer et al., 2016; Schmechtig et al., 2013) and thus do not necessarily refute previous positive observations. Rather, they point to the sensitivity of nicotine effects to changes in task design and thus underline the importance of identifying and addressing potential moderators and establishing transparent research standards.

3.3 Study III: Functional connectivity during SPEM

A brain network of cortical and subcortical areas controls SPEM. The main components of this network have been identified using neuroscientific methods. They include visual areas in occipital cortex such as V1 and V5, PPC, FEF, and SEF as well as subcortical structures including LGN (e.g., Lencer & Trillenberg, 2008; see also 1.3). Critically, little is known concerning the interaction of these brain areas in terms of functional connectivity during SPEM. The only study that assessed task-based functional connectivity (Acs & Greenlee, 2008) showed in a small sample that attention modulates the bottom-up connection from V1 to V5. In order to broaden our understanding of the interplay of these and other key regions of the oculomotor network during SPEM, this study aimed to investigate task-based functional connectivity in a large sample. Secondary aims were to explore the effects of target velocity on performance, regional brain activity, and functional connectivity and investigate brain-behaviour relationships in terms of individual differences.

A sample of 57 healthy participants performed a blocked sinusoidal SPEM task with two target velocities (0.2 Hz, 0.4 Hz) and baseline fixation blocks while undergoing fMRI assessment. Functional connectivity (gPPI; see 2.3.3) was analysed separately for both conditions (vs. baseline) and the velocity contrast (0.4 Hz vs. 0.2 Hz) for ten seed regions (LGN, V1, V5, PPC, and FEF in both hemispheres). Analyses of behavioural data yielded large target velocity effects in all three dependent variables (SPEM

gain, RMSE, and total saccade rate) indicative of decreased SPEM accuracy (lower gain, higher RMSE) and higher rates of saccades with faster targets.

Traditional analyses of regional BOLD activity during SPEM revealed increased BOLD response in both the low and high velocity contrasts in the known SPEM network, i.e., in occipito-temporal clusters (including visual areas V1 and V5), inferior and posterior divisions of the parietal cortex, FEF, SEF, middle cingulate gyrus, and in thalamus (encompassing LGN). Higher vs. lower target velocity was associated with increased BOLD response in occipital cortex.

The gPPI analyses revealed widespread networks for both velocity conditions and all seed regions (see Figure 17 for exemplary data for the left seed regions and the high target velocity vs. fixation contrast). Increased coupling from LGN during SPEM vs. fixation was found in occipital, cingulate, and subcortical brain regions. Connectivity from V1 was observed primarily in occipital cortex, similar to that of V5, which additionally encompassed parietal and frontal areas. The seed region in PPC showed connectivity to other parietal areas, as well as temporal, occipital, and frontal cortex and cerebellum. Connectivity from FEF spread across the entire cortex and encompassed frontal, parietal, occipital, temporal, insular, and cingulate brain areas. In addition, connectivity to subcortical structures, including putamen and thalamus, was observed. Connectivity patterns did not significantly differ between the high and low target velocity conditions.

Contrary to our expectations, there were no significant associations between the behavioural outcome variables and brain activity in whole-brain regression analyses and no significant correlations between the behavioural outcome variables and extracted brain activity from areas of interest (LGN, V1, V5, PPC, FEF).

The results of this study replicate previous findings that identified the components of the SPEM network (e.g., Berman et al., 1999; Lencer et al., 2004; Petit & Haxby, 1999). In addition, results point to the robustness of the behavioural velocity effect in SPEM (e.g., Collewijn & Tamminga, 1984; Lisberger et al., 1981; Meyhöfer et al., 2019). For the first time, functional connectivity during SPEM was investigated systematically and comprehensively, revealing the close interplay of the major components of the SPEM network. Functional connectivity from areas involved in early SPEM-related processes (LGN, V1, V5) was more regionally focused, especially in visual areas. Areas higher in the oculomotor hierarchy (PPC, FEF) showed more widespread connectivity patterns with a strong fronto-parietal focus.

These findings partially overlap with analyses of structural and resting-state connectivity (e.g., Caspers & Zilles; Genç, Schölvinck, Bergmann, Singer, & Kohler, 2016; Hampson, Olson, Leung, Skudlarski, & Gore, 2004; Hutchison et al., 2012). Interestingly, task-based functional connectivity was also found in areas outside the traditional oculomotor network, including DLPFC, suggesting a more elaborate interplay of these areas during SPEM (O'Reilly et al., 2012).

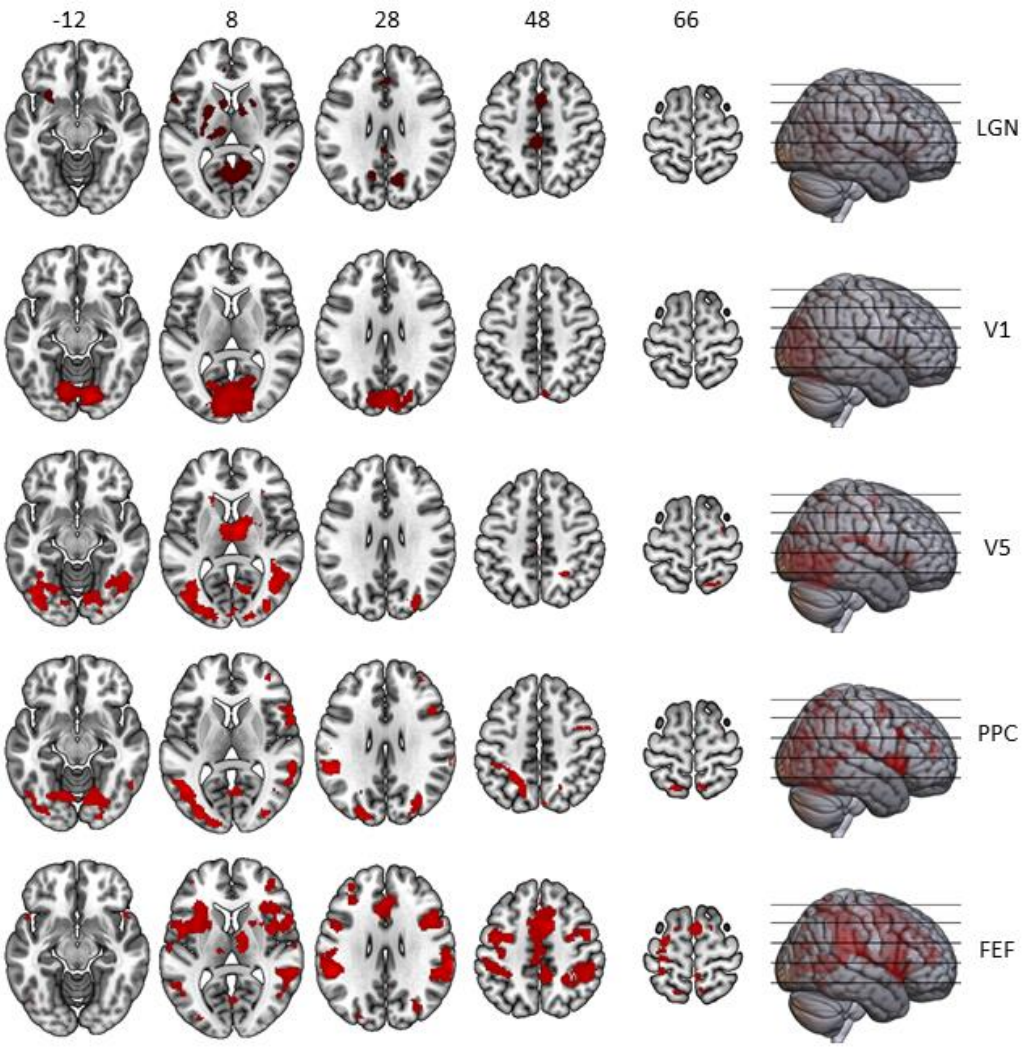

Figure 17: Exemplary key findings from Study III for one seed region and task contrast.

Note. Functional connectivity (gPPI) from the LGN (lateral geniculate nucleus), V1, V5, PPC (posterior parietal cortex), and FEF (frontal eye field) seed regions in the left hemisphere at high velocity SPEM (0.4 Hz) vs. fixation. Only clusters exceeding a 25 voxels minimum cluster size threshold are depicted. Results are corrected with whole-brain family-wise error rate correction (FWE; $p < .001$) at peak level. Labels at the top refer to the z-coordinate of the slices (Montreal Neurological Institute [MNI] space).

3.4 Study IV: Neural correlates of the background and velocity SPEM effects

As described above, SPEM performance is reliably degraded in the presence of a structured background and with faster targets (e.g., Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Meyhöfer et al., 2019; see 1.4.1 and 1.4.3). Crucially, the neural mechanisms of these effects are insufficiently understood (see 1.4.2 and 1.4.4). Evidence concerning the background effect is scarce. Results from fMRI, TMS, and lesion studies highlight the importance of different areas in the parietal cortex for SPEM performance with background stimuli (e.g., Haarmeier & Kammer, 2010;

Lawden et al., 1995; Ohlendorf et al., 2010; see also 1.4.2). Additionally, suppressing background distractors might involve frontal cortex, as observed in tasks requiring response inhibition (Wager et al., 2005). In some previous investigations, faster target velocity has been associated with increased BOLD response across the entire SPEM network, including V1, V5, lateral intraparietal area, FEF, and SEF (Nagel et al., 2008; Nagel et al., 2012). In investigations from our group, only visual cortex responded to faster targets when data were analysed in separate samples (Kasparbauer et al., 2016; Meyhöfer et al., 2015; Steffens et al., 2016) and jointly across samples (see **Study III**).

Therefore, this preregistered study aimed to investigate the neural mechanisms of the background and velocity effects in a sample of healthy participants with traditional and functional connectivity methods. Secondary aims were to explore brain-behaviour-relationships with multiple regression and correlation analysis approaches.

Thirty-three participants performed a sinusoidal SPEM task with the concurrent assessment of eye movements and BOLD response. Target stimuli were presented at two velocities (0.4 Hz and 0.6 Hz) in the presence and absence of a structured background (as in **Studies I** and **II**, Figure 14). SPEM blocks alternated with baseline fixation blocks without background stimuli. SPEM gain, catch-up saccade rate, and RMSE were calculated as SPEM performance outcomes.

Descriptively, for SPEM gain, background and velocity effects were observed in every single participant. This observation was further supported by substantial main effects at the group level, indicating decreased SPEM gain in the presence of a structured background and with faster targets. Similarly, catch-up saccade frequency increased with background and with faster targets. For RMSE, however, there was only a significant main effect of velocity, indicating higher position error with faster targets but no effect of background. There was no interaction of the two factors for any dependent measure.

At the neural level, analyses of regional BOLD response revealed task-related activity in the well-known SPEM network, including primary visual and motion processing areas, parietal cortex, FEF, SEF, cingulate gyrus, and LGN (Figure 18). For the background effect, enhanced BOLD response with background was found in visual cortex, parietal cortex, medial FEF, SEF, and LGN. Regarding the velocity effect, faster targets elicited BOLD response in visual cortex and left lateral FEF. There was no interaction effect of the background and velocity factors at the neural level: the quality of the BOLD task effect for one factor was independent of the expression of the other task factor.

In the SPEM vs. fixation contrast, gPPI connectivity from seed regions as in **Study III** was found to cortical and subcortical structures. Notably, there were no differences in task-related connectivity for the background and velocity effects and the background × velocity interaction. Task performance outcomes (SPEM gain, catch-up saccade rate, and RMSE) did not predict BOLD response in separate regression analyses for each condition. However, when correlating performance outcomes with

extracted activity from the main effect clusters, in the 0.6 Hz no background condition, poorer SPEM gain was associated with increased BOLD response in left V5. Moreover, catch-up saccade rate positively correlated with BOLD response in right FEF in that condition. In the 0.4 Hz conditions with background, increased SPEM gain was associated with higher BOLD response in left medial FEF. There were no significant correlations for any other condition and the task effects.

The results of this study again replicate the background and velocity effects at the behavioural level (Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Meyhöfer et al., 2019; although not for RMSE). In addition, BOLD response was found in brain areas previously identified as forming the SPEM network, substantiating findings from our own and other groups (e.g., Berman et al., 1999; Konen et al., 2005; Nagel et al., 2006 and **Study III**). Critically, the neural correlates of the background and velocity effects were studied jointly for the first time. The background effect relied on activity in widespread clusters with a strong visual and fronto-parietal focus. Interestingly, BOLD response in FEF was located more medially than in the standard SPEM contrast and in the conditions without background. This result – for the first time – points to functional specialisation of FEF subregions during SPEM, suggesting a stronger involvement of medial FEF in more complex cognitive processes, while lateral FEF might support motor function (Cieslik, Seidler, Laird, Fox, & Eickhoff, 2016; Jin et al., 2021; Lencer et al., 2004; McDowell, Dyckman, Austin, & Clementz, 2008).

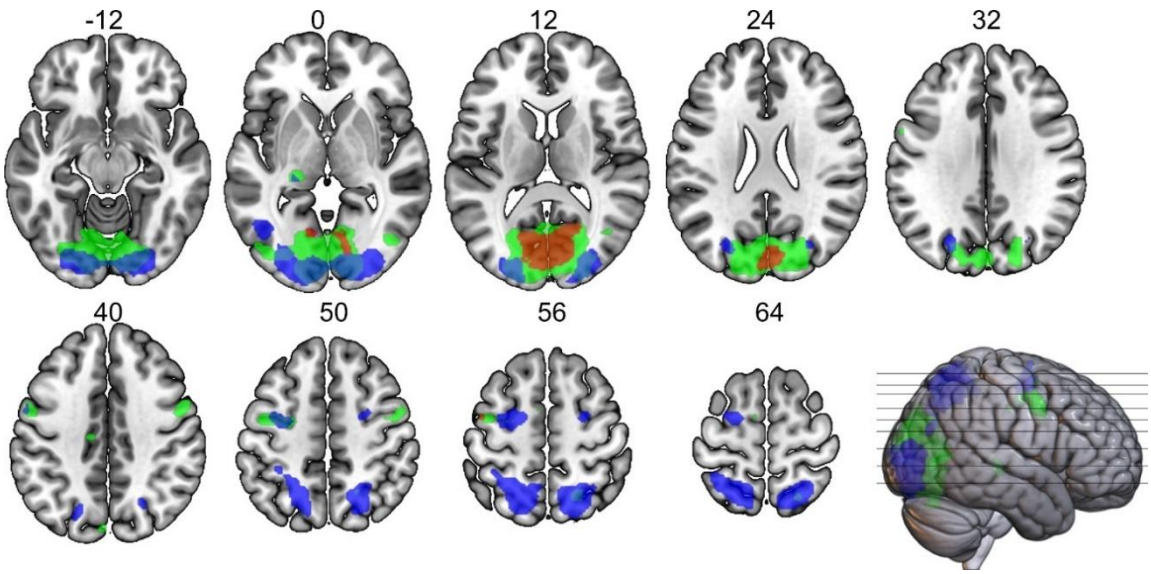

Figure 18: Key findings from Study IV.

Note. BOLD response during the SPEM task (all conditions vs. fixation; green) and in the background present vs. absent (blue) and the high (0.6 Hz) vs. low (0.4 Hz) target velocity (red) contrasts. Only clusters exceeding a 10 voxels minimum cluster size threshold are depicted. Results are corrected with whole-brain family-wise error rate correction (FWE; $p < .05$) at peak level. Labels at the top refer to the z-coordinate of the slices (Montreal Neurological Institute [MNI] space).

Reprinted from "Neural mechanisms of background and velocity effects in smooth pursuit eye movements" by Schröder R., Keidel, K., Trautner, P., Radbruch, A., & Ettinger, U., 2022, *Human Brain Mapping, 44*(3), 1002–1018. Licensed under CC BY-NC 4.0.

Increased BOLD response in parietal areas during SPEM with structured backgrounds is in line with the putative involvement of the parietal cortex in attentional processes and processing of movement relative to a frame of reference (Baumann & Greenlee, 2009; Ohlendorf et al., 2007; Ohlendorf et al., 2010; Trenner et al., 2008). In good agreement with our own previous work (**Study III**), the velocity effect was based on activity in visual cortex, and – for the first time with sinusoidal targets – there was also evidence for the involvement of left lateral FEF, potentially related to higher motor demands with faster targets (Cieslik et al., 2016; Nagel et al., 2008; Nagel et al., 2012). While task-based functional connectivity analyses largely replicated previous findings (**Study III**), no connectivity-related differences between the task conditions were identified.

3.5 Study V: Neural mechanisms of the SPEM BOLD response along the schizophrenia spectrum

Deficits in SPEM performance outcomes belong to the most robust biomarkers of schizophrenia spectrum disorders (e.g., Levy et al., 2010; O'Driscoll & Callahan, 2008; see also 1.6.3). Similar deficits have also been observed in schizotypy (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kendler et al., 1991; Lenzenweger & O'Driscoll, 2006; Meyhöfer et al., 2015; Smyrnis et al., 2007), a general tendency towards psychosis-like experiences and psychopathology at the subclinical level (see 1.6.2; Ettinger et al., 2014; Kwapil & Barrantes-Vidal, 2015). However, at the descriptive level, SPEM dysfunction is more subtle in high schizotypy than in schizophrenia spectrum disorders (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Lenzenweger & O'Driscoll, 2006; Meyhöfer et al., 2017; Smyrnis et al., 2007), and there is only partial overlap of deficits at the neural level when compared across studies (Hong et al., 2005; Lencer et al., 2005; Meyhöfer et al., 2015; Nagel et al., 2012).

So far, there is no direct comparison of patients with schizophrenia spectrum disorders and individuals scoring high and low on schizotypy regarding the neural mechanisms underlying SPEM. Even more importantly, these groups have not yet been compared in terms of task-based functional connectivity during SPEM, although dysconnectivity is a widely endorsed explanation for the pathophysiology of schizophrenia (Friston et al., 2016; Friston & Frith, 1995; Pettersson-Yeo et al., 2011; Stephan et al., 2009; see also 1.6.1).

This study aimed to close these significant gaps in the literature. In addition to traditional mass-univariate analyses of BOLD activity, machine learning analyses were applied to obtain classifiers distinguishing between patients and controls. This approach was chosen as it may be more sensitive to subtle group differences (Madsen et al., 2018). It was hypothesised that patients with schizophrenia spectrum disorders (the recent onset psychosis [ROP] group) can be significantly distinguished from healthy controls regarding behavioural performance, task-based BOLD activation, and functional

connectivity (gPPI). In case of significant classification, the machine learning classifiers were applied to groups of individuals scoring high on schizotypy to determine the likelihood of these participants being classified as either ROP or healthy controls with low schizotypy scores (LS).

A total of 183 participants (*N* = 34 ROP, *N* = 62 LS, *N* = 46 participants with high levels of negative schizotypy [HNS], *N* = 41 participants with high levels of positive schizotypy [HPS]) completed the study at two sites. Participants performed a SPEM task with alternating SPEM (two sinusoidal target velocities: 0.2 Hz, 0.4 Hz) and fixation blocks, and simultaneous measurement of BOLD activity and eye movements. Three SPEM parameters were calculated (SPEM gain, RMSE, and saccade frequency) and analysed for between-group differences. BOLD activity was compared between groups regarding two contrasts: a SPEM contrast (all SPEM blocks vs. fixation) and a velocity contrast (0.4 Hz vs. 0.2 Hz). In addition, gPPI analyses were carried out for both contrasts with seed spheres as in **Studies III** and **IV**. SVM machine learning analyses were computed for multivariate pattern classification for the behavioural data, both task contrasts, and each of the gPPI contrasts.

At the behavioural level, there was a significant group effect on RMSE, suggesting impaired SPEM in the ROP group, although the subsequent *t*-tests did not survive Bonferroni correction. In addition, there was a trend towards a group effect on SPEM gain but no effect on saccade rate. Pattern classification did not yield a significant classifier for the behavioural data.

At the BOLD level, the task elicited activity in the well-known SPEM network, and the velocity contrast revealed higher BOLD activity in visual cortex. However, there were no significant group differences for any of the task or gPPI contrasts. Pattern classification was not significant for the two task contrasts. The only significant classification for the gPPI contrasts was obtained for the connectivity analyses with right FEF as seed regions. Here, patients and controls were separated with a balanced accuracy of 62.4% (sensitivity = 73.3%; specificity = 51.5%; Figure 19). However, this classification was not significant when correcting for multiple testing. The classification was based on functional connectivity from right FEF to cortical and subcortical brain areas.

Applying the classifier to the two samples with high positive and negative schizotypy levels produced decision scores that fell between those of patients and controls at the descriptive level. However, decision scores did not significantly differ between the four groups. Regression analyses of the effects of decision scores on BOLD activity in the combined schizotypal samples (HPS and HNS) showed that a higher probability of being classified as ROP was associated with increased connectivity from right FEF to multiple brain areas. Stacked analyses, combining decision scores from the traditional BOLD and gPPI analysis levels separately for the SPEM and velocity contrasts, were not significant.

These results are largely at odds with previous investigations that yielded significant differences in SPEM performance between patients with schizophrenia and controls with medium to large effect sizes (O'Driscoll & Callahan, 2008).

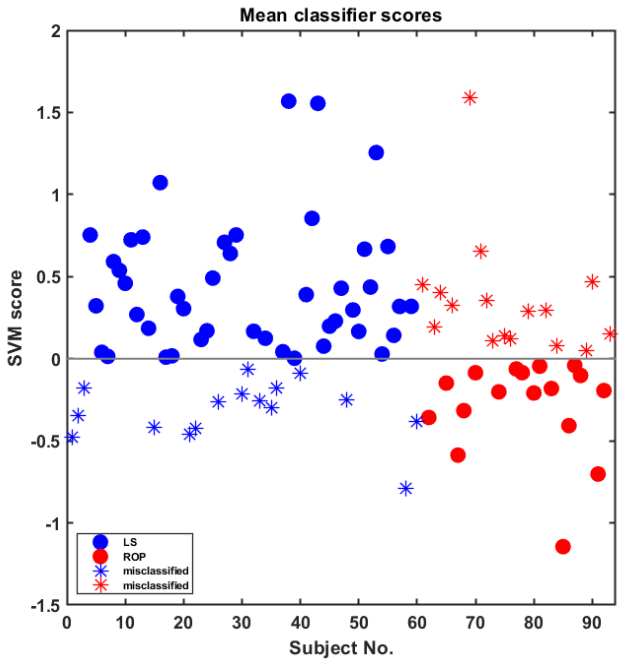

Figure 19: Key finding from Study V.

Note. Classification plot for the low schizotypy (LS) and recent onset psychosis (ROP) groups for the right frontal eye field connectivity analysis. Positive support vector machine (SVM) scores indicate a higher likeliness of belonging to the LS group, and negative SVM scores indicate a higher likeliness of belonging to the ROP group. Circles are correctly classified individuals, and asterisks are incorrectly classified individuals. All blue symbols belong to individuals from the LS group, and all red symbols belong to individuals from the ROP group. This classification reached a balanced accuracy of 62.4%, sensitivity of 73.3%, and specificity of 51.5%.

In addition, group differences in BOLD activity during SPEM previously found in various components of the SPEM network (e.g., Hong et al., 2005; Keedy et al., 2006; Lencer et al., 2005; Lencer et al., 2011; Nagel et al., 2007; Nagel et al., 2012; Tregellas et al., 2004) were also not detected at the neural level. The lack of significant results in the behavioural and mass-univariate BOLD analyses is unlikely due to low statistical power as revealed by power analyses and when compared to sample sizes of previous studies. Instead, relatively low performance accuracy in the LS group and diagnostic heterogeneity in the ROP group must be considered potentially relevant factors.

However, combining brain integration with machine learning approaches proved to be promising as using these methods a significant classification of patient and control data was obtained. Crucially, these results must be interpreted with great caution as they were not significant after correction for multiple analyses. The results tentatively point to both similarities and dissimilarities of individuals with high schizotypy and patients with ROP.

To summarise, this study was the first to directly compare individuals with ROP and high and low levels of schizotypy regarding BOLD activation and functional connectivity during SPEM with traditional and machine learning methods. As such, it addressed a fundamental shortcoming in the SPEM literature and laid the groundwork for further research.

4 Discussion

SPEM occur whenever the eyes follow a slowly moving stimulus, making them a highly relevant type of eye movement (Leigh & Zee, 2015). Their underlying mechanisms are still insufficiently understood. This dissertation presented data from different psychological and neurobiological levels to expand our knowledge of these mechanisms. Specifically, the behavioural, molecular, and neural mechanisms of two very robust findings in the SPEM literature, namely the velocity and background effects, were analysed (**Studies I**, **II** and **IV**). Another focus of this dissertation was to address the lack of research regarding functional connectivity of the brain areas involved in SPEM in healthy participants (**Studies III** and **IV**) as well as in individuals with schizophrenia and high levels of schizotypy (**Study V**).

4.1 Integration

4.1.1 Basic and neural mechanisms of SPEM

Data from **Studies I–V** demonstrated that participants were generally excellent at pursuing the SPEM target with an average SPEM gain of up to 0.96. Participants achieved these high gain scores even in unfamiliar and distracting environments such as MRI scanners (**Studies III–V**). However, SPEM was often interspersed with catch-up saccades, illustrating the close interplay of the SPEM and saccade systems in guiding eye movements (Goettker & Gegenfurtner, 2021; Orban de Xivry & Lefèvre, 2007). SPEM performance varied depending on specific task configurations, e.g., with the background conditions and levels of target velocity, which will be discussed in sections 4.1.2 and 4.1.3, respectively.

In **Study I**, the reliability of SPEM outcome measures was investigated with split-half and test-retest methods. SPEM gain achieved fair to good reliabilities for the slowest (and arguably easiest) target velocity condition without background stimuli and good to excellent reliabilities for all other conditions, corroborating previous results (Bargary et al., 2017; Calkins et al., 2003; Ettinger, Kumari, Crawford, et al., 2003; Roy-Byrne et al., 1995; Versino et al., 1993). These results underline not only the time-stability of SPEM outcomes also observed for other types of eye movements (Meyhöfer et al., 2016) but also their general applicability in individual difference research, where high reliability is a prerequisite for identifying correlations between psychological measures (Parsons, Kruijt, & Fox, 2019; Spearman, 1910). Critically, reliability was higher in the more challenging task conditions, e.g., with background stimuli and faster targets, and for the long task version. Hence, based on our findings, it can be recommended to prefer such task configurations in future studies focusing on individual

differences in SPEM and their correlation with other measures (e.g., schizotypy; Smyrnis et al., 2007). Reliability scores were higher for SPEM gain than catch-up saccade rate and RMSE, reinforcing the utility of SPEM gain as a powerful primary outcome measure in SPEM research (Smyrnis, 2008).

Studies III–V examined the neural mechanisms behind SPEM performance. All studies employed SPEM paradigms with two sinusoidal target velocities (0.2 Hz and 0.4 Hz in **Studies III** and **V** and 0.4 Hz and 0.6 Hz in **Study IV**). In **Study IV**, targets were presented either on a stationary structured background or a blank background. In **Studies III** and **V**, all target stimuli were presented on a blank background. BOLD correlates of the background and velocity effects will be discussed in sections 4.1.2 and 4.1.3, respectively.

BOLD response in the simple task contrasts (SPEM vs. fixation) was highly similar in all three studies, highlighting the remarkable consistency of the neural processes underlying SPEM in the presented velocity range. Specifically, increased BOLD response during SPEM execution was found in visual cortex (including V1 and V5), parietal cortex, frontal cortex (FEF and SEF), cerebellum, and cingulate gyrus as well as subcortically in LGN in all three studies. These findings substantiate previous evidence on the neural mechanisms of SPEM (e.g., Berman et al., 1999; Lencer et al., 2004; Petit & Haxby, 1999; see 1.3).

Another aim of **Studies III–V** was to investigate, for the first time, the functional connectivity of the SPEM network with a gPPI approach. Five brain areas (LGN, V1, V5, PPC, FEF) considered key components of the SPEM network were selected as seed regions. It was determined how BOLD activity across the whole brain correlated with activity in these regions in the context of the SPEM task. In **Study III**, functional connectivity from LGN was found primarily to visual cortex and subcortical structures. Similarly, connectivity from V1 mainly reached surrounding areas in occipital cortex and striatum. Analyses with V5 seed regions showed connectivity to other visual clusters, thalamus, and cerebellum but also higher cortical areas, including superior and posterior parietal cortex and FEF. Connectivity from PPC was found to other areas in parietal cortex and to occipital, temporal, and frontal cortex, including FEF and inferior frontal gyrus. Similarly, FEF connectivity was widely distributed and encompassed cortical and subcortical areas, extending beyond the SPEM network. In fact, effects were so strong that contrasts needed to be corrected with very strict thresholds to increase the interpretability of the results. In **Study IV,** similar findings were obtained. However, connectivity patterns covered a larger proportion of the cortex. Specifically, for V1, strong connectivity to frontal areas (e.g., FEF, SEF) was observed, which was not evident in **Study III**. In addition, connectivity from V5 reached frontal and parietal areas to a larger extent. In contrast, connectivity from PPC and FEF was less widespread in **Study IV** than in **Study III** but continued to show a fronto-parietal focus for both seed regions. In **Study V**, results (in the LS control group) were even more widespread than in **Study IV** from all seed regions, particularly from LGN. However, this result should be interpreted with caution

as LGN is a small structure (M. Li et al., 2012) and it cannot ultimately be ruled out that the seed spheres positioned at putative LGN also covered other parts of the thalamus. In general, more distributed connectivity observed in **Studies IV** and **V** might result from different statistical designs and greater power compared to **Study III**, as the low and high target velocity conditions were analysed jointly.

The findings obtained in **Studies III–V** for functional connectivity during SPEM highlight the remarkable interplay of the brain areas underlying SPEM. As expected, early components of the visual stream, such as LGN and V1, work closely together (Nassi & Callaway, 2009). Interestingly, however, they also showed connectivity to areas higher in the oculomotor hierarchy, such as FEF and PPC, in line with a previous investigation of task-dependent connectivity during attentional tasks (Griffis, Elkhetali, Burge, Chen, & Visscher, 2015). Of note, observations of increased gPPI connectivity between brain areas do not necessarily imply a direct causal influence of one area on another nor give insight into the direction of effects (O'Reilly et al., 2012). Therefore, the reported findings might reflect signal propagation along the visual hierarchy, negative feedback loops, or the influence of a common input source (e.g., a third brain area). The specific nature of these connections has to be clarified in future investigations with more precise analysis approaches such as dynamic causal modelling (DCM; Daunizeau, David, & Stephan, 2011; Friston et al., 2019).

The widespread functional interconnections of area V5 were particularly evident in **Studies IV** and **V** and match previous findings (C. M. Taylor, Olulade, Luetje, & Eden, 2018; Zeki, 2015). Based on the available evidence, it is clear that V5 is not only responsible for processing motion (Barton, Sharpe, & Raymond, 1996; Chawla et al., 1999) but that – in interaction with other areas – it is also involved in higher-order processes, including transformation between space coordinate systems and from sensory to motor signals (Kimmig et al., 2008). The claim that V5 additionally receives and processes extraretinal information is supported by evidence on three levels: (1) V5 activity is modulated by attentional input from PPC (Acs & Greenlee, 2008; Friston & Büchel, 2000), (2) V5 subregions respond more strongly during SPEM than during pure motion processing despite smaller retinal image motion (Barton, Simpson, et al., 1996), and (3) V5 subregions can be active without motion input (Dukelow et al., 2001). Our findings of close coupling between V5 and other components in and outside the SPEM network fit well with that line of reasoning.

The broad connectivity patterns from FEF and PPC found in **Study III** and replicated to a lesser extent in **Studies IV** and **V** parallel what has been found for these regions at rest (Bueichekú et al., 2015; Hutchison et al., 2012). In addition, the exceptionally close interplay of frontal (e.g., FEF) and parietal (e.g., PPC) brain areas during SPEM found in our studies echoes findings from cognitive tasks involved in attention (Corbetta, Shulman, Miezin, & Petersen, 1995; Markett et al., 2014; Thiebaut de Schotten et al., 2011). Similarly, both FEF and PPC have been associated with attentional processes during SPEM (Baumann & Greenlee, 2009; Jin et al., 2021; Ohlendorf et al., 2007). Consequently, it is reasonable to assume that the allocation of attentional resources during SPEM is controlled by the

functional interplay of FEF and PPC, which should be further corroborated by experimental findings. Other functions attributed to FEF and PPC are dynamic gain control of retinal and extraretinal signals (Gagnon et al., 2006; Ono, 2015) for the former and processing for target velocity relative to a frame of reference (Ohlendorf et al., 2010) for the later. These functions are inherently connectionist, reflecting the integration of information of different types. While our results are compatible with these views, our methodological approaches do not allow us to draw more precise conclusions on how the SPEM network supports these functions.

FEF showed enhanced connectivity to DLPFC during SPEM, an area not typically involved in standard SPEM tasks. Instead, BOLD response in DLPFC is usually only found in tasks requiring higher cognitive effort, e.g., when the target is briefly blanked (Kawawaki et al., 2006; Lencer et al., 2004; Nagel et al., 2006; Nagel et al., 2008). Connectivity between these areas points to a more intricate interplay during SPEM with a time course not simply represented by the boxcar function of the task (O'Reilly et al., 2012).

In summary of this section, the evidence presented here clearly substantiates earlier findings concerning the reliability of SPEM performance outcomes and the identification of areas involved in SPEM. In addition, new insights into the close interplay of these areas were presented. From our findings, it can be concluded that gPPI analyses are potent tools for studying functional connectivity of the oculomotor system. The results presented here call for a rethinking of the traditional approach of functional specialisation in the oculomotor system and prompt a transition towards a broader perspective of functional integration, in which the functional roles of specific areas are defined by their interconnections (Daunizeau et al., 2011).

4.1.2 The background effect

The so-called background effect refers to the degradation of SPEM performance in the presence of a structured background (see 1.4.1). In this dissertation, three studies were presented reporting data on this effect. Crucially and remarkably, the effect was found in all three publications (**Studies I, II,** and **IV**) for the primary outcome measure SPEM gain with large effect sizes (η_p^2 up to 0.72). **Studies I** (see Supplementary Material of the corresponding publication) and **IV** additionally reported results for catch-up saccade rate and RMSE. A large background effect was found for RMSE in **Study I** but not in **Study IV**. For catch-up saccade rate, the pattern of results was reversed: there was a large background effect in **Study IV** but no significant effect in **Study I** (as in Meyhöfer et al., 2019). Overall, these findings indicate that the background effect is highly robust for SPEM gain, which is well in line with previous evidence (e.g., Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Kaufman & Abel, 1986; Meyhöfer et al., 2019). However, the effect might not be as robust for other

outcomes of SPEM. A possible explanation for this pattern of results could be that performance degradation occurs mainly in the velocity domain of SPEM, primarily captured by SPEM gain. This claim is supported by the fact that in **Study IV**, exploratory data analyses found larger position error in the horizontal than in the vertical domain (data not shown). Vertically, background stimuli might even guide eye movements by serving as a visual barrier (Eggert et al., 2009; Ladda et al., 2007). This interpretation is also compatible with the inconsistent effect on catch-up saccade rate. While the need for compensatory saccades is increased with increasing velocity error, compensation does not necessarily have to occur in terms of increased saccade rate. Rather, catch-up saccades might be generated at the same rate but with larger amplitudes in the background condition, which should be further investigated in the future.

The reliability of the background effect was investigated in **Study I**. While this effect was found in virtually every participant, there were substantial individual differences between participants. The resulting reliability indices were good to excellent for all target velocity conditions. Test-retest reliabilities were descriptively higher for the longer version of the task (Cicchetti, 1994), and split-half reliabilities were higher at T2 than at T1. Comparing these reliabilities to those of difference measures in other cognitive tasks, it is apparent that the SPEM outcomes performed considerably better, suggesting that the so-called reliability paradox does not necessarily extend to oculomotor tasks (Hedge et al., 2018). This divergence might be explained by better ecological validity, lower task impurity, and less influence of response biases (Burgess et al., 2006; Draheim et al., 2019; Miller & Ulrich, 2013) in SPEM tasks compared to standard cognitive tasks. **Study I** thus provided the foundation for all future studies on the correlation of SPEM task effects and other outcomes, thereby following recent recommendations for sound scientific practice when presenting results of cognitive tasks (Parsons et al., 2019).

The neural mechanisms of the background effect were investigated in **Study IV.** Based on previous findings from fMRI and lesion studies, increased activity in parietal and frontal brain areas was expected. Consistent with this preregistered hypothesis, higher BOLD response in the conditions with compared to without a stationary background was found across almost the entire SPEM network. BOLD response was particularly strong in clusters encompassing occipital and parietal cortex. In addition, increased BOLD response was found in LGN, SEF, and FEF. Increased BOLD in early visual areas is not surprising, given the higher visual input of the background condition (Tootell et al., 1998). Findings in parietal cortex were widespread, which is in good agreement with what was expected based on previous findings (Lawden et al., 1995; Ohlendorf et al., 2010), underlining the notion that PPC might be relevant in processing target velocity relative to a frame of reference (Ohlendorf et al., 2010).

A particularly intriguing finding was the increased BOLD response in the background conditions in medial FEF. Based on our findings and results from the saccade literature, a specific functional specialisation of the FEF subregions during SPEM can be proposed. We argue that lateral FEF are

implicated with the more automatic motor aspects of SPEM, whereas medial FEF are involved in the more demanding cognitive control of SPEM, similar to a division of roles suggested for the control of saccadic eye movements (Cieslik et al., 2016; McDowell et al., 2008).

Crucially, there were no differences in connectivity between the background conditions. This finding is surprising at first sight since the connectivity maps for the simple SPEM contrast were very strong. However, it cannot be ruled out that statistical power was too low to detect differences in terms of connectivity (O'Reilly et al., 2012).

The background effect was observed behaviourally with a very large effect size in **Study II**. However, it was not influenced by nicotine which is not consistent with a previous investigation from our group that found an interaction of drug and background conditions indicative of a reduced background effect under nicotine compared to placebo (Meyhöfer et al., 2019). Therefore, our results cannot support previous claims that nicotine improves SPEM performance, particularly in the presence of background distractors, by enhancing attentional filtering or facilitating attentional control (Hahn, 2015; Meyhöfer et al., 2019). However, the discrepancy between our and the previous study should also be interpreted in the light of the absence of a main effect of nicotine discussed in 4.1.5.

4.1.3 The velocity effect

With increasing target velocities, SPEM performance accuracy declines, a phenomenon referred to as the velocity effect (e.g., Collewijn & Tamminga, 1984; Lisberger et al., 1981; Meyhöfer et al., 2019; Nagel et al., 2008). Strikingly, this effect was observed in all five publications integrated into this dissertation with large effect sizes (η^2_p up to 0.95, **Study IV**), highlighting the remarkable consistency of SPEM performance decreases with faster targets across different task designs and contexts. Of note, we found the effect in all dependent variables investigated here, i.e., in SPEM gain (**Studies I–V**), catch-up saccade rate (**Studies I, IV**), total saccade rate (**Studies III, V**), and RMSE (**Studies I, III–V**).

The reliabilities of the individual velocity effect (performance difference between the slowest and fastest target conditions) were determined in **Study I**. They were fair to excellent across all reliability types and for both background conditions. Test-retest reliabilities were descriptively higher for the longer version of the task, and split-half reliabilities were higher at T2 than at T1. Coinciding with the results of the background effect, these results imply that the reliability paradox (Hedge et al., 2018) does not necessarily apply to SPEM velocity effects. Therefore, these effects can be regarded as well suited for studying correlations with other outcomes such as schizotypal personality.

Neural correlates of the velocity effect were examined in **Studies III–V.** Echoing the results on the behavioural level, striking consistency across studies was obtained despite different target velocities and amplitudes. All three studies found higher BOLD response with faster compared to slower

targets in clusters in visual cortex surrounding visual area V1. In **Study IV**, there was an additional small cluster in left lateral FEF. Although these findings are all remarkably similar, they differ from previous investigations (Nagel et al., 2008; Nagel et al., 2012) that reported more widespread activations with faster targets. Of note, these broader activations encompassing V1, V5, lateral intraparietal cortex, lateral FEF, SEF, thalamus, putamen, and cerebellum were obtained with a wider velocity range (see 4.2), shorter targets more suitable to study SPEM initiation and regression analyses, impairing direct comparison with our statistical design. A systematic comparison of task configurations with different velocity patterns has yet to be realised.

From our findings, we can infer that processing of higher target velocities is associated with increased BOLD response in visual cortex, likely due to greater retinal slip (Ilg & Thier, 1996) as the SPEM system cannot fully meet the higher demands and lags behind the target. At the same time, higher cortical areas do not necessarily respond with stronger activity apart from left lateral FEF, which was significant in only one study. Thus, with target velocities in the medium range as employed in the studies here, the SPEM system does not appear to operate according to a more-is-more principle outside primary visual areas. Rather, once the system is turned on, it seems to work at similar levels of intensity even when faster targets place objectively higher demands on the system. The small cluster in left lateral FEF in **Study IV** and findings from additional analyses with lower statistical thresholds reported in the supplementary material of the same study (also evident but not reported in **Studies III** and **V**), however, imply that there might be very small BOLD increases also in higher areas that do not survive correction for multiple testing. Another explanation for our results is that neural mechanisms of the SPEM system are not only expressed in simple linear dependencies. Instead, certain areas might exhibit a non-linear association with target velocity, such as an inverted-U-shaped pattern that cannot be captured with our limited target velocity range (Chawla et al., 1999). An alternative line of argument would be that processing faster target velocity is accompanied by a change in functional connectivity. However, our findings from the gPPI analyses in **Studies III–V** did not provide evidence for this hypothesis. Despite the large effects in the simple task contrasts, no connectivity differences were observed between conditions with faster and slower targets in any of the three studies. While this might be explained by a lack of statistical power (O'Reilly et al., 2012), it could also reflect that the response to faster targets is simply not accompanied by a change in functional connectivity. Using target velocity conditions with a larger difference (e.g., 0.2 Hz and 0.6 Hz) could help uncover the mechanisms behind the velocity effect in the future.

The velocity effect was not influenced by nicotine (**Study II**) which is in contrast to a previous study that reported drug × velocity interactions, indicating a steeper reduction in catch-up saccade rate with nicotine compared to placebo at higher vs. lower target velocity (Meyhöfer et al., 2019). Again, these results must be considered in the context of the missing main effect of nicotine discussed below (4.1.5).

Comparing the velocity effect in participants with low and high schizotypy and schizophrenia spectrum disorders did not yield group differences at the behavioural or neural levels (**Study V)**. These findings imply that SPEM deficits in schizophrenia might not primarily rely on difficulties in processing target velocity. However, a prior study found altered neural response in a distributed network in response to SPEM with different target velocities in patients with schizophrenia compared to controls (Nagel et al., 2012). In contrast, there were no differences regarding the velocity effect at the neural level for schizotypy (Meyhöfer et al., 2015), in line with our finding in **Study V**. The fact that, at the behavioural level, we only observed a small deficit for one of three variables (see 4.1.6) hinders the interpretation of the non-findings at the neural level. Hence, our assumption that altered velocity processing is not the main reason for SPEM deficits in schizophrenia spectrum disorders must remain speculative. Previous findings suggest that various mechanisms, including impaired prediction, sensorimotor transformation, and motion processing (e.g., Chen, 2003; Hong et al., 2008; Trillenberg et al., 2017), are jointly responsible for these deficits (see 1.6.3).

4.1.4 Background and velocity interactions

Studies I, II, and **IV** additionally explored interactions between the background and velocity conditions. For SPEM gain, there were significant interactions in **Studies I** and **II**, indicating larger background effects at higher target velocities, in line with previous evidence (Hutton et al., 2000; Meyhöfer et al., 2019). This pattern was not found in **Study IV**. For RMSE, there was a significant interaction in **Study I**, showing higher RMSE in the background conditions at the intermediate and faster target velocity but not at the slowest target velocity. The significant interaction found in **Study I** for catch-up saccade rate indicated that there were more catch-up saccades in the background condition only at the intermediate target velocity but not at higher or lower target velocity. In **Study IV**, no significant interactions for any dependent variables were obtained.

These results underline that SPEM gain is not only the most reliable SPEM outcome measure but also the one that is most sensitive to task effects (see 4.1.1, 4.1.2, 4.1.3). Following additive factors logic (Sternberg, 2001), it can be inferred that background and target velocity processing partially relies on the same underlying resource to guide eye movements. As the effect was most robust in SPEM gain, which primarily reflects velocity information, it could be speculated that velocity perception is impeded both by background stimuli and faster targets (Raymond, Shapiro, & Rose, 1984). An alternative interpretation is that processing of background and target velocity both rely on limited attentional resources (Souto & Kerzel, 2021). The findings in **Study IV** did not help to elucidate the neural mechanisms of the background × velocity interactions. These should be explored in the future with larger samples.

4.1.5 Molecular mechanisms of SPEM

Previous studies on the effects of nicotine on SPEM revealed a heterogeneous picture with positive, negative, and null results (e.g., Meyhöfer et al., 2019; Schmechtig et al., 2013; Thaker et al., 1991). One aim of **Study II** was to explain these discrepancies with a pharmacogenetic approach. Specifically, the VNTR polymorphism in the *SLC6A3* gene coding for the DAT was identified as a candidate gene to explain this heterogeneity due to its hypothesised effects on dopamine neurotransmission. Nicotine was administered to a large sample of participants stratified for their VNTR genotype (9R-carriers vs. 10R-homozygotes), and SBR was assessed as a non-invasive and indirect measure of striatal dopamine function (Jongkees & Colzato, 2016). However, neither nicotine nor genotype had a significant effect on SPEM performance. More importantly, the two factors did not interact as had been hypothesised based on previous literature (e.g., Brewer et al., 2015; Franklin et al., 2011; see also 1.5.3). The moderated mediation model testing whether SBR acts as a mediator of the drug effect on SPEM and its influence by genotype was also not significant. The null effects of nicotine and genotype and their interaction were further supported by Bayesian analyses. However, significant drug effects on subjective experience and heart rate and the fact that participants identified the administered substance above chance level speak for the validity of our approach.

The attempt made in **Study II** to explain parts of the inconsistencies found in previous studies with a candidate gene approach focusing on dopamine neurotransmission thus proved unsuccessful. However, previous findings of genotype-dependent drug effects were primarily – but not exclusively (Millar et al., 2011) – obtained in samples with substance abuse disorders or nicotine dependency (e.g., Brewer et al., 2015; Franklin et al., 2009; Gelernter et al., 1994). This observation may lead to the speculation that the hypothesised pattern can be found only in smokers. Moreover, future studies might benefit from measuring dopamine activity using methods other than SBR, e.g., by assessing DAT availability in vivo with SPECT or PET (e.g., Kasparbauer et al., 2015).

Taken together, while the results obtained in **Study I** generally support the utility of SPEM in pharmacological and genetic studies, the findings from **Study II** did not help to decipher the molecular mechanisms underlying SPEM. Given the large body of previous evidence (see 1.5.2), it would be premature to conclude from our findings that nicotine does not affect SPEM performance in healthy non-smokers at all. Instead, the findings obtained here are another piece of evidence adding to the heterogeneous overall picture. Clearly, this calls for more systematic, large-scale experimental studies and meta-analyses focusing on the effects of nicotine on SPEM with different dosages, task designs, and in different populations (deprived and satiated smokers, non-smokers, patients with schizophrenia spectrum and other psychiatric disorders).

4.1.6 SPEM in the schizophrenia spectrum

Deficits in SPEM performance are among the most-replicated findings in schizophrenia (O'Driscoll & Callahan, 2008) and were also reported in other psychotic disorders (e.g., Campana et al., 1998; Lencer et al., 2010; Lencer et al., 2015) and in individuals scoring high on schizotypy (e.g., Gooding et al., 2000; Smyrnis et al., 2007). In **Study V**, SPEM performance and its neural correlates were investigated in patients with ROP and compared to high and low scorers on schizotypy. At the behavioural level, we obtained a significant group effect, indicating that patients with ROP and individuals with LS differed in RMSE. However, this effect was small and did not survive correction for multiple analyses. In a cumulative scientific process, a single non-replication does not necessarily refute previous evidence (Shrout & Rodgers, 2018), especially not in this case of such a strong prior research record synthesised in meta-analyses (Diefendorf & Dodge, 1908; Lencer et al., 2004; Levy et al., 2010; O'Driscoll & Callahan, 2008). Instead, some methodological considerations might help to explain this mismatch. Among these are diagnostic heterogeneity in the ROP group (Lencer et al., 2015), relatively low performance in the LS group (although reasons for this are unclear), and low cut-offs to assign an individual to the high schizotypy groups (but note previous investigations that did identify deficits with the same or even less strict cut-offs, Faiola et al., 2020; Koychev et al., 2016; Meyhöfer et al., 2017). In addition, some self-selection may have occurred as patients with severe symptoms might not have agreed to participate in a study with a potentially distressing MRI scan.

There were no significant group differences for the standard mass-univariate BOLD analyses nor the respective gPPI analyses. However, machine learning analyses trained on the ROP and LS controls were significant for one seed region (right FEF). The abnormal functional connectivity from FEF is in line with what has been reported before (Krishna et al., 2014), but it is also much more subtle than what might have been expected. Analyses of decision scores revealed that individuals with high positive and negative schizotypy were classified between ROP and LS individuals at the descriptive level, underscoring the existence of a continuum from healthy individuals with low schizotypy to individuals with high schizotypy to those with full-blown schizophrenia (Allardyce et al., 2007; van Os et al., 2009).

Overall, our results were not in line with our hypotheses, but they point to the general practicality of machine learning and connectivity methods for studying oculomotor deficits in the schizophrenia spectrum. Crucially, these methods allow us to uncover additional information about the brain, which might not be evident in mass-univariate analyses of regional brain activation (Dwyer et al., 2018; Gerchen et al., 2014; Madsen et al., 2018). Therefore, results obtained with these methods are compatible with the dysconnectivity approach to explaining schizophrenia pathophysiology (Friston et al., 2016).

4.2 Limitations

Some limitations should be considered when interpreting the results presented in this dissertation. First, the background effect was studied by comparing SPEM performance in conditions with and without a stationary structured background (**Studies I, II,** and **IV**). Of note, with this approach, the specific mechanisms involved in the background effect at the cognitive level cannot be disentangled. More precisely, whether the observed results are due to higher visual content, enhanced recruitment of attentional processes, inhibition of background stimuli, or a combination of these or other processes cannot be determined. Unravelling the specific mechanisms would require more elaborate study designs (Goettker et al., 2020; Ohlendorf et al., 2010).

A second yet related concern is that the background stimuli used in **Studies I, II**, and **IV** are highly artificial. For example, other studies examined SPEM performance to motion stimuli in dynamic film scenes (Agtzidis, Meyhöfer, Dorr, & Lencer, 2020; Silberg et al., 2019) and compared it to SPEM with blank backgrounds (Goettker et al., 2020). As it has been shown that the SPEM system is not only disturbed by background stimuli but that it can even use visual context information to improve accuracy (Eggert et al., 2009; Goettker et al., 2020; Ladda et al., 2007), the question of how different background stimuli influence SPEM performance has become even more interesting. The results presented in this dissertation should be regarded as the groundwork for future studies employing a broader and more naturalistic range of background stimuli to investigate the underlying cognitive and neural processes.

Third, for economic reasons, only a limited number of target velocities was presented. Especially in **Studies III–V**, it would have been interesting to examine a more extensive velocity range to map the neural basis of the velocity effect more precisely. For example, with a larger range it would also have been possible to examine whether BOLD response in V5 follows an inverted U-shape when performing SPEM (Chawla et al., 1999). Examining more target velocities would also have been valuable for exploring brain response outside the visual cortex in more detail (Nagel et al., 2008).

Last, we likely did not have sufficient statistical power to adequately analyse brain-behaviour relationships, although some preliminary findings were obtained in **Study IV**. These findings, however, did not survive correction for multiple analyses, which is why they should be interpreted with caution. Recently, it has been suggested that research questions focusing on correlations between brain structure or function and complex cognitive traits require large samples of several thousand participants (Marek et al., 2022). While this claim has subsequently been criticised and corrected to lower numbers when certain conditions are met, even less conservative estimations propose large samples of more than 200 participants (DeYoung et al., 2022). These sample sizes are still significantly larger than the ones used in this dissertation. Of note, however, our studies were not primarily designed to detect these correlations. Rather, our sample sizes were chosen to detect BOLD response to SPEM

stimuli as had been observed in previous studies, to detect the background and velocity effects at the behavioural and neural levels, and to detect – for the first time – functional connectivity of the SPEM network. Sufficient power for these aims was ensured by a priori power analyses and choosing larger sample sizes than prior SPEM BOLD studies.

4.3 Future research

In addition to the abovementioned suggestions for future research (see 4.1) and those derived from the limitations (see 4.2), I would like to propose four specific approaches that could be adopted in the future to substantially complement my own findings.

Studies III–V provided the groundwork for ensuing studies on the specific interplay of the SPEM network components. Exploring how these brain areas work together with more intricate analysis approaches might be interesting. Here, it could be worth exploring PPI whole-brain parcellation-based analyses that do not rely on the prior definition of seed regions (Gerchen et al., 2014). Even more interestingly, DCM should be applied to SPEM data to compare alternative models and to study effective connectivity (Friston, 2011; Friston et al., 2019).

While **Study II** did not provide conclusive evidence of how nicotine might influence SPEM in healthy individuals, revisiting nicotine effects in patients with schizophrenia may be worth further investigation, particularly when methodological deficits from prior studies are overcome. Performance-enhancing effects might only become evident in individuals with low baseline performance paralleling findings in other cognitive domains (Babin et al., 2011; Barr et al., 2008; Kumari & Postma, 2005; Smith et al., 2006). Seminal studies on SPEM point to potential improvements in performance under nicotine in samples of patients with schizophrenia (Avila et al., 2003; Dépatie et al., 2002; Olincy et al., 1998; Sherr et al., 2002; Tregellas et al., 2005), but note methodological deficits in these studies summarised in 1.5.2. In addition, it has yet to be investigated whether improvements in SPEM performance under nicotine are mediated by the reduction of hippocampal dysfunction observed in schizophrenia, as has been hypothesised but not explicitly tested in the past (Tanabe et al., 2006; Tregellas et al., 2004; Tregellas et al., 2005). Future studies should investigate these potential mechanisms by following state-of-the-art guidelines for psychopharmacological research, including sufficient power, double-blinding, placebo-control, and randomisation (Karpouzian et al., 2019).

In **Study IV**, evidence was obtained for functional specialisation of medial and lateral FEF subregions during SPEM (see 4.1.2). In addition, in **Study V**, FEF was the only seed region for which we found a significant classifier to differentiate patients with schizophrenia spectrum disorders and healthy controls. Both findings underscore the extraordinary role of FEF in SPEM guidance. However, as the effect in **Study V** did not survive correction for multiple analyses, and the interpretation of the

Study IV results was realised post hoc, future preregistered studies should focus on unravelling the specific roles assumed by FEF subregions during SPEM in healthy and psychiatric groups. This aim could be achieved with connectivity analyses (gPPI or DCM) with smaller seed regions in these subregions and specific tasks designed to tap the processes ascribed to the medial and lateral regions (see 4.1.2). For example, it can be explored whether lateral FEF shows more SPEM-related functional connectivity to areas associated with the motor aspects of SPEM, and medial FEF to areas associated with higher cognitive functions, such as DLPFC, paralleling results from the saccade literature (Cieslik et al., 2016).

There is preliminary evidence that background stimuli might affect patients with schizophrenia to a larger extent than healthy controls. In two early studies, SPEM performance of patients with schizophrenia was affected by a striped background only at higher but not lower target velocity (Yee et al., 1987), and SPEM was disturbed in patients with schizophrenia compared to healthy controls only in light but not in dark background conditions (Pivik, Bylsma, & Cooper, 1988). However, in a more recent study, patients with schizophrenia were not differentially affected by background stimuli compared to healthy controls (Hutton et al., 2000). For the velocity effect, the pattern of results is also inconsistent. While our research (**Study V**) did not find altered velocity effects in schizophrenia and schizotypy, another study did so (Nagel et al., 2012, see also 4.1.3). To evaluate if and how background and target velocity effects are altered along the schizophrenia spectrum, the individual task effects could be correlated with overall or specific scores on the schizotypy dimensions in the future. The reliability indices obtained in **Study I** laid the necessary foundations for such investigations.

4.4 Conclusion

SPEM performance is less accurate when the SPEM system is confronted with structured backgrounds and faster target velocities. The findings of the studies presented here highlight the broad applicability of these task effects in individual difference research due to their reliability and point to complex mechanisms supporting SPEM function in these environments. While SPEM deficits in schizophrenia were much more subtle in the data presented in **Study V** than in previous investigations, analyses of functional connectivity proved valuable for studying the neural mechanisms of SPEM in healthy individuals and patients with schizophrenia. Overall, a broad picture of the SPEM system was provided, including insights into basic molecular mechanisms, behavioural effects, neural systems, and clinical applications (Siebner et al., 2009), thereby expanding previous knowledge but also unveiling new questions. Therefore, I can only conclude with the remarks of Stephen Lisberger, one of the most influential SPEM researchers: “The apparent simplicity of the behavior [SPEM] belies its interesting neurobiological complexity” (Lisberger, 2015, p. 448). There is still so much more to explore.

References

Abe, H., Tani, T., Mashiko, H., Kitamura, N., Hayami, T., Watanabe, S., . . . Ichinohe, N. (2018). Axonal projections from the middle temporal area in the common marmoset. *Frontiers in Neuroanatomy*, *12*(89), 1–14. https://doi.org/10.3389/fnana.2018.00089

Acs, F., & Greenlee, M. W. (2008). Connectivity modulation of early visual processing areas during covert and overt tracking tasks. *NeuroImage*, *41*(2), 380–388. https://doi.org/10.1016/j.neuroimage.2008.02.007

Agtzidis, I., Meyhöfer, I., Dorr, M., & Lencer, R. (2020). Following Forrest Gump: Smooth pursuit related brain activation during free movie viewing. *NeuroImage*, *216*, 116491. https://doi.org/10.1016/j.neuroimage.2019.116491

Allardyce, J., Suppes, T., & van Os, J. (2007). Dimensions and the psychosis phenotype. *International Journal of Methods in Psychiatric Research*, *16*(S1), 34-40. https://doi.org/10.1002/mpr.214

Allen, A. J., Griss, M. E., Folley, B. S., Hawkins, K. A., & Pearlson, G. D. (2009). Endophenotypes in schizophrenia: A selective review. *Schizophrenia Research*, *109*(1-3), 24–37. https://doi.org/10.1016/j.schres.2009.01.016

Allman, A.-A., Ettinger, U., Joober, R., & O'Driscoll, G. A. (2012). Effects of methylphenidate on basic and higher-order oculomotor functions. *Journal of Psychopharmacology*, *26*(11), 1471–1479. https://doi.org/10.1177/0269881112446531

Almeida, N. L., Rodrigues, S. J., Gonçalves, L. M., Silverstein, S. M., Sousa, I. C., Gomes, G. H., . . . Santos, N. A. (2020). Opposite effects of smoking and nicotine intake on cognition. *Psychiatry Research*, *293*, 113357. https://doi.org/10.1016/j.psychres.2020.113357

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR)* (4th ed.). Arlington, VA. https://doi.org/10.1176/appi.books.9780890423349

Amiez, C., & Petrides, M. (2009). Anatomical organization of the eye fields in the human and non-human primate frontal cortex. *Progress in Neurobiology*, *89*(2), 220–230. https://doi.org/10.1016/j.pneurobio.2009.07.010

Aosaki, T., Miura, M., Suzuki, T., Nishimura, K., & Masuda, M. (2010). Acetylcholine-dopamine balance hypothesis in the striatum: An update. *Geriatrics & Gerontology International*, *10*(S1), 148-57. https://doi.org/10.1111/j.1447-0594.2010.00588.x

Armstrong, K. M., & Moore, T. (2007). Rapid enhancement of visual cortical response discriminability by microstimulation of the frontal eye field. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(22), 9499–9504. https://doi.org/10.1073/pnas.0701104104

Arolt, V., Teichert, H.-M., Steege, D., Lencer, R., & Heide, W. (1998). Distinguishing schizophrenic patients from healthy controls by quantitative measurement of eye movement parameters. *Biological Psychiatry*, *44*(6), 448–458. https://doi.org/10.1016/S0006-3223(97)00479-4

Ashby, F. G. (2019). *Statistical analysis of fMRI data* (2nd ed.). Cambridge, Massachussets: MIT Press.

Avila, M. T., Sherr, J. D., Hong, E., Myers, C. S., & Thaker, G. K. (2003). Effects of nicotine on leading saccades during smooth pursuit eye movements in smokers and nonsmokers with schizophrenia. *Neuropsychopharmacology*, *28*(12), 2184–2191. https://doi.org/10.1038/sj.npp.1300265

Babin, S. L., Hood, A. J., Wassef, A. A., Williams, N. G., Patel, S. S., & Sereno, A. B. (2011). Effects of haloperidol on cognition in schizophrenia patients depend on baseline performance: A saccadic eye movement study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*(7), 1753–1764. https://doi.org/10.1016/j.pnpbp.2011.06.004

Bannon, M. J., Michelhaugh, S. K., Wang, J., & Sacchetti, P. (2001). The human dopamine transporter gene: gene organization, transcriptional regulation, and potential involvement in neuropsychiatric disorders. *European Neuropsychopharmacology*, *11*(6), 449–455. https://doi.org/10.1016/S0924-977X(01)00122-5

Bareš, M., Brázdil, M., Kaňovský, P., Jurák, P., Daniel, P., Kukleta, M., & Rektor, I. (2003). The effect of apomorphine administration on smooth pursuit ocular movements in early Parkinsonian patients. *Parkinsonism & Related Disorders*, *9*(3), 139–144. https://doi.org/10.1016/S1353-8020(02)00015-9

Bargary, G., Bosten, J. M., Goodbourn, P. T., Lawrance-Owen, A. J., Hogg, R. E., & Mollon, J. D. (2017). Individual differences in human eye movements: An oculomotor signature? *Vision Research*, *141*, 157–169. https://doi.org/10.1016/j.visres.2017.03.001

Barnes, G. R. (1993). Visual-vestibular interaction in the control of head and eye movement: The role of visual feedback and predictive mechanisms. *Progress in Neurobiology*, *41*(4), 435–472. https://doi.org/10.1016/0301-0082(93)90026-O

Barnes, G. R. (2008). Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition*, *68*(3), 309–326. https://doi.org/10.1016/j.bandc.2008.08.020

Barnes, G. R., & Crombie, J. W. (1985). The interaction of conflicting retinal motion stimuli in oculomotor control. *Experimental Brain Research*, *59*(3), 548–558. https://doi.org/10.1007/BF00261346

Barr, R. S., Culhane, M. A., Jubelt, L. E., Mufti, R. S., Dyer, M. A., Weiss, A. P., . . . Evins, A. E. (2008). The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology*, *33*(3), 480–490. https://doi.org/10.1038/sj.npp.1301423

Barton, J. J., Sharpe, J. A., & Raymond, J. E. (1996). Directional defects in pursuit and motion perception in humans with unilateral cerebral lesions. *Brain*, *119*(5), 1535–1550. https://doi.org/10.1093/brain/119.5.1535

Barton, J. J., Simpson, T., Kiriakopoulos, E., Stewart, C., Crawley, A., Guthrie, B., . . . Mikulis, D. (1996). Functional MRI of lateral occipitotemporal cortex during pursuit and motion perception. *Annals of Neurology*, *40*(3), 387–398. https://doi.org/10.1002/ana.410400308

Baumann, O., & Greenlee, M. W. (2009). Effects of attention to auditory motion on cortical activations during smooth pursuit eye tracking. *PloS One*, *4*(9), e7110. https://doi.org/10.1371/journal.pone.0007110

Benowitz, N. L. (2010). Nicotine addiction. *The New England Journal of Medicine*, *362*(24), 2295–2303. https://doi.org/10.1056/NEJMra0809890

Benson, P. J., Beedie, S. A., Shephard, E., Giegling, I., Rujescu, D., & St Clair, D. (2012). Simple viewing tests can detect eye movement abnormalities that distinguish schizophrenia cases from controls with exceptional accuracy. *Biological Psychiatry*, *72*(9), 716–724. https://doi.org/10.1016/j.biopsych.2012.04.019

Bentall, R. P., Claridge, G. S., & Slade, P. D. (1989). The multidimensional nature of schizotypal traits: A factor analytic study with normal subjects. *The British Journal of Clinical Psychology*, *28*(4), 363–375. https://doi.org/10.1111/j.2044-8260.1989.tb00840.x

Berman, R. A., Colby, C. L., Genovese, C. R., Voyvodic, J. T., Luna, B., Thulborn, K. R., & Sweeney, J. A. (1999). Cortical networks subserving pursuit and saccadic eye movements in humans: An FMRI study. *Human Brain Mapping*, *8*(4), 209–225. https://doi.org/10.1002/(sici)1097-0193(1999)8:4<209::aid-hbm5>3.0.co;2-0

Berryhill, M. E., Chiu, T., & Hughes, H. C. (2006). Smooth pursuit of nonvisual motion. *Journal of Neurophysiology*, *96*(1), 461–465. https://doi.org/10.1152/jn.00152.2006

Bertrand, D., & Wallace, T. L. (2020). A review of the cholinergic system and therapeutic approaches to treat brain disorders. *Current Topics in Behavioral Neurosciences*, *45*, 1–28. https://doi.org/10.1007/7854_2020_141

Bogdan, R., Carré, J. M., & Hariri, A. R. (2012). Toward a mechanistic understanding of how variability in neurobiology shapes individual differences in behavior. *Current Topics in Behavioral Neurosciences*, *12*, 361–393. https://doi.org/10.1007/7854_2011_182

Bogren, M., Mattisson, C., Isberg, P.-E., & Nettelbladt, P. (2009). How common are psychotic and bipolar disorders? A 50-year follow-up of the Lundby population. *Nordic Journal of Psychiatry*, *63*(4), 336–346. https://doi.org/10.1080/08039480903009118

Bonci, A., Bernardi, G., Grillner, P., & Mercuri, N. B. (2003). The dopamine-containing neuron: Maestro or simple musician in the orchestra of addiction? *Trends in Pharmacological Sciences*, *24*(4), 172–177. https://doi.org/10.1016/S0165-6147(03)00068-3

Braff, D. L., Freedman, R., Schork, N. J., & Gottesman, I. I. (2007). Deconstructing schizophrenia: An overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin*, *33*(1), 21–32. https://doi.org/10.1093/schbul/sbl049

Brewer, A. J., Nielsen, D. A., Spellicy, C. J., Hamon, S. C., Gingrich, J., Thompson-Lake, D. G., . . . La Garza, R. de (2015). Genetic variation of the dopamine transporter (DAT1) influences the acute subjective responses to cocaine in volunteers with cocaine use disorders. *Pharmacogenetics and Genomics*, *25*(6), 296–304. https://doi.org/10.1097/FPC.0000000000000137

Bucher, S. F., Dieterich, M., Seelos, K. C., & Brandt, T. (1997). Sensorimotor cerebral activation during optokinetic nystagmus. *Neurology*, *49*(5), 1370–1377. https://doi.org/10.1212/WNL.49.5.1370

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin*, *35*(2), 383–402. https://doi.org/10.1093/schbul/sbn135

Bueichekú, E., Ventura-Campos, N., Palomar-García, M.-Á., Miró-Padilla, A., Parcet, M.-A., & Ávila, C. (2015). Functional connectivity between superior parietal lobule and primary visual cortex "at rest" predicts visual search efficiency. *Brain Connectivity*, *5*(8), 517–526. https://doi.org/10.1089/brain.2015.0352

Buizza, A., & Schmid, R. (1986). Velocity characteristics of smooth pursuit eye movements to different patterns of target motion. *Experimental Brain Research*, *63*(2), 395–401. https://doi.org/10.1007/BF00236858

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M.-A., Dawson, D. R., . . . Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*, *12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Burke, M. R., & Barnes, G. R. (2008). Brain and behavior: A task-dependent eye movement study. *Cerebral Cortex*, *18*(1), 126–135. https://doi.org/10.1093/cercor/bhm038

Bzdok, D., & Meyer-Lindenberg, A. (2018). Machine learning for precision psychiatry: Opportunities and challenges. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, *3*(3), 223–230. https://doi.org/10.1016/j.bpsc.2017.11.007

Cachope, R., Mateo, Y., Mathur, B. N., Irving, J., Wang, H.-L., Morales, M., . . . Cheer, J. F. (2012). Selective activation of cholinergic interneurons enhances accumbal phasic dopamine release: Setting the tone for reward processing. *Cell Reports*, *2*(1), 33–41. https://doi.org/10.1016/j.celrep.2012.05.011

Calkins, M. E., Iacono, W. G., & Curtis, C. E. (2003). Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *49*(2), 139–146. https://doi.org/10.1016/S0167-8760(03)00101-6

Calkins, M. E., Iacono, W. G., & Ones, D. S. (2008). Eye movement dysfunction in first-degree relatives of patients with schizophrenia: A meta-analytic evaluation of candidate endophenotypes. *Brain and Cognition*, *68*(3), 436–461. https://doi.org/10.1016/j.bandc.2008.09.001

Campana, A., Gambini, O., & Scarone, S. (1998). Delusional disorder and eye tracking dysfunction: preliminary evidence of biological and clinical heterogeneity. *Schizophrenia Research*, *30*(1), 51–58. https://doi.org/10.1016/S0920-9964(97)00106-0

Campion, D., Thibaut, F., Denise, P., Courtin, P., Pottier, M., & Levillain, D. (1992). SPEM impairment in drug-naive schizophrenic patients: Evidence for a trait marker. *Biological Psychiatry*, *32*(10), 891–902. https://doi.org/10.1016/0006-3223(92)90178-3

Carney, C. P., Jones, L., & Woolson, R. F. (2006). Medical comorbidity in women and men with schizophrenia: A population-based controlled study. *Journal of General Internal Medicine*, *21*(11), 1133–1137. https://doi.org/10.1111/j.1525-1497.2006.00563.x

Carpenter, R. (1994). Frontal cortex: Choosing where to look. *Current Biology*, *4*(4), 341–343. https://doi.org/10.1016/S0960-9822(00)00074-9

Caspers, S., & Zilles, K. Chapter 3 - Microarchitecture and connectivity of the parietal lobe. In *Handbook of clinical neurology* (Vol. 151, pp. 53–72). https://doi.org/10.1016/B978-0-444-63622-5.00003-6

Castelhano, M. S., & Henderson, J. M. (2008). Stable individual differences across images in human saccadic eye movements. *Canadian Journal of Experimental Psychology = Revue Canadienne De Psychologie Experimentale*, *62*(1), 1–14. https://doi.org/10.1037/1196-1961.62.1.1

Chang, W. C., Wong, C. S. M., Chen, E. Y. H., Lam, L. C. W., Chan, W. C., Ng, R. M. K., . . . Bebbington, P. (2017). Lifetime prevalence and correlates of schizophrenia-spectrum, affective, and other non-affective psychotic disorders in the chinese adult population. *Schizophrenia Bulletin*, *43*(6), 1280–1290. https://doi.org/10.1093/schbul/sbx056

Chawla, D., Buechel, C., Edwards, R., Howseman, A., Josephs, O., Ashburner, J., & Friston, K. J. (1999). Speed-dependent responses in V5: A replication study. *NeuroImage*, *9*(5), 508–515. https://doi.org/10.1006/nimg.1999.0432

Chen, Y. (2003). Processing of global, but not local, motion direction is deficient in schizophrenia. *Schizophrenia Research*, *61*(2-3), 215–227. https://doi.org/10.1016/S0920-9964(02)00222-0

Chen, Y., Levy, D. L., Nakayama, K., Matthysse, S., Palafox, G., & Holzman, P. S. (1999). Dependence of impaired eye tracking on deficient velocity discrimination in schizophrenia. *Archives of General Psychiatry*, *56*(2), 155–161. https://doi.org/10.1001/archpsyc.56.2.155

Chen, Y., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Psychophysical isolation of a motion-processing deficit in schizophrenics and their relatives and its association with impaired smooth pursuit. *Proceedings of the National Academy of Sciences*, *96*(8), 4724–4729. https://doi.org/10.1073/pnas.96.8.4724

Chong, H. Y., Teoh, S. L., Wu, D. B.-C., Kotirum, S., Chiou, C.-F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: A systematic review. *Neuropsychiatric Disease and Treatment*, *12*, 357–373. https://doi.org/10.2147/NDT.S96649

Cicchetti, D. V. (1994). Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment*, *6*(4), 284–290. https://doi.org/10.1037/1040-3590.6.4.284

Cieslik, E. C., Seidler, I., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2016). Different involvement of subregions within dorsal premotor and medial frontal cortex for pro- and antisaccades. *Neuroscience and Biobehavioral Reviews*, *68*, 256–269. https://doi.org/10.1016/j.neubiorev.2016.05.012

Cisler, J. M., Bush, K., & Steele, J. S. (2014). A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *NeuroImage*, *84*, 1042–1052. https://doi.org/10.1016/j.neuroimage.2013.09.018

Claridge, G. (1997). *Schizotypy*. Oxford: Oxford University Press. https://doi.org/10.1093/med:psych/9780198523536.001.0001

Coiner, B., Pan, H., Bennett, M. L., Bodien, Y. G., Iyer, S., O'Neil-Pirozzi, T. M., . . . Stern, E. (2019). Functional neuroanatomy of the human eye movement network: A review and atlas. *Brain Structure and Function*, *224*(8), 2603–2617. https://doi.org/10.1007/s00429-019-01932-7

Collewijn, H., & Tamminga, E. P. (1984). Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *The Journal of Physiology*, *351*(1), 217–250. https://doi.org/10.1113/jphysiol.1984.sp015242

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*(12), e113-25. https://doi.org/10.1016/j.biopsych.2011.03.028

Cools, R., Frank, M. J., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2009). Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *Journal of Neuroscience*, *29*(5), 1538–1543. https://doi.org/10.1523/JNEUROSCI.4467-08.2009

Corbetta, M., Shulman, G. L., Miezin, F. M., & Petersen, S. E. (1995). Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science*, *270*(5237), 802–805. https://doi.org/10.1126/science.270.5237.802

Costa, A., La Fougère, C., Pogarell, O., Möller, H.-J., Riedel, M., & Ettinger, U. (2013). Impulsivity is related to striatal dopamine transporter availability in healthy males. *Psychiatry Research*, *211*(3), 251–256. https://doi.org/10.1016/j.pscychresns.2012.07.011

Costa, A., Riedel, M., Müller, U., Möller, H.-J., & Ettinger, U. (2011). Relationship between SLC6A3 genotype and striatal dopamine transporter availability: A meta-analysis of human single photon emission computed tomography studies. *Synapse*, *65*(10), 998–1005. https://doi.org/10.1002/syn.20927

Dani, J. A., & Bertrand, D. (2007). Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annual Review of Pharmacology and Toxicology*, *47*, 699–729. https://doi.org/10.1146/annurev.pharmtox.47.120505.105214

Daunizeau, J., David, O., & Stephan, K. E. (2011). Dynamic causal modelling: A critical review of the biophysical and statistical foundations. *NeuroImage*, *58*(2), 312–322. https://doi.org/10.1016/j.neuroimage.2009.11.062

De Haas, B., Iakovidis, A. L., Schwarzkopf, D. S., & Gegenfurtner, K. R. (2019). Individual differences in visual salience vary along semantic dimensions. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(24), 11687–11692. https://doi.org/10.1073/pnas.1820553116

Dépatie, L., O'Driscoll, G. A., Holahan, A.-L. V., Atkinson, V., Thavundayil, J. X., Kin, N. N. Y., & Lal, S. (2002). Nicotine and behavioral markers of risk for schizophrenia: A double-blind, placebo-controlled, cross-over study. *Neuropsychopharmacology*, *27*(6), 1056–1070. https://doi.org/10.1016/S0893-133X(02)00372-X

DeRosse, P., & Karlsgodt, K. H. (2015). Examining the psychosis continuum. *Current Behavioral Neuroscience Reports*, *2*(2), 80–89. https://doi.org/10.1007/s40473-015-0040-7

DeYoung, C. G., Sassenberg, T., Abend, R., Allen, T., Beaty, R., Bellgrove, M. A., . . . Wacker, J. (2022). *Reproducible between-person brain-behavior associations do not always require thousands of individuals*. https://doi.org/10.31234/osf.io/sfnmk

Diefendorf, A. R., & Dodge, R. (1908). An experimental study of the ocular reactions of the insane from photographic records. *Brain*, *31*(3), 451–489. https://doi.org/10.1093/brain/31.3.451

Dieterich, M. (1998). Horizontal or vertical optokinetic stimulation activates visual motion- sensitive, ocular motor and vestibular cortex areas with right hemispheric dominance. An fMRI study. *Brain*, *121*(8), 1479–1495. https://doi.org/10.1093/brain/121.8.1479

Dieterich, M., Bense, S., Stephan, T., Yousry, T. A., & Brandt, T. (2003). fMRI signal increases and decreases in cortical areas during small-field optokinetic stimulation and central fixation. *Experimental Brain Research*, *148*(1), 117–127. https://doi.org/10.1007/s00221-002-1267-6

Dieterich, M., Muller-Schunk, S., Stephan, T., Bense, S., Seelos, K., & Yousry, T. A. (2009). Functional magnetic resonance imaging activations of cortical eye fields during saccades, smooth pursuit, and optokinetic nystagmus. *Annals of the New York Academy of Sciences*, *1164*(1), 282–292. https://doi.org/10.1111/j.1749-6632.2008.03718.x

Domino, E. F., Ni, L. S., & Zhang, H. (1997). Effects of tobacco smoking on human ocular smooth pursuit. *Clinical Pharmacology and Therapeutics*, *61*(3), 349–359. https://doi.org/10.1016/S0009-9236(97)90168-5

Draheim, C., Mashburn, C. A., Martin, J. D., & Engle, R. W. (2019). Reaction time in differential and developmental research: A review and commentary on the problems and alternatives. *Psychological Bulletin*, *145*(5), 508–535. https://doi.org/10.1037/bul0000192

Drew, A. S., & van Donkelaar, P. (2007a). The contribution of the human FEF and SEF to smooth pursuit initiation. *Cerebral Cortex*, *17*(11), 2618–2624. https://doi.org/10.1093/cercor/bhl169

Drew, A. S., & van Donkelaar, P. (2007b). The contribution of the human PPC to the orienting of visuospatial attention during smooth pursuit. *Experimental Brain Research*, *179*(1), 65–73. https://doi.org/10.1007/s00221-006-0769-z

D'Souza, M. S., & Markou, A. (2012). Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. *Neuropharmacology*, *62*(3), 1564–1573. https://doi.org/10.1016/j.neuropharm.2011.01.044

Duchowski, A. T. (2017). *Eye tracking methodology: Theory and practice* (3rd ed.). Cham: Springer. https://doi.org/10.1007/978-3-319-57883-5

Dukelow, S. P., DeSouza, J. F., Culham, J. C., van den Berg, A V, Menon, R. S., & Vilis, T. (2001). Distinguishing subregions of the human MT+ complex using visual fields and pursuit eye movements. *Journal of Neurophysiology*, *86*(4), 1991–2000. https://doi.org/10.1152/jn.2001.86.4.1991

Dunkley, B. T., Freeman, T. C. A., Muthukumaraswamy, S. D., & Singh, K. D. (2013). Cortical oscillatory changes in human middle temporal cortex underlying smooth pursuit eye movements. *Human Brain Mapping*, *34*(4), 837–851. https://doi.org/10.1002/hbm.21478

Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual Review of Clinical Psychology*, *14*(1), 91–118. https://doi.org/10.1146/annurev-clinpsy-032816-045037

Eggert, T., Ladda, J., & Straube, A. (2009). Inferring the future target trajectory from visual context: is visual background structure used for anticipatory smooth pursuit? *Experimental Brain Research*, *196*(2), 205–215. https://doi.org/10.1007/s00221-009-1840-3

Eibenberger, K., Ring, M., & Haslwanter, T. (2012). Sustained effects for training of smooth pursuit plasticity. *Experimental Brain Research*, *218*(1), 81–89. https://doi.org/10.1007/s00221-012-3009-8

Estanol, B., Romero, R., & Corvera, J. (1979). Effects of cerebellectomy on eye movements in man. *Archives of Neurology*, *36*(5), 281–284. https://doi.org/10.1001/archneur.1979.00500410059008

Ettinger, U., & Kumari, V. (2019). Effects of nicotine on inhibitory control in humans. In V. R. Preedy (Ed.), *Neuroscience of nicotine: Mechanisms and treatment* (pp. 151–158). London: Elsevier/Academic Press. https://doi.org/10.1016/B978-0-12-813035-3.00019-8

Ettinger, U., Kumari, V., Crawford, T. J., Corr, P. J., Das, M., Zachariah, E., . . . Sharma, T. (2004). Smooth pursuit and antisaccade eye movements in siblings discordant for schizophrenia. *Journal of Psychiatric Research*, *38*(2), 177–184. https://doi.org/10.1016/S0022-3956(03)00105-5

Ettinger, U., Kumari, V., Crawford, T. J., Davis, R. E., Sharma, T., & Corr, P. J. (2003). Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology*, *40*(4), 620–628. https://doi.org/10.1111/1469-8986.00063

Ettinger, U., Kumari, V., Zachariah, E., Galea, A., Crawford, T. J., Corr, P. J., . . . Sharma, T. (2003). Effects of procyclidine on eye movements in schizophrenia. *Neuropsychopharmacology*, *28*(12), 2199–2208. https://doi.org/10.1038/sj.npp.1300286

Ettinger, U., Merten, N., & Kambeitz, J. (2016). Meta-analysis of the association of the SLC6A3 3′-UTR VNTR with cognition. *Neuroscience & Biobehavioral Reviews*, *60*, 72–81. https://doi.org/10.1016/j.neubiorev.2015.09.021

Ettinger, U., Meyhöfer, I., Steffens, M., Wagner, M., & Koutsouleris, N. (2014). Genetics, cognition, and neurobiology of schizotypal personality: A review of the overlap with schizophrenia. *Frontiers in Psychiatry*, *5*, 18. https://doi.org/10.3389/fpsyt.2014.00018

Evans, D. E., & Drobes, D. J. (2009). Nicotine self-medication of cognitive-attentional processing. *Addiction Biology*, *14*(1), 32–42. https://doi.org/10.1111/j.1369-1600.2008.00130.x

Faiola, E., Meyhöfer, I., & Ettinger, U. (2020). Mechanisms of smooth pursuit eye movements in schizotypy. *Cortex*, *125*, 190–202. https://doi.org/10.1016/j.cortex.2019.12.008

Faraone, S. V., Spencer, T. J., Madras, B. K., Zhang-James, Y., & Biederman, J. (2014). Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: A meta-analysis. *Molecular Psychiatry*, *19*(8), 880–889. https://doi.org/10.1038/mp.2013.126

Ferrari, R., Le Novère, N., Picciotto, M. R., Changeux, J. P., & Zoli, M. (2002). Acute and long-term changes in the mesolimbic dopamine pathway after systemic or local single nicotine injections. *The European Journal of Neuroscience*, *15*(11), 1810–1818. https://doi.org/10.1046/j.1460-9568.2001.02009.x

Fonseca-Pedrero, E., Lemos-Giráldez, S., Paino, M., Sierra-Baigrie, S., & Muñiz, J. (2011). Psychotic-like experiences. In R. J. R. Levesque (Ed.), *Encyclopedia of Adolescence* (pp. 2233–2239). New York, NY: Springer New York. https://doi.org/10.1007/978-1-4419-1695-2_294

Fonseca-Pedrero, E., Paino, M., Lemos-Giráldez, S., Sierra-Baigrie, S., & Muñiz, J. (2011). Measurement invariance of the Schizotypal Personality Questionnaire-Brief across gender and age. *Psychiatry Research*, *190*(2-3), 309–315. https://doi.org/10.1016/j.psychres.2011.05.021

Fornito, A., Yücel, M., Patti, J., Wood, S., & Pantelis, C. (2009). Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research*, *108*(1-3), 104–113. https://doi.org/10.1016/j.schres.2008.12.011

Frank, M. J., & Fossella, J. A. (2011). Neurogenetics and pharmacology of learning, motivation, and cognition. *Neuropsychopharmacology*, *36*(1), 133–152. https://doi.org/10.1038/npp.2010.96

Franklin, T. R., Lohoff, F. W., Wang, Z., Sciortino, N., Harper, D., Li, Y., . . . Childress, A. R. (2009). DAT genotype modulates brain and behavioral responses elicited by cigarette cues. *Neuropsychopharmacology*, *34*(3), 717–728. https://doi.org/10.1038/npp.2008.124

Franklin, T. R., Wang, Z., Li, Y., Suh, J. J., Goldman, M., Lohoff, F. W., . . . Childress, A. R. (2011). Dopamine transporter genotype modulation of neural responses to smoking cues: Confirmation in a new cohort: DAT genotype effects on SCs. *Addiction Biology*, *16*(2), 308–322. https://doi.org/10.1111/j.1369-1600.2010.00277.x

Fransson, P. A., Patel, M., Magnusson, M., Berg, S., Almbladh, P., & Gomez, S. (2008). Effects of 24-hour and 36-hour sleep deprivation on smooth pursuit and saccadic eye movements. *Journal of Vestibular Research: Equilibrium & Orientation*, *18*(4), 209–222. https://doi.org/10.3233/VES-2008-18404

Frei, K. (2020). Abnormalities of smooth pursuit in Parkinson's disease: A systematic review. *Clinical Parkinsonism & Related Disorders*, *4*, 100085. https://doi.org/10.1016/j.prdoa.2020.100085

Friston, K. J. (2011). Functional and effective connectivity: A review. *Brain Connectivity*, *1*(1), 13–36. https://doi.org/10.1089/brain.2011.0008

Friston, K. J., Brown, H. R., Siemerkus, J., & Stephan, K. E. (2016). The dysconnection hypothesis (2016). *Schizophrenia Research*, *176*(2-3), 83–94. https://doi.org/10.1016/j.schres.2016.07.014

Friston, K. J., & Büchel, C. (2000). Attentional modulation of effective connectivity from V2 to V5/MT in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(13), 7591–7596. https://doi.org/10.1073/pnas.97.13.7591

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, *6*(3), 218–229. https://doi.org/10.1006/nimg.1997.0291

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience*, *3*(2), 89–97.

Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI time-series revisited. *NeuroImage*, *2*(1), 45–53. https://doi.org/10.1006/nimg.1995.1007

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D., & Frackowiak, R. S. (1994). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*(4), 189–210. https://doi.org/10.1002/hbm.460020402

Friston, K. J., Preller, K. H., Mathys, C., Cagnan, H., Heinzle, J., Razi, A., & Zeidman, P. (2019). Dynamic causal modelling revisited. *NeuroImage*, *199*, 730–744. https://doi.org/10.1016/j.neuroimage.2017.02.045

Fukushima, K., Fukushima, J., Warabi, T., & Barnes, G. R. (2013). Cognitive processes involved in smooth pursuit eye movements: behavioral evidence, neural substrate and clinical correlation. *Frontiers in Systems Neuroscience*, *7*(4), 1–28. https://doi.org/10.3389/fnsys.2013.00004

Fukushima, K., Yamanobe, T., Shinmei, Y., & Fukushima, J. (2002). Predictive responses of periarcuate pursuit neurons to visual target motion. *Experimental Brain Research*, *145*(1), 104–120. https://doi.org/10.1007/s00221-002-1088-7

Fukushima, K., Yamanobe, T., Shinmei, Y., Fukushima, J., Kurkin, S., & Peterson, B. W. (2002). Coding of smooth eye movements in three-dimensional space by frontal cortex. *Nature*, *419*(6903), 157–162. https://doi.org/10.1038/nature00953

Fusar-Poli, P., Tantardini, M., Simone, S. de, Ramella-Cravaro, V., Oliver, D., Kingdon, J., . . . McGuire, P. (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *40*, 65–75. https://doi.org/10.1016/j.eurpsy.2016.09.003

Gagnon, D., Paus, T., Grosbras, M.-H., Pike, G. B., & O'Driscoll, G. A. (2006). Transcranial magnetic stimulation of frontal oculomotor regions during smooth pursuit. *Journal of Neuroscience*, *26*(2), 458–466. https://doi.org/10.1523/JNEUROSCI.2789-05.2006

Gaymard, B., Rivaud, S., Cassarini, J. F., Dubard, T., Rancurel, G., Agid, Y., & Pierrot-Deseilligny, C. (1998). Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Experimental Brain Research*, *120*(2), 173–183. https://doi.org/10.1007/s002210050391

Gelernter, J., Kranzler, H. R., Satel, S. L., & Rao, P. A. (1994). Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. *Neuropsychopharmacology*, *11*(3), 195–200. https://doi.org/10.1038/sj.npp.1380106

Genç, E., Schölvinck, M. L., Bergmann, J., Singer, W., & Kohler, A. (2016). Functional connectivity patterns of visual cortex reflect its anatomical organization. *Cerebral Cortex*, *26*(9), 3719–3731. https://doi.org/10.1093/cercor/bhv175

Gerchen, M. F., Bernal-Casas, D., & Kirsch, P. (2014). Analyzing task-dependent brain network changes by whole-brain psychophysiological interactions: A comparison to conventional analysis. *Human Brain Mapping*, *35*(10), 5071–5082. https://doi.org/10.1002/hbm.22532

Giros, B., el Mestikawy, S., Godinot, N., Zheng, K., Han, H., Yang-Feng, T., & Caron, M. G. (1992). Cloning, pharmacological characterization, and chromosome assignment of the human dopamine transporter. *Molecular Pharmacology*, *42*(3), 383–390.

Gitelman, D. R., Penny, W. D., Ashburner, J., & Friston, K. J. (2003). Modeling regional and psychophysiologic interactions in fMRI: The importance of hemodynamic deconvolution. *NeuroImage*, *19*(1), 200–207. https://doi.org/10.1016/s1053-8119(03)00058-2

Glahn, D. C., Knowles, E. E. M., McKay, D. R., Sprooten, E., Raventós, H., Blangero, J., . . . Almasy, L. (2014). Arguments for the sake of endophenotypes: Examining common misconceptions about the use of endophenotypes in psychiatric genetics. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *165B*(2), 122–130. https://doi.org/10.1002/ajmg.b.32221

Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., . . . Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: Application of anatomic likelihood estimation and network analysis. *Biological Psychiatry*, *64*(9), 774–781. https://doi.org/10.1016/j.biopsych.2008.03.031

Glahn, D. C., Ragland, J. D., Abramoff, A., Barrett, J., Laird, A. R., Bearden, C. E., & Velligan, D. I. (2005). Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping*, *25*(1), 60–69. https://doi.org/10.1002/hbm.20138

Goettker, A., Agtzidis, I., Braun, D. I., Dorr, M., & Gegenfurtner, K. R. (2020). From Gaussian blobs to naturalistic videos: Comparison of oculomotor behavior across different stimulus complexities. *Journal of Vision*, *20*(8), 1–16. https://doi.org/10.1167/jov.20.8.26

Goettker, A., & Gegenfurtner, K. R. (2021). A change in perspective: The interaction of saccadic and pursuit eye movements in oculomotor control and perception. *Vision Research*, *188*, 283–296. https://doi.org/10.1016/j.visres.2021.08.004

Gooding, D. C., Iacono, W. G., & Beiser, M. (1994). Temporal stability of smooth-pursuit eye tracking in first-episode psychosis. *Psychophysiology*, *31*(1), 62–67. https://doi.org/10.1111/j.1469-8986.1994.tb01025.x

Gooding, D. C., Miller, M. D., & Kwapil, T. R. (2000). Smooth pursuit eye tracking and visual fixation in psychosis-prone individuals. *Psychiatry Research*, *93*(1), 41–54. https://doi.org/10.1016/S0165-1781(00)00113-X

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *The American Journal of Psychiatry*, *160*(4), 636–645. https://doi.org/10.1176/appi.ajp.160.4.636

Gottlieb, J. P., MacAvoy, M. G., & Bruce, C. J. (1994). Neural responses related to smooth-pursuit eye movements and their correspondence with electrically elicited smooth eye movements in the primate frontal eye field. *Journal of Neurophysiology*, *72*(4), 1634–1653. https://doi.org/10.1152/jn.1994.72.4.1634

Grant, P., Kuepper, Y., Mueller, E. A., Wielpuetz, C., Mason, O., & Hennig, J. (2013). Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)—a suitable endophenotype of schizophrenia. *Frontiers in Human Neuroscience*, *7*(1), 1–11. https://doi.org/10.3389/fnhum.2013.00001

Griffis, J. C., Elkhetali, A. S., Burge, W. K., Chen, R. H., & Visscher, K. M. (2015). Retinotopic patterns of background connectivity between V1 and fronto-parietal cortex are modulated by task demands. *Frontiers in Human Neuroscience*, *9*(338). https://doi.org/10.3389/fnhum.2015.00338

Haarmeier, T., & Kammer, T. (2010). Effect of TMS on oculomotor behavior but not perceptual stability during smooth pursuit eye movements. *Cerebral Cortex*, *20*(9), 2234–2243. https://doi.org/10.1093/cercor/bhp285

Hahn, B. (2015). Nicotinic receptors and attention. In D. J. K. Balfour & M. R. Munafò (Eds.), *The Neurobiology and Genetics of Nicotine and Tobacco* (Vol. 23, pp. 103–135). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-13665-3_5

Haijma, S. V., van Haren, N., Cahn, W., Koolschijn, P. C. M. P., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin*, *39*(5), 1129–1138. https://doi.org/10.1093/schbul/sbs118

Haller, S., Fasler, D., Ohlendorf, S., Radue, E. W., & Greenlee, M. W. (2008). Neural activation associated with corrective saccades during tasks with fixation, pursuit and saccades. *Experimental Brain Research*, *184*(1), 83–94. https://doi.org/10.1007/s00221-007-1077-y

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*(6792), 147–150. https://doi.org/10.1038/35018000

Hampson, M., Olson, I. R., Leung, H.-C., Skudlarski, P., & Gore, J. C. (2004). Changes in functional connectivity of human MT/V5 with visual motion input. *Neuroreport*, *15*(8), 1315–1319. https://doi.org/10.1097/01.wnr.0000129997.95055.15

Hansson, A., Rasmussen, T., & Kraiczi, H. (2017). Single-dose and multiple-dose pharmacokinetics of nicotine 6 mg gum. *Nicotine & Tobacco Research*, *19*(4), 477–483. https://doi.org/10.1093/ntr/ntw211

Haraldsson, H. M., Ettinger, U., Magnusdottir, B. B., Sigmundsson, T., Sigurdsson, E., & Petursson, H. (2008). Eye movement deficits in schizophrenia: Investigation of a genetically homogenous Icelandic sample. *European Archives of Psychiatry and Clinical Neuroscience*, *258*(6), 373–383. https://doi.org/10.1007/s00406-008-0806-y

Hariri, A. R. (2009). The neurobiology of individual differences in complex behavioral traits. *Annual Review of Neuroscience*, *32*(1), 225–247. https://doi.org/10.1146/annurev.neuro.051508.135335

Haslam, N., McGrath, M. J., Viechtbauer, W., & Kuppens, P. (2020). Dimensions over categories: A meta-analysis of taxometric research. *Psychological Medicine*, *50*(9), 1–15. https://doi.org/10.1017/S003329172000183X

Haupt, C. (2008). How axons see their way - axonal guidance in the visual system. *Frontiers in Bioscience*, *13*(8), 3136–3149. https://doi.org/10.2741/2915

Hawton, K., Sutton, L., Haw, C., Sinclair, J., & Deeks, J. J. (2005). Schizophrenia and suicide: Systematic review of risk factors. *British Journal of Psychiatry*, *187*(1), 9–20. https://doi.org/10.1192/bjp.187.1.9

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., . . . Carpenter, W. (2013). Structure of the psychotic disorders classification in DSM-5. *Schizophrenia Research*, *150*(1), 11–14. https://doi.org/10.1016/j.schres.2013.04.039

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods*, *50*(3), 1166–1186. https://doi.org/10.3758/s13428-017-0935-1

Heide, W., Kurzidim, K., & Kömpf, D. (1996). Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain*, *119*(6), 1951–1969. https://doi.org/10.1093/brain/119.6.1951

Heinrichs, R. W. (2004). Meta-analysis and the science of schizophrenia: Variant evidence or evidence of variants? *Neuroscience & Biobehavioral Reviews*, *28*(4), 379–394. https://doi.org/10.1016/j.neubiorev.2004.06.003

Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*, *210*(4), 453–469. https://doi.org/10.1007/s00213-010-1848-1

Holahan, A.-L. V., & O'Driscoll, G. A. (2005). Antisaccade and smooth pursuit performance in positive- and negative-symptom schizotypy. *Schizophrenia Research*, *76*(1), 43–54. https://doi.org/10.1016/j.schres.2004.10.005

Holmqvist, K., Nyström, M. L. U., Andersson, R. L. U., Dewhurst, R. L. U., Halszka, J., & van de Weijer, J. L. (2011). *Eye tracking: A comprehensive guide to methods and measures*. Oxford: Oxford University Press.

Holmqvist, K., Örbom, S. L., Hooge, I. T. C., Niehorster, D. C., Alexander, R. G., Andersson, R., . . . Hessels, R. S. (2022). Eye tracking: Empirical foundations for a minimal reporting guideline. *Behavior Research Methods.* Advance online publication. https://doi.org/10.3758/s13428-021-01762-8

Holst, E. von, & Mittelstaedt, H. (1950). Das Reafferenzprinzip. *Naturwissenschaften*, *37*(20), 464–476. https://doi.org/10.1007/BF00622503

Holzman, P. S., Proctor, L. R., & Hughes, D. W. (1973). Eye-tracking patterns in schizophrenia. *Science*, *181*(4095), 179–181. https://doi.org/10.1126/science.181.4095.179

Hong, L. E., Tagamets, M., Avila, M., Wonodi, I., Holcomb, H., & Thaker, G. K. (2005). Specific motion processing pathway deficit during eye tracking in schizophrenia: A performance-matched functional magnetic resonance imaging study. *Biological Psychiatry*, *57*(7), 726–732. https://doi.org/10.1016/j.biopsych.2004.12.015

Hong, L. E., Turano, K. A., O'Neill, H., Hao, L., Wonodi, I., McMahon, R. P., . . . Thaker, G. K. (2008). Refining the predictive pursuit endophenotype in schizophrenia. *Biological Psychiatry*, *63*(5), 458–464. https://doi.org/10.1016/j.biopsych.2007.06.004

Hooker, C., & Park, S. (2000). Trajectory estimation in schizophrenia. *Schizophrenia Research*, *45*(1-2), 83–92. https://doi.org/10.1016/S0920-9964(99)00166-8

Hor, K., & Taylor, M. (2010). Suicide and schizophrenia: A systematic review of rates and risk factors. *Journal of Psychopharmacology*, *24*(4 Suppl), 81–90. https://doi.org/10.1177/1359786810385490

Horn, A. K. E., & Straka, H. (2021). Functional organization of extraocular motoneurons and eye muscles. *Annual Review of Vision Science*, *7*, 793–825. https://doi.org/10.1146/annurev-vision-100119-125043

Howard, I. P., & Marton, C. (1992). Visual pursuit over textured backgrounds in different depth planes. *Experimental Brain Research*, *90*(3), 625–629. https://doi.org/10.1007/BF00230947

Huettel, S. A., Song, A. W., & McCarthy, G. (2014). *Functional magnetic resonance imaging* (3rd ed.). Sunderland, Massachusetts: Sinauer Associates. Inc. Publishers.

Huppert, J. D., Weiss, K. A., Lim, R., Pratt, S., & Smith, T. E. (2001). Quality of life in schizophrenia: contributions of anxiety and depression. *Schizophrenia Research*, *51*(2-3), 171–180. https://doi.org/10.1016/S0920-9964(99)00151-6

Hutchison, R. M., Gallivan, J. P., Culham, J. C., Gati, J. S., Menon, R. S., & Everling, S. (2012). Functional connectivity of the frontal eye fields in humans and macaque monkeys investigated with resting-state fMRI. *Journal of Neurophysiology*, *107*(9), 2463–2474. https://doi.org/10.1152/jn.00891.2011

Hutton, S. B. (2008). Cognitive control of saccadic eye movements. *Brain and Cognition*, *68*(3), 327–340. https://doi.org/10.1016/j.bandc.2008.08.021

Hutton, S. B. (2019). Eye Tracking Methodology. In C. Klein & U. Ettinger (Eds.), *Studies in Neuroscience, Psychology and Behavioral Economics. Eye movement research: An introduction to its scientific foundations and applications* (pp. 277–308). Cham: Springer Nature. https://doi.org/10.1007/978-3-030-20085-5_8

Hutton, S. B., Crawford, T. J., Gibbins, H., Cuthbert, I., Barnes, T., Kennard, C., & Joyce, E. (2001). Short and long term effects of antipsychotic medication on smooth pursuit eye tracking in schizophrenia. *Psychopharmacology*, *157*(3), 284–291. https://doi.org/10.1007/s002130100803

Hutton, S. B., Crawford, T. J., Kennard, C., Barnes, T. R., & Joyce, E. M. (2000). Smooth pursuit eye tracking over a structured background in first-episode schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience*, *250*(5), 221–225. https://doi.org/10.1007/s004060070011

Hutton, S. B., Crawford, T. J., Puri, B. K., Duncan, L.-J., Chapman, M., Kennard, C., . . . Joyce, E. (1998). Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. *Psychological Medicine*, *28*(3), 685–692. https://doi.org/10.1017/s0033291798006722

Hutton, S. B., & Tegally, D. (2005). The effects of dividing attention on smooth pursuit eye tracking. *Experimental Brain Research*, *163*(3), 306–313. https://doi.org/10.1007/s00221-004-2171-z

Hutton, S. B., & Weekes, B. S. (2007). Low frequency rTMS over posterior parietal cortex impairs smooth pursuit eye tracking. *Experimental Brain Research*, *183*(2), 195–200. https://doi.org/10.1007/s00221-007-1033-x

Ilg, U. J., & Thier, P. (1996). Inability of rhesus monkey area V1 to discriminate between self-induced and externally induced retinal image slip. *European Journal of Neuroscience*, *8*(6), 1156–1166. https://doi.org/10.1111/j.1460-9568.1996.tb01283.x

Ilg, U. J., & Thier, P. (2008). The neural basis of smooth pursuit eye movements in the rhesus monkey brain. *Brain and Cognition*, *68*(3), 229–240. https://doi.org/10.1016/j.bandc.2008.08.014

Jakobson Mo, S., Axelsson, J., Stiernman, L. J., Larsson, A., Bjerkén, S. af, Bäckström, D., . . . Riklund, K. (2022). VNTR polymorphism in the SLC6A3 gene does not influence dopamine transporter availability measured by 18FFE-PE2I PET or 123IFP-Cit SPECT. *Nuclear Medicine Communications*, *43*(3), 247–255. https://doi.org/10.1097/MNM.0000000000001514

Jin, Z., Gou, R., Zhang, J., & Li, L. (2021). The role of frontal pursuit area in interaction between smooth pursuit eye movements and attention: A TMS study. *Journal of Vision*, *21*(3), 11. https://doi.org/10.1167/jov.21.3.11

Jongkees, B. J., & Colzato, L. S. (2016). Spontaneous eye blink rate as predictor of dopamine-related cognitive function—A review. *Neuroscience & Biobehavioral Reviews*, *71*, 58–82. https://doi.org/10.1016/j.neubiorev.2016.08.020

Kalman, D., & Smith, S. S. (2005). Does nicotine do what we think it does? A meta-analytic review of the subjective effects of nicotine in nasal spray and intravenous studies with smokers and nonsmokers. *Nicotine & Tobacco Research*, *7*(3), 317–333. https://doi.org/10.1080/14622200500125385

Kambeitz, J., Romanos, M., & Ettinger, U. (2014). Meta-analysis of the association between dopamine transporter genotype and response to methylphenidate treatment in ADHD. *The Pharmacogenomics Journal*, *14*(1), 77–84. https://doi.org/10.1038/tpj.2013.9

Kang, A., Palmatier, M. A., & Kidd, K. K. (1999). Global variation of a 40-bp VNTR in the 3′-untranslated region of the dopamine transporter gene (SLC6A3). *Biological Psychiatry*, *46*(2), 151–160. https://doi.org/10.1016/S0006-3223(99)00101-8

Karpouzian, T., Petrovsky, N., Ettinger, U., & Reilly, J. (2019). Eye movements as biomarkers to evaluate pharmacological effects on brain systems. In C. Klein & U. Ettinger (Eds.), *Studies in Neuroscience, Psychology and Behavioral Economics. Eye movement research: An introduction to its scientific foundations and applications* (pp. 775–816). Cham: Springer Nature. https://doi.org/10.1007/978-3-030-20085-5_18

Kasparbauer, A.-M., Meyhöfer, I., Steffens, M., Weber, B., Aydin, M., Kumari, V., . . . Ettinger, U. (2016). Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. *NeuroImage*, *141*, 52–59. https://doi.org/10.1016/j.neuroimage.2016.07.012

Kasparbauer, A.-M., Rujescu, D., Riedel, M., Pogarell, O., Costa, A., Meindl, T., . . . Ettinger, U. (2015). Methylphenidate effects on brain activity as a function of SLC6A3 genotype and striatal dopamine transporter availability. *Neuropsychopharmacology*, *40*(3), 736–745. https://doi.org/10.1038/npp.2014.240

Katsanis, J., & Iacono, W. G. (1991). Clinical, neuropsychological, and brain structural correlates of smooth-pursuit eye tracking performance in chronic schizophrenia. *Journal of Abnormal Psychology*, *100*(4), 526–534. https://doi.org/10.1037/0021-843X.100.4.526

Kaufman, S. R., & Abel, L. A. (1986). The effects of distraction on smooth pursuit in normal subjects. *Acta Oto-Laryngologica*, *102*(1-2), 57–64. https://doi.org/10.3109/00016488609108647

Kawawaki, D., Shibata, T., Goda, N., Doya, K., & Kawato, M. (2006). Anterior and superior lateral occipito-temporal cortex responsible for target motion prediction during overt and covert visual pursuit. *Neuroscience Research*, *54*(2), 112–123. https://doi.org/10.1016/j.neures.2005.10.015

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Keedy, S. K., Ebens, C. L., Keshavan, M. S., & Sweeney, J. A. (2006). Functional magnetic resonance imaging studies of eye movements in first episode schizophrenia: Smooth pursuit, visually guided saccades and the oculomotor delayed response task. *Psychiatry Research*, *146*(3), 199–211. https://doi.org/10.1016/j.pscychresns.2006.01.003

Keller, E. L., & Khan, N. S. (1986). Smooth-pursuit initiation in the presence of a textured background in monkey. *Vision Research*, *26*(6), 943–955. https://doi.org/10.1016/0042-6989(86)90152-5

Kendler, K. S., Ochs, A. L., Gorman, A. M., Hewitt, J. K., Ross, D. E., & Mirsky, A. F. (1991). The structure of schizotypy: A pilot multitrait twin study. *Psychiatry Research*, *36*(1), 19–36. https://doi.org/10.1016/0165-1781(91)90114-5

Kerkhoff, G., Reinhart, S., Ziegler, W., Artinger, F., Marquardt, C., & Keller, I. (2013). Smooth pursuit eye movement training promotes recovery from auditory and visual neglect: A randomized controlled study. *Neurorehabilitation and Neural Repair*, *27*(9), 789–798. https://doi.org/10.1177/1545968313491012

Kimmig, H., Miles, F. A., & Schwarz, U. (1992). Effects of stationary textured backgrounds on the initiation of pursuit eye movements in monkeys. *Journal of Neurophysiology*, *68*(6), 2147–2164. https://doi.org/10.1152/jn.1992.68.6.2147

Kimmig, H., Ohlendorf, S., Speck, O., Sprenger, A., Rutschmann, R. M., Haller, S., & Greenlee, M. W. (2008). fMRI evidence for sensorimotor transformations in human cortex during smooth pursuit eye movements. *Neuropsychologia*, *46*(8), 2203–2213. https://doi.org/10.1016/j.neuropsychologia.2008.02.021

Klein, C., & Ettinger, U. (2008). A hundred years of eye movement research in psychiatry. *Brain and Cognition*, *68*(3), 215–218. https://doi.org/10.1016/j.bandc.2008.08.012

Kloet, S. F. de, Mansvelder, H. D., & Vries, T. J. de (2015). Cholinergic modulation of dopamine pathways through nicotinic acetylcholine receptors. *Biochemical Pharmacology*, *97*(4), 425–438. https://doi.org/10.1016/j.bcp.2015.07.014

Knapp, M., Mangalore, R., & Simon, J. (2004). The global costs of schizophrenia. *Schizophrenia Bulletin*, *30*(2), 279–293. https://doi.org/10.1093/oxfordjournals.schbul.a007078

Konen, C. S., & Kastner, S. (2008). Representation of eye movements and stimulus motion in topographically organized areas of human posterior parietal Cortex. *Journal of Neuroscience*, *28*(33), 8361–8375. https://doi.org/10.1523/JNEUROSCI.1930-08.2008

Konen, C. S., Kleiser, R., Seitz, R. J., & Bremmer, F. (2005). An fMRI study of optokinetic nystagmus and smooth-pursuit eye movements in humans. *Experimental Brain Research*, *165*(2), 203–216. https://doi.org/10.1007/s00221-005-2289-7

Kowler, E., Rubinstein, J. F., Santos, E. M., & Wang, J. (2019). Predictive smooth pursuit eye movements. *Annual Review of Vision Science*, *5*(1), 223–246. https://doi.org/10.1146/annurev-vision-091718-014901

Koychev, I., Joyce, D., Barkus, E., Ettinger, U., Schmechtig, A., Dourish, C. T., . . . Deakin, J. F. W. (2016). Cognitive and oculomotor performance in subjects with low and high schizotypy: implications for translational drug development studies. *Translational Psychiatry*, *6*(5), e811. https://doi.org/10.1038/tp.2016.64

Kraiczi, H., Hansson, A., & Perfekt, R. (2011). Single-dose pharmacokinetics of nicotine when given with a novel mouth spray for nicotine replacement therapy. *Nicotine & Tobacco Research*, *13*(12), 1176–1182. https://doi.org/10.1093/ntr/ntr139

Kreyenmeier, P., Fooken, J., & Spering, M. (2017). Context effects on smooth pursuit and manual interception of a disappearing target. *Journal of Neurophysiology*, *118*(1), 404–415. https://doi.org/10.1152/jn.00217.2017

Krishna, N., O'Neill, H., Sanchez-Morla, E. M., & Thaker, G. K. (2014). Long range frontal/posterior phase synchronization during remembered pursuit task is impaired in schizophrenia. *Schizophrenia Research*, *157*(1-3), 198–203. https://doi.org/10.1016/j.schres.2014.05.035

Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: The self medication hypotheses. *Neuroscience & Biobehavioral Reviews*, *29*(6), 1021–1034. https://doi.org/10.1016/j.neubiorev.2005.02.006

Kwapil, T. R., & Barrantes-Vidal, N. (2015). Schizotypy: Looking back and moving forward. *Schizophrenia Bulletin*, *41*(Suppl 2), S366-73. https://doi.org/10.1093/schbul/sbu186

Ladda, J., Eggert, T., Glasauer, S., & Straube, A. (2007). Velocity scaling of cue-induced smooth pursuit acceleration obeys constraints of natural motion. *Experimental Brain Research*, *182*(3), 343–356. https://doi.org/10.1007/s00221-007-0988-y

Lambert, N. M., & Hartsough, C. S. (1998). Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *Journal of Learning Disabilities*, *31*(6), 533–544. https://doi.org/10.1177/002221949803100603

Lambert, T. J. R., Velakoulis, D., & Pantelis, C. (2003). Medical comorbidity in schizophrenia. *Medical Journal of Australia*, *178*(S9), S67-S70. https://doi.org/10.5694/j.1326-5377.2003.tb05311.x

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess early mortality in schizophrenia. *Annual Review of Clinical Psychology*, *10*(1), 425–448. https://doi.org/10.1146/annurev-clinpsy-032813-153657

Lawden, M. C., Bagelmann, H., Crawford, T. J., Matthews, T. D., & Kennard, C. (1995). An effect of structured backgrounds on smooth pursuit eye movements in patients with cerebral lesions. *Brain*, *118*(Pt 1), 37–48. https://doi.org/10.1093/brain/118.1.37

Leichnetz, G. R. (2001). Connections of the medial posterior parietal cortex (area 7m) in the monkey. *The Anatomical Record*, *263*(2), 215–236. https://doi.org/10.1002/ar.1082

Leigh, R. J., & Zee, D. S. (2015). *The neurology of eye movements* (5th ed.). New York: Oxford University Press. https://doi.org/10.1093/med/9780199969289.001.0001

Lekwuwa, G. U., & Barnes, G. R. (1996). Cerebral control of eye movements. I. The relationship between cerebral lesion sites and smooth pursuit deficits. *Brain*, *119*(2), 473–490. https://doi.org/10.1093/brain/119.2.473

Lencer, R., Keedy, S. K., Reilly, J. L., McDonough, B. E., Harris, M. S. H., Sprenger, A., & Sweeney, J. A. (2011). Altered transfer of visual motion information to parietal association cortex in untreated first-episode psychosis: Implications for pursuit eye tracking. *Psychiatry Research*, *194*(1), 30–38. https://doi.org/10.1016/j.pscychresns.2011.06.011

Lencer, R., Nagel, M., Sprenger, A., Heide, W., & Binkofski, F. (2005). Reduced neuronal activity in the V5 complex underlies smooth-pursuit deficit in schizophrenia: Evidence from an fMRI study. *NeuroImage*, *24*(4), 1256–1259. https://doi.org/10.1016/j.neuroimage.2004.11.013

Lencer, R., Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Heide, W., & Binkofski, F. (2004). Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *The European Journal of Neuroscience*, *19*(5), 1430–1436. https://doi.org/10.1111/j.1460-9568.2004.03229.x

Lencer, R., Reilly, J. L., Harris, M. S., Sprenger, A., Keshavan, M. S., & Sweeney, J. A. (2010). Sensorimotor transformation deficits for smooth pursuit in first-episode affective psychoses and schizophrenia. *Biological Psychiatry*, *67*(3), 217–223. https://doi.org/10.1016/j.biopsych.2009.08.005

Lencer, R., Sprenger, A., Harris, M. S. H., Reilly, J. L., Keshavan, M. S., & Sweeney, J. A. (2008). Effects of second-generation antipsychotic medication on smooth pursuit performance in antipsychotic-naive schizophrenia. *Archives of General Psychiatry*, *65*(10), 1146–1154. https://doi.org/10.1001/archpsyc.65.10.1146

Lencer, R., Sprenger, A., Reilly, J. L., McDowell, J. E., Rubin, L. H., Badner, J. A., . . . Sweeney, J. A. (2015). Pursuit eye movements as an intermediate phenotype across psychotic disorders: Evidence from the B-SNIP study. *Schizophrenia Research*, *169*(1-3), 326–333. https://doi.org/10.1016/j.schres.2015.09.032

Lencer, R., Sprenger, A., & Trillenberg, P. (2019). Smooth eye movements in humans: Smooth pursuit, optokinetic nystagmus and vestibular ocular reflex. In C. Klein & U. Ettinger (Eds.), *Studies in Neuroscience, Psychology and Behavioral Economics. Eye movement research: An introduction to its scientific foundations and applications* (pp. 117–163). Cham: Springer Nature. https://doi.org/10.1007/978-3-030-20085-5_4

Lencer, R., & Trillenberg, P. (2008). Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition*, *68*(3), 219–228. https://doi.org/10.1016/j.bandc.2008.08.013

Lenzenweger, M. F. (2006). Schizotypy. *Current Directions in Psychological Science*, *15*(4), 162–166. https://doi.org/10.1111/j.1467-8721.2006.00428.x

Lenzenweger, M. F. (2013). Thinking clearly about the endophenotype-intermediate phenotype-biomarker distinctions in developmental psychopathology research. *Development and Psychopathology*, *25*(4 Pt 2), 1347–1357. https://doi.org/10.1017/S0954579413000655

Lenzenweger, M. F., & Dworkin, R. H. (1996). The dimensions of schizophrenia phenomenology. Not one or two, at least three, perhaps four. *British Journal of Psychiatry*, *168*(4), 432–440. https://doi.org/10.1192/bjp.168.4.432

Lenzenweger, M. F., & O'Driscoll, G. A. (2006). Smooth pursuit eye movement and schizotypy in the community. *Journal of Abnormal Psychology*, *115*(4), 779–786. https://doi.org/10.1037/0021-843X.115.4.779

Leon, J. de, & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research*, *76*(2-3), 135–157. https://doi.org/10.1016/j.schres.2005.02.010

Levin, E. D., Conners, C. K., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., . . . March, J. (1996). Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology*, *123*(1), 55–63. https://doi.org/10.1007/BF02246281

Levy, D. L., Lajonchere, C. M., Dorogusker, B., Min, D., Lee, S., Tartaglini, A., . . . Mendell, N. R. (2000). Quantitative characterization of eye tracking dysfunction in schizophrenia. *Schizophrenia Research*, *42*(3), 171–185. https://doi.org/10.1016/S0920-9964(99)00122-X

Levy, D. L., Sereno, A. B., Gooding, D. C., & O'Driscoll, G. A. (2010). Eye tracking dysfunction in schizophrenia: Characterization and pathophysiology. *Current Topics in Behavioral Neurosciences*, *4*, 311–347. https://doi.org/10.1007/7854_2010_60

Li, K., Guo, L., Nie, J., Li, G., & Liu, T. (2009). Review of methods for functional brain connectivity detection using fMRI. *Computerized Medical Imaging and Graphics: The Official Journal of the Computerized Medical Imaging Society*, *33*(2), 131–139. https://doi.org/10.1016/j.compmedimag.2008.10.011

Li, M., He, H. G., Shi, W., Li, J., Lv, B., Wang, C. H., . . . Sabel, B. A. (2012). Quantification of the human lateral geniculate nucleus in vivo using MR imaging based on morphometry: Volume loss with age. *AJNR. American Journal of Neuroradiology*, *33*(5), 915–921. https://doi.org/10.3174/ajnr.A2884

Li, W., Yang, Y., An, F.-R., Zhang, L., Ungvari, G. S., Jackson, T., . . . Xiang, Y.-T. (2020). Prevalence of comorbid depression in schizophrenia: A meta-analysis of observational studies. *Journal of Affective Disorders*, *273*, 524–531. https://doi.org/10.1016/j.jad.2020.04.056

Liddle, P. F. (1987). The symptoms of chronic schizophrenia. *British Journal of Psychiatry*, *151*(2), 145–151. https://doi.org/10.1192/bjp.151.2.145

Lindner, A., Haarmeier, T., Erb, M., Grodd, W., & Thier, P. (2006). Cerebrocerebellar circuits for the perceptual cancellation of eye-movement-induced retinal image motion. *Journal of Cognitive Neuroscience*, *18*(11), 1899–1912. https://doi.org/10.1162/jocn.2006.18.11.1899

Lindner, A., & Ilg, U. J. (2006). Suppression of optokinesis during smooth pursuit eye movements revisited: The role of extra-retinal information. *Vision Research*, *46*(6-7), 761–767. https://doi.org/10.1016/j.visres.2005.09.033

Lindner, A., Schwarz, U., & Ilg, U. J. (2001). Cancellation of self-induced retinal image motion during smooth pursuit eye movements. *Vision Research*, *41*(13), 1685–1694. https://doi.org/10.1016/S0042-6989(01)00050-5

Linka, M., & de Haas, B. (2020). OSIEshort: A small stimulus set can reliably estimate individual differences in semantic salience. *Journal of Vision*, *20*(9), 13. https://doi.org/10.1167/jov.20.9.13

Lisberger, S. G. (2015). Visual guidance of smooth pursuit eye movements. *Annual Review of Vision Science*, *1*, 447–468. https://doi.org/10.1146/annurev-vision-082114-035349

Lisberger, S. G., Evinger, C., Johanson, G. W., & Fuchs, A. F. (1981). Relationship between eye acceleration and retinal image velocity during foveal smooth pursuit in man and monkey. *Journal of Neurophysiology*, *46*(2), 229–249. https://doi.org/10.1152/jn.1981.46.2.229

Lisberger, S. G., Morris, E. J., & Tychsen, L. (1987). Visual motion processing and sensory-motor integration for smooth pursuit eye movements. *Annual Review of Neuroscience*, *10*(1), 97–129. https://doi.org/10.1146/annurev.ne.10.030187.000525

Logemann, H. N. A., Böcker, K. B. E., Deschamps, P. K. H., Kemner, C., & Kenemans, J. L. (2014). Differences between nicotine-abstinent smokers and non-smokers in terms of visuospatial attention and inhibition before and after single-blind nicotine administration. *Neuroscience*, *277*, 375–382. https://doi.org/10.1016/j.neuroscience.2014.07.016

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–878. https://doi.org/10.1038/nature06976

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annual Review of Physiology*, *66*, 735–769. https://doi.org/10.1146/annurev.physiol.66.082602.092845

Lott, D. C., Kim, S.-J., Cook, E. H., & Wit, H. de (2005). Dopamine transporter gene associated with diminished subjective response to amphetamine. *Neuropsychopharmacology*, *30*(3), 602–609. https://doi.org/10.1038/sj.npp.1300637

The Lundbeck Institute (2016). Synaptic dopamine reuptake and degradation. Retrieved from https://us-institute.progress.im/en/content/synaptic-dopamine-reuptake-and-degradation-0

MacAvoy, M. G., Gottlieb, J. P., & Bruce, C. J. (1991). Smooth-pursuit eye movement representation in the primate frontal eye field. *Cerebral Cortex*, *1*(1), 95–102. https://doi.org/10.1093/cercor/1.1.95

Madsen, K. H., Krohne, L. G., Cai, X., Wang, Y., & Chan, R. C. K. (2018). Perspectives on machine learning for classification of schizotypy using fMRI data. *Schizophrenia Bulletin*, *44*(suppl 2), S480-S490. https://doi.org/10.1093/schbul/sby026

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., . . . Dosenbach, N. U. F. (2022). Reproducible brain-wide association studies require thousands of individuals. *Nature*, *603*(7902), 654–660. https://doi.org/10.1038/s41586-022-04492-9

Markett, S., Reuter, M., Montag, C., Voigt, G., Lachmann, B., Rudorf, S., . . . Weber, B. (2014). Assessing the function of the fronto-parietal attention network: Insights from resting-state fMRI and the attentional network test. *Human Brain Mapping*, *35*(4), 1700–1709. https://doi.org/10.1002/hbm.22285

Mason, O. (2015). The assessment of schizotypy and its clinical relevance. *Schizophrenia Bulletin*, *41*(suppl 2), S374-S385. https://doi.org/10.1093/schbul/sbu194

Mason, O., & Claridge, G. (2006). The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): Further description and extended norms. *Schizophrenia Research*, *82*(2-3), 203–211. https://doi.org/10.1016/j.schres.2005.12.845

Mason, O., Claridge, G., & Jackson, M. (1995). New scales for the assessment of schizotypy. *Personality and Individual Differences*, *18*(1), 7–13. https://doi.org/10.1016/0191-8869(94)00132-C

Mason, O., Linney, Y., & Claridge, G. (2005). Short scales for measuring schizotypy. *Schizophrenia Research*, *78*(2-3), 293–296. https://doi.org/10.1016/j.schres.2005.06.020

Masson, G., Proteau, L., & Mestre, D. R. (1995). Effects of stationary and moving textured backgrounds on the visuo-oculo-manual tracking in humans. *Vision Research*, *35*(6), 837–852. https://doi.org/10.1016/0042-6989(94)00185-O

Maunsell, J. H., & van Essen, D. C. (1983). The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *Journal of Neuroscience*, *3*(12), 2563–2586. https://doi.org/10.1523/JNEUROSCI.03-12-02563.1983

McClernon, F. J., & Kollins, S. H. (2008). ADHD and smoking: From genes to brain to behavior. *Annals of the New York Academy of Sciences*, *1141*(1), 131–147. https://doi.org/10.1196/annals.1441.016

McDowell, J. E., Dyckman, K. A., Austin, B. P., & Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. *Brain and Cognition*, *68*(3), 255–270. https://doi.org/10.1016/j.bandc.2008.08.016

McHugh, P. C., & Buckley, D. A. (2015). The structure and function of the dopamine transporter and its role in CNS diseases. *Vitamins and Hormones*, *98*, 339–369. https://doi.org/10.1016/bs.vh.2014.12.009

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *NeuroImage*, *61*(4), 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Meehl, P. E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders*, *4*(1), 1–99. https://doi.org/10.1521/pedi.1990.4.1.1

Meyer, C. H., Lasker, A. G., & Robinson, D. A. (1985). The upper limit of human smooth pursuit velocity. *Vision Research*, *25*(4), 561–563. https://doi.org/10.1016/0042-6989(85)90160-9

Meyer, J. S., & Quenzer, L. F. (2013). *Psychopharmacology: Drugs, the brain, and behavior* (2nd ed.). Sunderland, Massachusetts: Sinauer Associates Inc.

Meyer, U. A. (2004). Pharmacogenetics - five decades of therapeutic lessons from genetic diversity. *Nature Reviews. Genetics*, *5*(9), 669–676. https://doi.org/10.1038/nrg1428

Meyhöfer, I., Bertsch, K., Esser, M., & Ettinger, U. (2016). Variance in saccadic eye movements reflects stable traits. *Psychophysiology*, *53*(4), 566–578. https://doi.org/10.1111/psyp.12592

Meyhöfer, I., Kasparbauer, A.-M., Steffens, M., & Ettinger, U. (2019). Effects of nicotine on smooth pursuit eye movements in healthy non-smokers. *Psychopharmacology*, *236*(7), 2259–2271. https://doi.org/10.1007/s00213-019-05223-1

Meyhöfer, I., Steffens, M., Faiola, E., Kasparbauer, A.-M., Kumari, V., & Ettinger, U. (2017). Combining two model systems of psychosis: The effects of schizotypy and sleep deprivation on oculomotor control and psychotomimetic states. *Psychophysiology*, *54*(11), 1755–1769. https://doi.org/10.1111/psyp.12917

Meyhöfer, I., Steffens, M., Kasparbauer, A.-M., Grant, P., Weber, B., & Ettinger, U. (2015). Neural mechanisms of smooth pursuit eye movements in schizotypy. *Human Brain Mapping*, *36*(1), 340–353. https://doi.org/10.1002/hbm.22632

Millar, A., Smith, D., Choueiry, J., Fisher, D., Albert, P., & Knott, V. (2011). The moderating role of the dopamine transporter 1 gene on P50 sensory gating and its modulation by nicotine. *Neuroscience*, *180*, 148–156. https://doi.org/10.1016/j.neuroscience.2011.02.008

Miller, J., & Ulrich, R. (2013). Mental chronometry and individual differences: Modeling reliabilities and correlations of reaction time means and effect sizes. *Psychonomic Bulletin & Review*, *20*(5), 819–858. https://doi.org/10.3758/s13423-013-0404-5

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of General Psychiatry*, *66*(8), 811–822. https://doi.org/10.1001/archgenpsychiatry.2009.91

Missal, M., & Heinen, S. J. (2001). Facilitation of smooth pursuit initiation by eectrical stimulation in the supplementary eye fields. *Journal of Neurophysiology*, *86*(5), 2413–2425. https://doi.org/10.1152/jn.2001.86.5.2413

Missal, M., & Heinen, S. J. (2004). Supplementary eye fields stimulation facilitates anticipatory pursuit. *Journal of Neurophysiology*, *92*(2), 1257–1262. https://doi.org/10.1152/jn.01255.2003

Missal, M., & Heinen, S. J. (2017). Stopping smooth pursuit. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *372*(1718), 20160200. https://doi.org/10.1098/rstb.2016.0200

Mohrmann, H., & Thier, P. (1995). The influence of structured visual backgrounds on smooth-pursuit initiation, steady-state pursuit and smooth-pursuit termination. *Biological Cybernetics*, *73*(1), 83–93. https://doi.org/10.1007/BF00199058

Molitor, R. J., Ko, P. C., & Ally, B. A. (2015). Eye movements in Alzheimer's disease. *Journal of Alzheimer's Disease*, *44*(1), 1–12. https://doi.org/10.3233/JAD-141173

Montag, C., Ebstein, R. P., Jawinski, P., & Markett, S. (2020). Molecular genetics in psychology and personality neuroscience: On candidate genes, genome wide scans, and new research strategies. *Neuroscience and Biobehavioral Reviews*, *118*, 163–174. https://doi.org/10.1016/j.neubiorev.2020.06.020

Morgan, C. J. A., Bedford, N. J., O'Regan, A., & Rossell, S. L. (2009). Is semantic processing impaired in individuals with high schizotypy? *The Journal of Nervous and Mental Disease*, *197*(4), 232–238. https://doi.org/10.1097/NMD.0b013e31819dc127

Morita, K., Miura, K., Kasai, K., & Hashimoto, R. (2020). Eye movement characteristics in schizophrenia: A recent update with clinical implications. *Neuropsychopharmacology Reports*, *40*(1), 2–9. https://doi.org/10.1002/npr2.12087

Mustari, M. J., Ono, S., & Das, V. E. (2009). Signal processing and distribution in cortical-brainstem pathways for smooth pursuit eye movements. *Annals of the New York Academy of Sciences*, *1164*(1), 147–154. https://doi.org/10.1111/j.1749-6632.2009.03859.x

Myers, C. S., Taylor, R. C., Moolchan, E. T., & Heishman, S. J. (2008). Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology*, *33*(3), 588–598. https://doi.org/10.1038/sj.npp.1301425

Nagel, M., Sprenger, A., Hohagen, F., Binkofski, F., & Lencer, R. (2008). Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *NeuroImage*, *41*(2), 483–492. https://doi.org/10.1016/j.neuroimage.2008.02.058

Nagel, M., Sprenger, A., Nitschke, M., Zapf, S., Heide, W., Binkofski, F., & Lencer, R. (2007). Different extraretinal neuronal mechanisms of smooth pursuit eye movements in schizophrenia: An fMRI study. *NeuroImage*, *34*(1), 300–309. https://doi.org/10.1016/j.neuroimage.2006.08.025

Nagel, M., Sprenger, A., Steinlechner, S., Binkofski, F., & Lencer, R. (2012). Altered velocity processing in schizophrenia during pursuit eye tracking. *PloS One*, *7*(6), e38494. https://doi.org/10.1371/journal.pone.0038494

Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Kompf, D., Heide, W., . . . Lencer, R. (2006). Parametric modulation of cortical activation during smooth pursuit with and without target blanking. An fMRI study. *NeuroImage*, *29*(4), 1319–1325. https://doi.org/10.1016/j.neuroimage.2005.08.050

Naicker, P., Anoopkumar-Dukie, S., Grant, G. D., & Kavanagh, J. J. (2017). Medications influencing central cholinergic neurotransmission affect saccadic and smooth pursuit eye movements in healthy young adults. *Psychopharmacology*, *234*(1), 63–71. https://doi.org/10.1007/s00213-016-4436-1

Nassi, J. J., & Callaway, E. M. (2009). Parallel processing strategies of the primate visual system. *Nature Reviews Neuroscience*, *10*(5), 360–372. https://doi.org/10.1038/nrn2619

Nelson, M. T., Seal, M. L., Pantelis, C., & Phillips, L. J. (2013). Evidence of a dimensional relationship between schizotypy and schizophrenia: A systematic review. *Neuroscience & Biobehavioral Reviews*, *37*(3), 317–327. https://doi.org/10.1016/j.neubiorev.2013.01.004

Niemann, T., & Hoffmann, K.-P. (1997). The influence of stationary and moving textured backgrounds on smooth-pursuit initiation and steady state pursuit in humans. *Experimental Brain Research*, *3*(115), 531–540. https://doi.org/10.1007/PL00005723

Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology*, *67*(1), 53–83. https://doi.org/10.1016/S0301-0082(02)00011-4

Nisell, M., Nomikos, G. G., & Svensson, T. H. (1994). Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. *Synapse*, *16*(1), 36–44. https://doi.org/10.1002/syn.890160105

Nuding, U., Kalla, R., Muggleton, N. G., Büttner, U., Walsh, V., & Glasauer, S. (2009). TMS evidence for smooth pursuit gain control by the frontal eye fields. *Cerebral Cortex*, *19*(5), 1144–1150. https://doi.org/10.1093/cercor/bhn162

Nyberg, G., Panfilov, V., Sivertsson, R., & Wilhelmsen, L. (1982). Cardiovascular effect of nicotine chewing gum in healthy non-smokers. *European Journal of Clinical Pharmacology*, *23*(4), 303–307. https://doi.org/10.1007/BF00613610

Nyffeler, T., Rivaud-Pechoux, S., Wattiez, N., & Gaymard, B. (2008). Involvement of the supplementary eye field in oculomotor predictive behavior. *Journal of Cognitive Neuroscience*, *20*(9), 1583–1594. https://doi.org/10.1162/jocn.2008.20073

O'Driscoll, G. A., & Callahan, B. L. (2008). Smooth pursuit in schizophrenia: A meta-analytic review of research since 1993. *Brain and Cognition*, *68*(3), 359–370. https://doi.org/10.1016/j.bandc.2008.08.023

O'Driscoll, G. A., Lenzenweger, M. F., & Holzman, P. S. (1998). Antisaccades and smooth pursuit eye tracking and schizotypy. *Archives of General Psychiatry*, *55*(9), 837–843. https://doi.org/10.1001/archpsyc.55.9.837

O'Driscoll, G. A., Strakowski, S. M., Alpert, N. M., Matthysse, S., Rauch, S. L., Levy, D. L., & Holzman, P. S. (1998). Differences in cerebral activation during smooth pursuit and saccadic eye movements using positron-emission tomography. *Biological Psychiatry*, *44*(8), 685–689. https://doi.org/10.1016/S0006-3223(98)00047-X

O'Driscoll, G. A., Wolff, A. L., Benkelfat, C., Florencio, P. S., Lal, S., & Evans, A. C. (2000). Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport*, *11*(6), 1335–1340. https://doi.org/10.1097/00001756-200004270-00037

Ogawa, S., & Lee, T. M. (1990). Magnetic resonance imaging of blood vessels at high fields: In vivo and in vitro measurements and image simulation. *Magnetic Resonance in Medicine*, *16*(1), 9–18. https://doi.org/10.1002/mrm.1910160103

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(24), 9868–9872. https://doi.org/10.1073/pnas.87.24.9868

Ogawa, S., Lee, T. M., Nayak, A. S., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance in Medicine*, *14*(1), 68–78. https://doi.org/10.1002/mrm.1910140108

Ohlendorf, S., Kimmig, H., Glauche, V., & Haller, S. (2007). Gaze pursuit, 'attention pursuit' and their effects on cortical activations. *The European Journal of Neuroscience*, *26*(7), 2096–2108. https://doi.org/10.1111/j.1460-9568.2007.05824.x

Ohlendorf, S., Sprenger, A., Speck, O., Glauche, V., Haller, S., & Kimmig, H. (2010). Visual motion, eye motion, and relative motion: A parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. *Journal of Vision*, *10*(14), 21. https://doi.org/10.1167/10.14.21

Ohtsuka, K., & Enoki, T. (1998). Transcranial magnetic stimulation over the posterior cerebellum during smooth pursuit eye movements in man. *Brain*, *121*(3), 429–435. https://doi.org/10.1093/brain/121.3.429

Olincy, A., Johnson, L., & Ross, R. G. (2003). Differential effects of cigarette smoking on performance of a smooth pursuit and a saccadic eye movement task in schizophrenia. *Psychiatry Research*, *117*(3), 223–236. https://doi.org/10.1016/S0165-1781(03)00022-2

Olincy, A., Ross, R. G., Young, D. A., Roath, M., & Freedman, R. (1998). Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. *Neuropsychopharmacology*, *18*(3), 175–185. https://doi.org/10.1016/S0893-133X(97)00095-X

Ono, S. (2015). The neuronal basis of on-line visual control in smooth pursuit eye movements. *Vision Research*, *110*(Pt B), 257–264. https://doi.org/10.1016/j.visres.2014.06.008

Orban de Xivry, J.-J., & Lefèvre, P. (2007). Saccades and pursuit: Two outcomes of a single sensorimotor process. *The Journal of Physiology*, *584*(Pt 1), 11–23. https://doi.org/10.1113/jphysiol.2007.139881

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E. J., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: Psychophysiological interactions and functional connectivity. *Social Cognitive and Affective Neuroscience*, *7*(5), 604–609. https://doi.org/10.1093/scan/nss055

Orrù, G., Pettersson-Yeo, W., Marquand, A. F., Sartori, G., & Mechelli, A. (2012). Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. *Neuroscience & Biobehavioral Reviews*, *36*(4), 1140–1152. https://doi.org/10.1016/j.neubiorev.2012.01.004

Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., . . . Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics*, *50*(3), 381–389. https://doi.org/10.1038/s41588-018-0059-2

Park, H. R., Lim, V. K., Kirk, I. J., & Waldie, K. E. (2015). P50 sensory gating deficits in schizotypy. *Personality and Individual Differences*, *82*, 142–147. https://doi.org/10.1016/j.paid.2015.03.025

Parsons, S., Kruijt, A.-W., & Fox, E. (2019). Psychological science needs a standard practice of reporting the reliability of cognitive-behavioral measurements. *Advances in Methods and Practices in Psychological Science*, *2*(4), 378–395. https://doi.org/10.1177/2515245919879695

Penetar, D. M., Haegerstrom-Portnoy, G., & Jones, R. T. (1988). Combined atropine and 2-PAM Cl effects on tracking performance and visual, physiological, and psychological functions. *Aviation, Space, and Environmental Medicine*, *59*(12), 1125–1132.

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., . . . Lönnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, *64*(1), 19–28. https://doi.org/10.1001/archpsyc.64.1.19

Peralta, V., & Cuesta, M. J. (2001). How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. *Schizophrenia Research*, *49*(3), 269–285. https://doi.org/10.1016/S0920-9964(00)00071-2

Petit, L., Clark, V. P., Ingeholm, J., & Haxby, J. V. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *Journal of Neurophysiology*, *77*(6), 3386–3390. https://doi.org/10.1152/jn.1997.77.6.3386

Petit, L., & Haxby, J. V. (1999). Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *Journal of Neurophysiology*, *82*(1), 463–471. https://doi.org/10.1152/jn.1999.82.1.463

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: Where are we now? *Neuroscience and Biobehavioral Reviews*, *35*(5), 1110–1124. https://doi.org/10.1016/j.neubiorev.2010.11.004

Piccini, P. P. (2003). Dopamine transporter: Basic aspects and neuroimaging. *Movement Disorders*, *18*(S7), S3-S8. https://doi.org/10.1002/mds.10571

Pierrot-Deseilligny, C., Gray, F., & Brunet, P. (1986). Infarcts of both inferior parietal lobules with impairment of visually guided eye movements, peripheral visual inattention and optic ataxia. *Brain*, *109 (Pt 1)*, 81–97. https://doi.org/10.1093/brain/109.1.81

Pierrot-Deseilligny, C., Müri, R. M., Ploner, C. J., Gaymard, B., Demeret, S., & Rivaud-Pechoux, S. (2003). Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain*, *126*(6), 1460–1473. https://doi.org/10.1093/brain/awg148

Pivik, R. T., Bylsma, F. W., & Cooper, P. M. (1988). Dark condition normalization of smooth pursuit tracking: Evidence of cerebellar dysfunction in psychosis. *European Archives of Psychiatry and Neurological Sciences*, *237*(6), 334–342. https://doi.org/10.1007/BF00380976

Poorthuis, R. B., & Mansvelder, H. D. (2013). Nicotinic acetylcholine receptors controlling attention: Behavior, circuits and sensitivity to disruption by nicotine. *Biochemical Pharmacology*, *86*(8), 1089–1098. https://doi.org/10.1016/j.bcp.2013.07.003

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., . . . Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*, *17*(1), 49–66. https://doi.org/10.1002/wps.20490

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive-perceptual, Interpersonal, and Disorganized Features of Schizotypal Personality. *Schizophrenia Bulletin*, *20*(1), 191–201. https://doi.org/10.1093/schbul/20.1.191

Rashbass, C. (1961). The relationship between saccadic and smooth tracking eye movements. *The Journal of Physiology*, *159*(2), 326–338. https://doi.org/10.1113/jphysiol.1961.sp006811

Raymond, J. E., Shapiro, K. L., & Rose, D. J. (1984). Optokinetic backgrounds affect perceived velocity during ocular tracking. *Perception & Psychophysics*, *36*(3), 221–224. https://doi.org/10.3758/BF03206362

Reilly, J. L., Lencer, R., Bishop, J. R., Keedy, S. K., & Sweeney, J. A. (2008). Pharmacological treatment effects on eye movement control. *Brain and Cognition*, *68*(3), 415–435. https://doi.org/10.1016/j.bandc.2008.08.026

Reine, G., Lançon, C., Di Tucci, S., Sapin, C., & Auquier, P. (2003). Depression and subjective quality of life in chronic phase schizophrenic patients. *Acta Psychiatrica Scandinavica*, *108*(4), 297–303. https://doi.org/10.1034/j.1600-0447.2003.00132.x

Reynolds, C. A., Raine, A., Mellingen, K., Venables, P. H., & Mednick, S. A. (2000). Three-factor model of schizotypal personality: Invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophrenia Bulletin*, *26*(3), 603–618. https://doi.org/10.1093/oxfordjournals.schbul.a033481

Rezvani, A. H., & Levin, E. D. (2001). Cognitive effects of nicotine. *Biological Psychiatry*, *49*(3), 258–267. https://doi.org/10.1016/S0006-3223(00)01094-5

Rincón-Pérez, I., Sánchez-Carmona, A. J., Albert, J., & Hinojosa, J. A. (2018). The association of monoamine-related gene polymorphisms with behavioural correlates of response inhibition: A meta-analytic review. *Neuroscience and Biobehavioral Reviews*, *84*, 49–62. https://doi.org/10.1016/j.neubiorev.2017.11.009

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., Holmans, P. A., . . . O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Rogers, B. P., Morgan, V. L., Newton, A. T., & Gore, J. C. (2007). Assessing functional connectivity in the human brain by fMRI. *Magnetic Resonance Imaging*, *25*(10), 1347–1357. https://doi.org/10.1016/j.mri.2007.03.007

Rosano, C., Krisky, C. M., Welling, J. S., Eddy, W. F., Luna, B., Thulborn, K. R., & Sweeney, J. A. (2002). Pursuit and saccadic eye movement subregions in human frontal eye field: A high-resolution fMRI investigation. *Cerebral Cortex*, *12*(2), 107–115. https://doi.org/10.1093/cercor/12.2.107

Ross, R. G., Olincy, A., Zerbe, G., & Radant, A. (2001). Which duration of postsaccadic slowing identifies anticipatory saccades during smooth pursuit eye movements? *Psychophysiology*, *38*(2), 325–333. https://doi.org/10.1111/1469-8986.3820325

Roy-Byrne, P., Radant, A., Wingerson, D., & Cowley, D. S. (1995). Human oculomotor function: Reliability and diurnal variation. *Biological Psychiatry*, *38*(2), 92–97. https://doi.org/10.1016/0006-3223(94)00225-R

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry*, *64*(10), 1123–1131. https://doi.org/10.1001/archpsyc.64.10.1123

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Medicine*, *2*(5), e141. https://doi.org/10.1371/journal.pmed.0020141

Salatino-Oliveira, A., Rohde, L. A., & Hutz, M. H. (2018). The dopamine transporter role in psychiatric phenotypes. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *177*(2), 211–231. https://doi.org/10.1002/ajmg.b.32578

Sami, M. B., Annibale, L., O'Neill, A., Collier, T., Onyejiaka, C., Eranti, S., . . . Bhattacharyya, S. (2021). Eye movements in patients in early psychosis with and without a history of cannabis use. *NPJ Schizophrenia*, *7*(24), 1–7. https://doi.org/10.1038/s41537-021-00155-2

Schmah, T., Yourganov, G., Zemel, R. S., Hinton, G. E., Small, S. L., & Strother, S. C. (2010). Comparing classification methods for longitudinal fMRI studies. *Neural Computation*, *22*(11), 2729–2762. https://doi.org/10.1162/NECO_a_00024

Schmechtig, A., Lees, J., Grayson, L., Craig, K. J., Dadhiwala, R., Dawson, G. R., . . . Ettinger, U. (2013). Effects of risperidone, amisulpride and nicotine on eye movement control and their modulation by schizotypy. *Psychopharmacology*, *227*(2), 331–345. https://doi.org/10.1007/s00213-013-2973-4

Schmid, A., Rees, G., Frith, C., & Barnes, G. R. (2001). An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport*, *12*(7), 1409–1414. https://doi.org/10.1097/00001756-200105250-00023

Schraa-Tam, C. K. L., van der Lugt, A., Frens, M. A., Smits, M., van Broekhoven, P. C. A., & van der Geest, J. N. (2008). An fMRI study on smooth pursuit and fixation suppression of the optokinetic reflex using similar visual stimulation. *Experimental Brain Research*, *185*(4), 535–544. https://doi.org/10.1007/s00221-007-1176-9

Schraa-Tam, C. K. L., van der Lugt, A., Smits, M., Frens, M. A., van Broekhoven, P. C. A., & van der Geest, J. N. (2008). fMRI of optokinetic eye movements with and without a contribution of smooth pursuit. *Journal of Neuroimaging*, *18*(2), 158–167. https://doi.org/10.1111/j.1552-6569.2007.00204.x

Schraa-Tam, C. K. L., van der Lugt, A., Smits, M., Frens, M. A., van Broekhoven, P. C. A., & van der Geest, J. N. (2009). Differences between smooth pursuit and optokinetic eye movements using limited lifetime dot stimulation: A functional magnetic resonance imaging study. *Clinical Physiology and Functional Imaging*, *29*(4), 245–254. https://doi.org/10.1111/j.1475-097X.2009.00858.x

Schröder, R., Baumert, P. M., & Ettinger, U. (2021). Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements. *Acta Psychologica*, *219*, 103364. https://doi.org/10.1016/j.actpsy.2021.103364

Schröder, R., Faiola, E., Fernanda Urquijo, M., Bey, K., Meyhöfer, I., Steffens, M., . . . Ettinger, U. (2022). Neural correlates of smooth pursuit eye movements in schizotypy and recent onset psychosis: A multivariate pattern classification approach. *Schizophrenia Bulletin Open*, *3*(1), 1–13. https://doi.org/10.1093/schizbullopen/sgac034

Schröder, R., Kasparbauer, A.-M., Meyhöfer, I., Steffens, M., Trautner, P., & Ettinger, U. (2020). Functional connectivity during smooth pursuit eye movements. *Journal of Neurophysiology*, *124*(6), 1839–1856. https://doi.org/10.1152/jn.00317.2020

Schröder, R., Keidel, K., Trautner, P., Radbruch, A., & Ettinger, U. (2022). Neural mechanisms of background and velocity effects in smooth pursuit eye movements. *Human Brain Mapping*, *44*(3), 1002–1018. https://doi.org/10.1002/hbm.26127

Schröder, R., Reuter, M., Faßbender, K., Plieger, T., Poulsen, J., Lui, S. S. Y., . . . Ettinger, U. (2022). The role of the SLC6A3 3' UTR VNTR in nicotine effects on cognitive, affective, and motor function. *Psychopharmacology*, *239*(2), 489–507. https://doi.org/10.1007/s00213-021-06028-x

Shaikh, A. G., & Zee, D. S. (2018). Eye movement research in the twenty-first century-a window to the brain, mind, and more. *Cerebellum*, *17*(3), 252–258. https://doi.org/10.1007/s12311-017-0910-5

Sharpe, J. A. (2008). Neurophysiology and neuroanatomy of smooth pursuit: Lesion studies. *Brain and Cognition*, *68*(3), 241–254. https://doi.org/10.1016/j.bandc.2008.08.015

Sherr, J. D., Myers, C., Avila, M. T., Elliott, A., Blaxton, T. A., & Thaker, G. K. (2002). The effects of nicotine on specific eye tracking measures in schizophrenia. *Biological Psychiatry*, *52*(7), 721–728. https://doi.org/10.1016/S0006-3223(02)01342-2

Shiffman, S., Fant, R. V., Buchhalter, A. R., Gitchell, J. G., & Henningfield, J. E. (2005). Nicotine delivery systems. *Expert Opinion on Drug Delivery*, *2*(3), 563–577. https://doi.org/10.1517/17425247.2.3.563

Shiino, T., Miura, K., Fujimoto, M., Kudo, N., Yamamori, H., Yasuda, Y., . . . Hashimoto, R. (2020). Comparison of eye movements in schizophrenia and autism spectrum disorder. *Neuropsychopharmacology Reports*, *40*(1), 92–95. https://doi.org/10.1002/npr2.12085

Shrout, P. E., & Rodgers, J. L. (2018). Psychology, science, and knowledge construction: Broadening perspectives from the replication crisis. *Annual Review of Psychology*, *69*(1), 487–510. https://doi.org/10.1146/annurev-psych-122216-011845

Sibony, P. A., Evinger, C., & Manning, K. A. (1988). The effects of tobacco smoking on smooth pursuit eye movements. *Annals of Neurology*, *23*(3), 238–241. https://doi.org/10.1002/ana.410230305

Siebner, H. R., Callicott, J. H., Sommer, T., & Mattay, V. S. (2009). From the genome to the phenome and back: Linking genes with human brain function and structure using genetically informed neuroimaging using genetically informed neuroimaging. *Neuroscience*, *164*(1), 1–6. https://doi.org/10.1016/j.neuroscience.2009.09.009

Siero, J. C. W., Bhogal, A., & Jansma, J. M. (2013). Blood Oxygenation Level-dependent/Functional Magnetic Resonance Imaging: Underpinnings, Practice, and Perspectives. *PET Clinics*, *8*(3), 329–344. https://doi.org/10.1016/j.cpet.2013.04.003

Silberg, J. E., Agtzidis, I., Startsev, M., Fasshauer, T., Silling, K., Sprenger, A., . . . Lencer, R. (2019). Free visual exploration of natural movies in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(4), 407–418. https://doi.org/10.1007/s00406-017-0863-1

Sim, K., Mahendran, R., Siris, S. G., Heckers, S., & Chong, S. A. (2004). Subjective quality of life in first episode schizophrenia spectrum disorders with comorbid depression. *Psychiatry Research*, *129*(2), 141–147. https://doi.org/10.1016/j.psychres.2004.07.007

Singh, I., & Rose, N. (2009). Biomarkers in psychiatry. *Nature*, *460*(7252), 202–207. https://doi.org/10.1038/460202a

Siris, S. G. (2001). Suicide and schizophrenia. *Journal of Psychopharmacology*, *15*(2), 127–135. https://doi.org/10.1177/026988110101500209

Smith, R. C., Warner-Cohen, J., Matute, M., Butler, E., Kelly, E., Vaidhyanathaswamy, S., & Khan, A. (2006). Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology*, *31*(3), 637–643. https://doi.org/10.1038/sj.npp.1300881

Smyrnis, N. (2008). Metric issues in the study of eye movements in psychiatry. *Brain and Cognition*, *68*(3), 341–358. https://doi.org/10.1016/j.bandc.2008.08.022

Smyrnis, N., Amado, I., Krebs, M.-O., & Sweeney, J. A. (2019). Eye movements in psychiatry. In C. Klein & U. Ettinger (Eds.), *Studies in Neuroscience, Psychology and Behavioral Economics. Eye movement research: An introduction to its scientific foundations and applications* (Vol. 29, pp. 703–748). Cham: Springer Nature. https://doi.org/10.1007/978-3-030-20085-5_16

Smyrnis, N., Evdokimidis, I., Mantas, A., Kattoulas, E., Stefanis, N. C., Constantinidis, T. S., . . . Stefanis, C. N. (2007). Smooth pursuit eye movements in 1,087 men: Effects of schizotypy, anxiety, and depression. *Experimental Brain Research*, *179*(3), 397–408. https://doi.org/10.1007/s00221-006-0797-8

Souto, D., & Kerzel, D. (2021). Visual selective attention and the control of tracking eye movements: A critical review. *Journal of Neurophysiology*, *125*(5), 1552–1576. https://doi.org/10.1152/jn.00145.2019

Spearman, C. (1910). Correlation calculated from faulty data. *British Journal of Psychology, 1904-1920*, *3*(3), 271–295. https://doi.org/10.1111/j.2044-8295.1910.tb00206.x

Spering, M., Dias, E. C., Sanchez, J. L., Schütz, A. C., & Javitt, D. C. (2013). Efference copy failure during smooth pursuit eye movements in schizophrenia. *Journal of Neuroscience*, *33*(29), 11779–11787. https://doi.org/10.1523/JNEUROSCI.0578-13.2013

Spering, M., & Gegenfurtner, K. R. (2007). Contextual effects on smooth-pursuit eye movements. *Journal of Neurophysiology*, *97*(2), 1353–1367. https://doi.org/10.1152/jn.01087.2006

Spering, M., & Gegenfurtner, K. R. (2008). Contextual effects on motion perception and smooth pursuit eye movements. *Brain Research*, *1225*, 76–85. https://doi.org/10.1016/j.brainres.2008.04.061

Stanton, G. B., Friedman, H. R., Dias, E. C., & Bruce, C. J. (2005). Cortical afferents to the smooth-pursuit region of the macaque monkey's frontal eye field. *Experimental Brain Research*, *165*(2), 179–192. https://doi.org/10.1007/s00221-005-2292-z

Steen, R. G., Mull, C., McClure, R., Hamer, R. M., & Lieberman, J. (2006). Brain volume in first-episode schizophrenia: Systematic review and meta-analysis of magnetic resonance imaging studies. *The British Journal of Psychiatry: The Journal of Mental Science*, *188*(6), 510–518. https://doi.org/10.1192/bjp.188.6.510

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., . . . van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, *32*(2), 347–358. https://doi.org/10.1017/s0033291701005141

Steffens, M., Becker, B., Neumann, C., Kasparbauer, A.-M., Meyhöfer, I., Weber, B., . . . Ettinger, U. (2016). Effects of ketamine on brain function during smooth pursuit eye movements. *Human Brain Mapping*, *37*(11), 4047–4060. https://doi.org/10.1002/hbm.23294

Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia Bulletin*, *35*(3), 509–527. https://doi.org/10.1093/schbul/sbn176

Sternberg, S. (2001). Separate modifiability, mental modules, and the use of pure and composite measures to reveal them. *Acta Psychologica*, *106*(1-2), 147–246. https://doi.org/10.1016/S0001-6918(00)00045-7

Stolerman, I. P., & Price, L. H. (2015a). Pharmacodynamics. In I. P. Stolerman & L. H. Price (Eds.), *Springer eBook Collection Biomedical and Life Sciences. Encyclopedia of Psychopharmacology* (p. 1275). Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-642-36172-2_200739

Stolerman, I. P., & Price, L. H. (2015b). Psychopharmacology. In I. P. Stolerman & L. H. Price (Eds.), *Springer eBook Collection Biomedical and Life Sciences. Encyclopedia of Psychopharmacology* (p. 1389). Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-642-36172-2_200170

Suehiro, K., Miura, K., Kodaka, Y., Inoue, Y., Takemura, A., & Kawano, K. (1999). Effects of smooth pursuit eye movement on ocular responses to sudden background motion in humans. *Neuroscience Research*, *35*(4), 329–338. https://doi.org/10.1016/S0168-0102(99)00098-X

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*(12), 1187–1192. https://doi.org/10.1001/archpsyc.60.12.1187

Sweeney, J. A., Haas, G. L., & Li, S. (1992). Neuropsychological and eye movement abnormalities in first-episode and chronic schizophrenia. *Schizophrenia Bulletin*, *18*(2), 283–293. https://doi.org/10.1093/schbul/18.2.283

Tabor, H. K., Risch, N. J., & Myers, R. M. (2002). Candidate-gene approaches for studying complex genetic traits: Practical considerations. *Nature Reviews. Genetics*, *3*(5), 391–397. https://doi.org/10.1038/nrg796

Takagi, M., Zee, D. S., & Tamargo, R. J. (2000). Effects of lesions of the oculomotor cerebellar vermis on eye movements in primate: Smooth pursuit. *Journal of Neurophysiology*, *83*(4), 2047–2062. https://doi.org/10.1152/jn.2000.83.4.2047

Tanabe, J. L., Tregellas, J., Martin, L. F., & Freedman, R. (2006). Effects of nicotine on hippocampal and cingulate activity during smooth pursuit eye movement in schizophrenia. *Biological Psychiatry*, *59*(8), 754–761. https://doi.org/10.1016/j.biopsych.2005.09.004

Tanabe, J. L., Tregellas, J., Miller, D., Ross, R. G., & Freedman, R. (2002). Brain activation during smooth-pursuit eye movements. *NeuroImage*, *17*(3), 1315–1324. https://doi.org/10.1006/nimg.2002.1263

Tanaka, M., & Lisberger, S. G. (2001). Regulation of the gain of visually guided smooth-pursuit eye movements by frontal cortex. *Nature*, *409*(6817), 191–194. https://doi.org/10.1038/35051582

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008). Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia Research*, *102*(1-3), 1–18. https://doi.org/10.1016/j.schres.2008.04.011

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophrenia Research*, *110*(1-3), 1–23. https://doi.org/10.1016/j.schres.2009.03.005

Taylor, C. M., Olulade, O. A., Luetje, M. M., & Eden, G. F. (2018). An fMRI study of coherent visual motion processing in children and adults. *NeuroImage*, *173*, 223–239. https://doi.org/10.1016/j.neuroimage.2018.02.001

Taylor, S. F., Kang, J., Brege, I. S., Tso, I. F., Hosanagar, A., & Johnson, T. D. (2012). Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biological Psychiatry*, *71*(2), 136–145. https://doi.org/10.1016/j.biopsych.2011.09.007

Thaker, G. K., Ellsberry, R., Moran, M., Lahti, A., & Tamminga, C. (1991). Tobacco smoking increases square-wave jerks during pursuit eye movements. *Biological Psychiatry*, *29*(1), 82–88. https://doi.org/10.1016/0006-3223(91)90212-5

Thaker, G. K., Ross, D. E., Buchanan, R. W., Adami, H. M., & Medoff, D. R. (1999). Smooth pursuit eye movements to extra-retinal motion signals: Deficits in patients with schizophrenia. *Psychiatry Research*, *88*(3), 209–219. https://doi.org/10.1016/s0165-1781(99)00084-0

Thakkar, K. N., Diwadkar, V. A., & Rolfs, M. (2017). Oculomotor prediction: A window into the psychotic mind. *Trends in Cognitive Sciences*, *21*(5), 344–356. https://doi.org/10.1016/j.tics.2017.02.001

Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuo-spatial attention. *Nature Neuroscience*, *14*(10), 1245–1246. https://doi.org/10.1038/nn.2905

Threlfell, S., Lalic, T., Platt, N. J., Jennings, K. A., Deisseroth, K., & Cragg, S. J. (2012). Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. *Neuron*, *75*(1), 58–64. https://doi.org/10.1016/j.neuron.2012.04.038

Tikhonov, A., Haarmeier, T., Thier, P., Braun, C., & Lutzenberger, W. (2004). Neuromagnetic activity in medial parietooccipital cortex reflects the perception of visual motion during eye movements. *NeuroImage*, *21*(2), 593–600. https://doi.org/10.1016/j.neuroimage.2003.09.045

Tootell, R. B., Hadjikhani, N. K., Vanduffel, W., Liu, A. K., Mendola, J. D., Sereno, M. I., & Dale, A. M. (1998). Functional analysis of primary visual cortex (V1) in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 811–817. https://doi.org/10.1073/pnas.95.3.811

Tregellas, J., Olincy, A., Johnson, L., Tanabe, J. L., Shatti, S., Martin, L. F., . . . Freedman, R. (2010). Functional magnetic resonance imaging of effects of a nicotinic agonist in schizophrenia. *Neuropsychopharmacology*, *35*(4), 938–942. https://doi.org/10.1038/npp.2009.196

Tregellas, J., Tanabe, J. L., Martin, L. F., & Freedman, R. (2005). fMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. *The American Journal of Psychiatry*, *162*(2), 391–393. https://doi.org/10.1176/appi.ajp.162.2.391

Tregellas, J., Tanabe, J. L., Miller, D. E., Ross, R. G., Olincy, A., & Freedman, R. (2004). Neurobiology of smooth pursuit eye movement deficits in schizophrenia: An fMRI study. *The American Journal of Psychiatry*, *161*(2), 315–321. https://doi.org/10.1176/appi.ajp.161.2.315

Trenner, M. U., Fahle, M., Fasold, O., Heekeren, H. R., Villringer, A., & Wenzel, R. (2008). Human cortical areas involved in sustaining perceptual stability during smooth pursuit eye movements. *Human Brain Mapping*, *29*(3), 300–311. https://doi.org/10.1002/hbm.20387

Trillenberg, P., Sprenger, A., Talamo, S., Herold, K., Helmchen, C., Verleger, R., & Lencer, R. (2017). Visual and non-visual motion information processing during pursuit eye tracking in schizophrenia and bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *267*(3), 225–235. https://doi.org/10.1007/s00406-016-0671-z

Tsai, J., & Rosenheck, R. A. (2013). Psychiatric comorbidity among adults with schizophrenia: A latent class analysis. *Psychiatry Research*, *210*(1), 16–20. https://doi.org/10.1016/j.psychres.2013.05.013

Tu, P., Buckner, R. L., Zollei, L., Dyckman, K. A., Goff, D. C., & Manoach, D. S. (2010). Reduced functional connectivity in a right-hemisphere network for volitional ocular motor control in schizophrenia. *Brain*, *133*(2), 625–637. https://doi.org/10.1093/brain/awp317

Van Essen, D. C. (2004). Organization of visual areas in macaque and human cerebral cortex. In L. M. Chalupa & J. S. Werne (Eds.), *Bradford Bks. The visual neurosciences* (pp. 507–521). Cambridge, Mass: MIT Press.

Van Os, J., & Kapur, S. (2009). Schizophrenia. *The Lancet*, *374*(9690), 635–645. https://doi.org/10.1016/S0140-6736(09)60995-8

Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine*, *39*(2), 179–195. https://doi.org/10.1017/S0033291708003814

Van Tricht, M. J., Nieman, D. H., Bour, L. J., Boerée, T., Koelman, J. H. T. M., Haan, L. de, & Linszen, D. H. (2010). Increased saccadic rate during smooth pursuit eye movements in patients at Ultra High Risk for developing a psychosis. *Brain and Cognition*, *73*(3), 215–221. https://doi.org/10.1016/j.bandc.2010.05.005

Vandenbergh, D. J., Persico, A. M., Hawkins, A. L., Griffin, C. A., Li, X., Jabs, E. W., & Uhl, G. R. (1992). Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics*, *14*(4), 1104–1106. https://doi.org/10.1016/S0888-7543(05)80138-7

Versino, M., Castelnovo, G., Bergamaschi, R., Romani, A., Beltrami, G., Zambarbieri, D., & Cosi, V. (1993). Quantitative evaluation of saccadic and smooth pursuit eye movements. Is it reliable? *Investigative Ophthalmology & Visual Science*, *34*(5), 1702–1709.

Wager, T. D., Sylvester, C.-Y. C., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *NeuroImage*, *27*(2), 323–340. https://doi.org/10.1016/j.neuroimage.2005.01.054

Wagner, A. K., Scanion, J. M., Becker, C. R., Ritter, A. C., Niyonkuru, C., Dixon, C. E., . . . Price, J. C. (2014). The influence of genetic variants on striatal dopamine transporter and D2 receptor binding after TB. *Journal of Cerebral Blood Flow & Metabolism*, *34*(8), 1328–1339. https://doi.org/10.1038/jcbfm.2014.87

Wang, Y., Matsuzaka, Y., Shima, K., & Tanji, J. (2004). Cingulate cortical cells projecting to monkey frontal eye field and primary motor cortex. *Neuroreport*, *15*(10), 1559–1563. https://doi.org/10.1097/01.wnr.0000133300.62031.9b

Waterson, J. A., Barnes, G. R., & Grealy, M. A. (1992). A quantitative study of eye and head movements during smooth pursuit in patients with cerebellar disease. *Brain*, *115*(5), 1343–1358. https://doi.org/10.1093/brain/115.5.1343

Waterston, J. A., Barnes, G. R., Grealy, M. A., & Collins, S. (1996). Abnormalities of smooth eye and head movement control in Parkinson's disease. *Annals of Neurology*, *39*(6), 749–760. https://doi.org/10.1002/ana.410390611

Weickert, C. S., Weickert, T. W., Pillai, A., & Buckley, P. F. (2013). Biomarkers in schizophrenia: A brief conceptual consideration. *Disease Markers*, *35*(1), 3–9. https://doi.org/10.1155/2013/510402

White, O. B., Saint-Cyr, J. A., Tomlinson, R. D., & Sharpe, J. A. (1983). Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain*, *106*(3), 571–587. https://doi.org/10.1093/brain/106.3.571

Wolff, K. (2015). Pharmacokinetics. In I. P. Stolerman & L. H. Price (Eds.), *Springer eBook Collection Biomedical and Life Sciences. Encyclopedia of Psychopharmacology* (pp. 1280–1291). Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-642-36172-2_24

World Health Organization (1993). *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*. Geneva: World Health Organization.

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited—again. *NeuroImage*, *2*(3), 173–181. https://doi.org/10.1006/nimg.1995.1023

Wuthrich, V. M., & Bates, T. C. (2006). Confirmatory factor analysis of the three-factor structure of the schizotypal personality questionnaire and Chapman schizotypy scales. *Journal of Personality Assessment*, *87*(3), 292–304. https://doi.org/10.1207/s15327752jpa8703_10

Wyatt, H. J., & Pola, J. (1983). Smooth pursuit eye movements under open-loop and closed-loop conditions. *Vision Research*, *23*(10), 1121–1131. https://doi.org/10.1016/0042-6989(83)90025-1

Yang, S., Boudier-Revéret, M., Choo, Y. J., & Chang, M. C. (2020). Association between chronic pain and alterations in the mesolimbic dopaminergic system. *Brain Sciences*, *10*(10). https://doi.org/10.3390/brainsci10100701

Yee, R. D., Baloh, R. W., Marder, S. R., Levy, D. L., Sakala, S. M., & Honrubia, V. (1987). Eye movements in schizophrenia. *Investigative Ophthalmology & Visual Science*, *28*(2), 366–374.

Yee, R. D., Daniels, S. A., Jones, O. W., Baloh, R. W., & Honrubia, V. (1983). Effects of an optokinetic background on pursuit eye movements. *Investigative Ophthalmology & Visual Science*, *24*(8), 1115–1122.

Zeki, S. (2015). Area V5-a microcosm of the visual brain. *Frontiers in Integrative Neuroscience*, *9*, 21. https://doi.org/10.3389/fnint.2015.00021

List of Figures

Figure 1: Schematic depiction of SPEM performance with different types of saccades. 12
Figure 2: Target velocity patterns to investigate SPEM. 13
Figure 3: Schematic depiction of the neural network underlying SPEM. 19
Figure 4: Exemplary depiction of different target displays used as background stimuli for SPEM. 21
Figure 5: The dopaminergic and cholinergic systems. 26
Figure 6: Synaptic dopamine reuptake and degradation. 29
Figure 7: Schematic depiction of the schizophrenia (or psychosis) spectrum. 34
Figure 8: Exemplary SPEM performance in a healthy individual and a patient with schizophrenia. ... 36
Figure 9: Schematic depiction of the neurobiological levels tapped in this dissertation. 40
Figure 10: Depiction of a typical BOLD haemodynamic response function. 46
Figure 11: Schematic depiction of the fMRI data analysis flow. 48
Figure 12: Generation of the psychophysiological interaction (PPI) term. 50
Figure 13: Illustration of the pattern classification procedure with support vector machines. 52
Figure 14: Schematic depiction of the target display. 55
Figure 15: Key findings from Study I. 56
Figure 16: Key findings from Study II. 59
Figure 17: Exemplary key findings from Study III for one seed region and task contrast. 62
Figure 18: Key findings from Study IV. 64
Figure 19: Key finding from Study V. 67

List of Tables

Table 1: Exemplary items for each scale of the O-LIFE questionnaire 53
Table 2: Overview of the experimental studies integrated in this dissertation. 54

List of Abbreviations

Abbreviation	Meaning
ADHD	Attention Deficit Hyperactivity Disorder
BOLD	Blood Oxygen Level Dependent
CEF	Cingulate Eye Field
CV	Cross Validation
DCM	Dynamic Causal Modelling
DLPFC	Dorsolateral Prefrontal Cortex
dMST	Dorsal Medial Superior Temporal Visual Area
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EOG	Electrooculography
FEF	Frontal Eye Field
fMRI	Functional Magnetic Resonance Imaging
GABA	γ-Aminobutyric Acid
GLM	General Linear Model
gPPI	Generalized Psychophysiological Interaction
HNS	High Negative Schizotypy
HPS	High Positive Schizotypy
HRF	Haemodynamic Response Function
ICC	Intraclass Correlat
ICD	International Classification of Diseases
IPS	Intraparietal Sulcus
LGN	Lateral Geniculate Nucleus
LS	Low Schizotypy
lMST	Lateral Medial Superior Temporal Visual Area
MEG	Magnetoencephalography

MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MST	Medial Superior Temporal Visual Area
MT	Middle Temporal Visual Area
nAChR	Nicotinic Acetylcholine Receptor
OKN	Optokinetic Nystagmus
O-LIFE	Oxford-Liverpool Inventory of Feelings and Experiences
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PET	Positron Emission Tomography
PPC	Posterior Parietal Cortex
PPI	Psychophysiological Interaction
RMSE	Root Mean Square Error
ROP	Recent Onset Psychosis
SBR	Spontaneous Blink Rate
SEF	Supplementary Eye Field
SPECT	Single Photon Emission Computed Tomography
SPEM	Smooth Pursuit Eye Movements
SVM	Support Vector Machine
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TPJ	Temporo-Parietal Junction
TR	Repetition Time
VCPCR	Video-Based Combined Pupil and Corneal Reflection
VTA	Ventral Tegmental Area

Appendix A | Study I

Schröder, R., Baumert, P. M., & Ettinger, U. (2021). Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements. *Acta Psychologica*, *219*, 103364. https://doi.org/10.1016/j.actpsy.2021.103364

Licensed under CC BY-NC-ND 4.0.

Acta Psychologica 219 (2021) 103364

Contents lists available at ScienceDirect

Acta Psychologica

journal homepage: www.elsevier.com/locate/actpsy

Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements

Rebekka Schröder, Philine Margarete Baumert, Ulrich Ettinger *

Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, 53111 Bonn, Germany

ARTICLE INFO

Keywords:
Smooth pursuit eye movements
Reliability
Replicability
Reliability paradox
Individual differences

ABSTRACT

When we follow a slowly moving target with our eyes, we perform smooth pursuit eye movements (SPEM). Previous investigations point to significantly and robustly reduced SPEM performance in the presence of a stationary background and at higher compared to lower target velocities. However, the reliability of these background and target velocity effects has not yet been investigated systematically.

To address this issue, 45 healthy participants (17 m, 28 f) took part in two experimental sessions 7 days apart. In each session, participants were instructed to follow a horizontal SPEM target moving sinusoidally between ±7.89° at three different target velocities, corresponding to frequencies of 0.2, 0.4 and 0.6 Hz. Each target velocity was presented once with and once without a stationary background, resulting in six blocks. The blocks were presented twice per session in order to additionally explore potential task length effects. To assess SPEM performance, velocity gain was calculated as the ratio of eye to target velocity.

In line with previous research, detrimental background and target velocity effects were replicated robustly in both sessions with large effect sizes. Good to excellent test-retest reliabilities were obtained at higher target velocities and in the presence of a stationary background, whereas lower reliabilities occurred with slower targets and in the absence of background stimuli. Target velocity and background effects resulted in largely good to excellent reliabilities.

These findings not only replicated robust experimental effects of background and target velocity at group level, but also revealed that these effects can be translated into reliable individual difference measures.

1. Introduction

When we follow a small, slowly moving target with our eyes, we perform smooth pursuit eye movements (SPEM) in order to hold the image of the target on the fovea (Leigh & Zee, 2015; Lisberger, 2015; Lisberger et al., 1987). SPEM represent a complex sensorimotor behaviour incorporating various perceptual, motor and cognitive processes including attention, prediction and inhibition (Barnes, 2008; Lisberger, 2015). Parameters used to quantify SPEM accuracy include measures such as pursuit velocity gain (ratio of eye velocity to target velocity) or root mean square error (RMSE) as well as more specific measures such as the number of intrusive (e.g. anticipatory saccades) or compensatory saccades (e.g. catch-up saccades) (Barnes, 2008; Lencer & Trillenberg, 2008; Smyrnis, 2008). Velocity gain is considered the primary measure of performance of the smooth pursuit system (Barnes, 2008; Lencer & Trillenberg, 2008; Smyrnis, 2008).

A well-established experimental finding is that SPEM accuracy is reduced in the presence of task irrelevant, visual distractors or structured backgrounds (Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Kaufman & Abel, 1986; Mohrmann & Thier, 1995; Niemann & Hoffmann, 1997; Spering et al., 2006). It has been argued that the optokinetic drive induced by the background slows pursuit eye movements (Barnes, 2008). This process can be influenced by attention directed to enhance target processing and/or reduce background processing (Barnes, 2008), a process related to inhibitory control (Friedman & Miyake, 2004). Importantly, increased deployment of attention may counter, but does not fully abolish the detrimental influence of task irrelevant background stimuli, leading to the replicable observation of this background effect in the literature (Collewijn & Tamminga, 1984; Hutton et al., 2000; Kaufman & Abel, 1986; Mohrmann & Thier, 1995; Niemann & Hoffmann, 1997; Spering et al., 2006).

SPEM is also highly sensitive to target velocity (or target frequency). Horizontal SPEM targets typically either have a constant velocity or follow a sinusoidal velocity pattern, i.e. decelerating towards the

* Corresponding author.
E-mail address: ulrich.ettinger@uni-bonn.de (U. Ettinger).

https://doi.org/10.1016/j.actpsy.2021.103364
Received 6 January 2021; Received in revised form 23 June 2021; Accepted 1 July 2021
Available online 7 July 2021
0001-6918/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

turnings points and accelerating towards the center of the screen. The latter are described by their peak velocity and/or their temporal frequency given a specific amplitude of target excursion. It has been shown that performance reliably deteriorates with increasing target velocity (or frequency) (Collewijn & Tamminga, 1984; Lisberger et al., 1981). This effect indicates that increasing demands on the system at higher target velocities cannot be fully addressed, leading to the observed performance decreases. The effect might be attributed to eye velocity and/or acceleration saturation at higher target velocities (Buizza & Schmid, 1986).

A recent study replicated the background effect, i.e. a general performance decrease in the presence of a stationary background (Meyhöfer et al., 2019). In addition, it was shown that the background effect interacted with the detrimental effects of target velocity on velocity gain, as performance decrements with increasing target velocity were particularly strong in the presence of a stationary background (Meyhöfer et al., 2019). This suggests that the inhibition of the influence of background stimuli and the precise matching of eye to target velocity compete for the same limited cognitive resources or rely on the same underlying system, possibly related to spatial attention or motion processing (Spering & Montagnini, 2011; Van Donkelaar & Drew, 2002).

Whereas the background and target velocity effects on SPEM have been consistently reported in the literature and are thus highly replicable at group level, less is known about their reliability at the level of individual differences. In this context, we refer to replicability as obtaining a similar finding with different random samples that capture the most important facets of the original research (Asendorpf et al., 2013). In contrast, reliability refers to the extent to which a measure consistently ranks individuals (Hedge et al., 2018).

In a widely noted recent methodological analysis, it was argued that robust and replicable experimental task effects at group level cannot necessarily be translated into reliable individual difference measures due to low between-subject variability, a phenomenon referred to as the reliability paradox (Hedge et al., 2018). In this context, Hedge et al. (2018) showed that several classic, attention demanding inhibitory tasks such as the Stroop and Eriksen flanker tasks show relatively poor test-retest reliability despite producing replicable task effects at group level. This phenomenon can be traced back to different objectives in experimental and correlative research fields concerning within- and between-subjects variance maximization.

Previous studies on the reliability of smooth pursuit performance have yielded mostly moderate to good reliability scores (Bargary et al., 2017; Calkins et al., 2003; Ettinger et al., 2003; Roy-Byrne et al., 1995; Versino et al., 1993). Importantly, the only study that distinguished between different target velocities reported better reliability for faster targets (Ettinger et al., 2003), suggesting that reliability might dependent on overall demands on the pursuit system, i.e. task difficulty. Most strikingly, to our knowledge, no previous study has reported the reliability of the background or target velocity effects in SPEM. This is an important gap in the literature, particularly given the observation of strong within-subject variance in these highly replicable group-level effects.

Although SPEM has long been studied in experimental or group designs (Barnes & Asselman, 1991; Haraldsson et al., 2008; Holzman et al., 1973), more recently, there has been an increasing focus on individual differences in SPEM using correlational designs (Bargary et al., 2017; Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007). Many of these studies have investigated correlations between SPEM measures and psychosis-spectrum personality traits, based on the continuum hypothesis of individual differences in personality and psychopathology (Ettinger et al., 2014; Haslam et al., 2020). Interestingly, studies on the relationship between SPEM performance and psychosis-related personality traits such as schizotypy typically yield only small correlations (Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007), possibly due to low reliability of task performance (as has been argued regarding cognitive tasks; Hedge et al., 2018). Therefore, the current study will focus on exploring the reliability of smooth pursuit in a paradigm with and without a stationary background and at different target velocities in a group of healthy participants, in order to estimate the reliability not only of pursuit performance in general but, specifically, of the target velocity and background effects.

In addition to this important primary objective, this study will address a number of related, secondary questions. As a secondary issue, the role of task duration in measuring reliability will be addressed. In experimental investigations, shorter tasks carry several advantages including economic efficiency, higher acceptability and easier applicability in patient or developmental populations. However, compared to longer tasks they bear the risk of lower reliability (Hedge et al., 2018; Wöstmann et al., 2013). The extent, to which task duration influences the reliability of SPEM, and in particular of the target velocity and background effects, has not yet been characterised. Therefore, this study will also address this issue using a modification of a task that has previously been shown to produce robust background and target velocity effects at group level (Meyhöfer et al., 2019). Specifically, in each session (test, retest), the task is presented twice, in two blocks, and reliability indices are calculated for the short (one block) as well as the long (two blocks) version of the task in order to characterise effects of task duration on reliability.

A further aim of this study is to explore how repeated exposure to the task both across sessions (test, retest) and in each session (first block, second block) influences the magnitude of the background and target velocity effects. While in standard SPEM tasks, in the absence of a background, no or only small effects of repeated exposure on pursuit performance across time points have been observed (Calkins et al., 2003; Ettinger et al., 2003), less is known about the influence of task repetition on the robustness of the background and target velocity effects. Complex interactions between perceptual and motor learning may help to automate behaviour and improve performance over time (Censor et al., 2012; Ostry & Gribble, 2016). By presenting the task in two blocks in each session and twice across two sessions over the course of one week, we aim to investigate whether the background and target velocity effects can be replicated robustly within the same sample and to what extent they are affected by time. If interactions between time or block and background or target velocity are revealed, it is crucial to address this issue in future studies as they can act as confounding factors in longitudinal designs.

In summary, this study had six specific aims: (1) to replicate earlier findings of reduced smooth pursuit performance in the presence of a stationary background and at higher target velocities, (2) to explore the test-retest and split-half reliability of smooth pursuit performance at different target velocities with and without a stationary background, (3) to specifically explore the reliability of the background and target velocity effects, (4) to investigate whether reliability increases when using a longer version of the task, (5) to explore the effects of repeated task blocks on performance, and finally, (6) to explore how repeated exposure to the task across sessions influences the magnitude of the background and target velocity effects.

2. Materials and methods

2.1. Power

To detect a significant intraclass correlation ICC of 0.40 (the threshold for fair reliability according to Cicchetti, 1994) compared to no correlation at all with 0.80 power, a sample size of least 39.5 participants is necessary (Walter et al., 1998). With at least 43.5 participants it is possible to detect a difference between fair (0.40) and good (0.60) reliabilities with 0.80 power (Walter et al., 1998). Concerning the background and target velocity effects, at least 26 participants were needed to detect a large effect ($\eta_p^2 = 0.26$) with at least 0.80 power (Faul et al., 2007). Thus, the minimum sample size we aimed for was 44 participants.

2.2. Participants

Participants were recruited via advertisements on the campus of the University of Bonn, circular emails and social media. Exclusion criteria were current diagnosis of physical, psychiatric or neurological condition and current consumption of prescription or over-the-counter medication (except for oral contraceptives in women, nutritional supplements or thyroid drugs). Smokers were asked to abstain from smoking for at least 2 h prior to the sessions. Participants were included if they were healthy university students aged 18–35 years. All participants had normal or corrected-to-normal vision. The study procedures were approved by the research ethics committee of the Department of Psychology at the University of Bonn. Participants provided written, informed consent and received course credits for participation.

2.3. Study design and procedure

Upon recruitment, participants were asked to confirm inclusion and exclusion criteria and to fill in a short online questionnaire to assess demographic information (age, sex, current occupation, years of education, and handedness, assessed via the Edinburgh Handedness Inventory (Oldfield, 1971)). If suitable, they were invited to take part in two sessions in the eye-tracking laboratory. The assessments were carried out at the same time of the day (± 2 h) in two sessions (T1, T2) approximately one week apart (7 days, ± 2 days).

In each session, the task described in 2.4 was carried out two times (block A vs. block B) with a short break in between. In total, one session took no longer than 15 min.

2.4. Task

The task was the same as the one used by Meyhöfer et al. (2019) and is available here (https://osf.io/qbtcf). It was written using Experiment Builder (SR Research Ltd., Ontario, Canada, version 1.10) and presented on the inner 1680 × 1050 px of a flat-screen BenQ monitor (screen dimensions 42.9 × 22.2 cm; resolution 1920 × 1080 pixels; refresh rate 144 Hz). The task was presented on a black background (RGB = 0, 0, 0) in a block design in randomized order. The target was a grey circle (RGB = 128, 128, 128; diameter = 15px/0.27°, stroke width = 5px/0.09°) moving horizontally between ±432px (7.89°) across the screen in a sinusoidal waveform at three different target velocities (corresponding to frequencies of 0.2 Hz, 0.4 Hz, 0.6 Hz), always starting from the central position (0°, 0°). The sinusoidal pattern indicates that target velocity constantly changed over time, accelerating towards the center of the screen, and decelerating towards the turning points. Peak and average velocities were 9.91°/s and 6.31°/s for the 0.2 Hz target, 19.83°/s and 12.62°/s for the 0.4 Hz target and 29.74°/s and 18.94°/s for the 0.6 Hz target. Target trajectories for the three target velocity conditions are depicted in Fig. 1 along with exemplary eye position data from one participant.

Each target velocity condition was presented once on a blank and once on a structured stationary background (Fig. 2), resulting in a total of 6 blocks, each lasting 30 s. The stationary background consisted of a six-by-six grid of white circles (RGB = 255, 255, 255; diameter = 15px/0.27°, stroke width = 5px/0.09°) symmetrically distributed along the horizontal and vertical plane of the screen (corner coordinates in pixels: 408, 310; 408, 740; 1272, 310; 1272, 740).

Between blocks, a fixation circle was presented. Participants rested their head on a chin-rest and were instructed to follow the target as accurately as possible with their eyes while keeping their head still. At

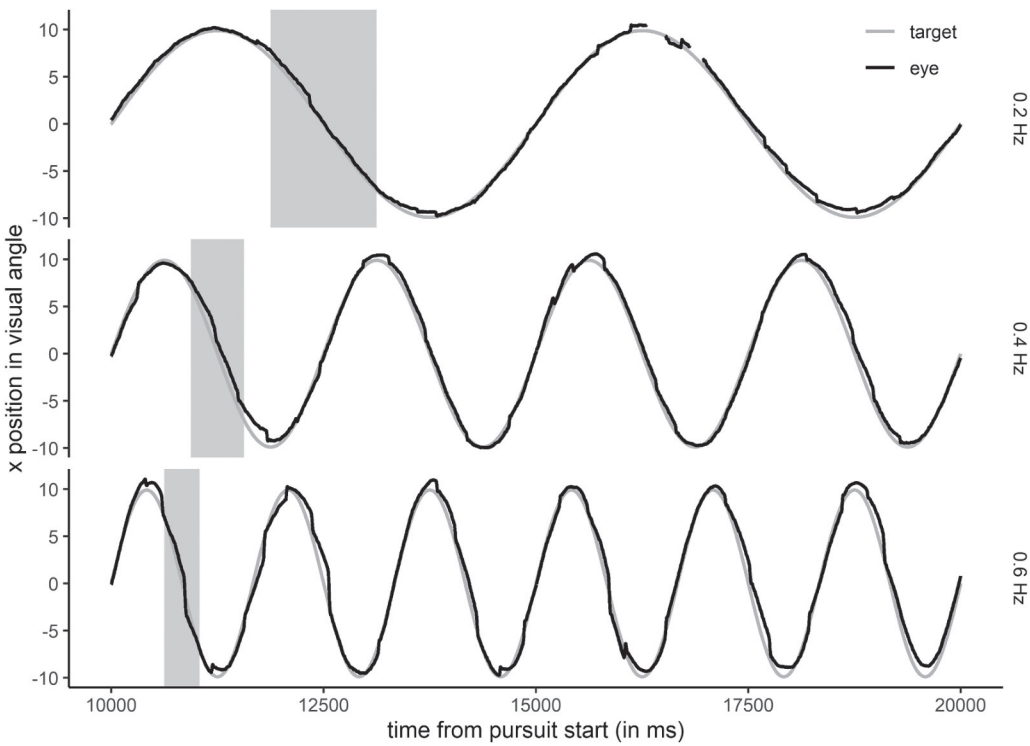

Fig. 1. Target and eye trajectories for the three different target velocities and window of gain analysis.
Legend: Trajectories of the target and exemplary eye data of one participant for the middle 10 s of each target velocity condition without background. Missing eye data indicate blinks. Grey shaded areas show the critical interval for gain analysis (only shown for the first half-ramp) for each of the target velocity conditions.

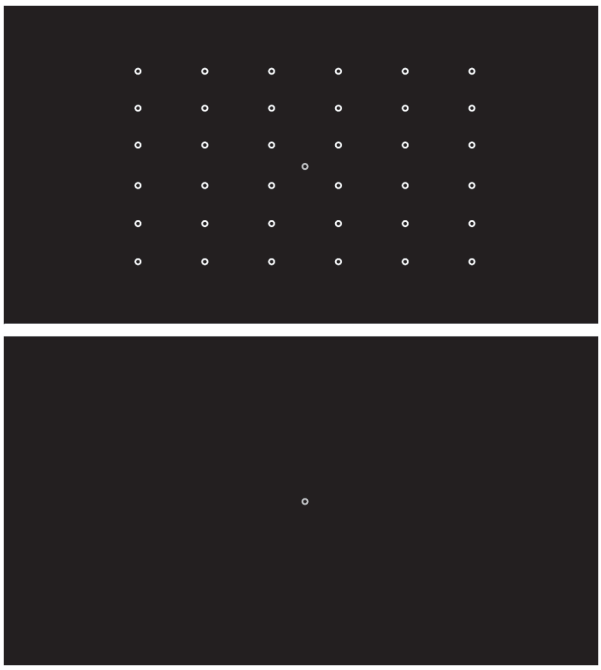

Fig. 2. Smooth pursuit target display.
Legend: The upper panel depicts the target display in the background condition. The lower panel depicts the target display in the no background condition. Both panels show the grey target at the center of the screen.

the beginning of each session, they performed a brief practice block in order to get familiarized with the task. The practise block consisted of four trials, each lasting 5 s in the following order: 0.4 Hz without structured background, 0.2 Hz with structured background, 0.4 Hz with structured background, 0.6 Hz without structured background.

2.5. Eye movement recording

To record eye movements, a desktop-mounted video-based combined pupil and corneal reflection eye-tracker (EyeLink 1000, SR Research, Ottawa, Ontario, Canada) was used. A centroid pupil-tracking algorithm was employed to detect pupil and corneal reflection of the right eye at a sampling rate of 1000 Hz. Prior to the task, a five-point horizontal-vertical calibration was performed. Distance from eye to monitor was approximately 70 cm.

2.6. Eye movement preprocessing

Eye movement data were preprocessed in Matlab R2019B. As we were not interested in the initiation phase of pursuit, the first excursion of the target from the centre to the peripheral turnaround point was excluded from the analyses.

Velocity gain was calculated as the average ratio of mean eye velocity and mean target velocity for the middle 50% of each half-cycle (the excursion of the target from one peripheral turnaround point to the other) for segments longer than 50 ms excluding blinks and saccades. The critical interval for gain analysis is depicted in Fig. 1. Saccades were identified using velocity ($\geq 22°/s$) and acceleration ($\geq 3800°/s^2$) criteria. Exclusion of blinks and saccades resulted in segments of different lengths that were time-weighted in the averaging procedure according to the duration of the segments.

To compare reliability between the short and long versions of the task, all dependent variables were also calculated for a joint version of blocks A and B of each session. To do so, data of relevant segments (i. e. after exclusion of blinks or saccades) of blocks A and B were again time-weighted according to the duration of the segment and then averaged.

Background effects were calculated separately for each target velocity condition by subtracting the gain values of the background condition from the no background condition. Target velocity effects were calculated separately for each background condition by subtracting the gain values of the 0.6 Hz condition from the 0.2 Hz condition.

The present paper focuses on pursuit gain as the primary outcome variable of pursuit. However, other outcomes are also important (Orban de Xivry & Lefèvre, 2007). Therefore, additional analyses of catch-up saccade rate and root mean square error (RMSE) are provided in the Supplementary Material.

2.7. Statistical analysis

Statistical analyses were carried out using R with the following packages: *ez* V.4.4.0 for analyses of variance (ANOVAs) (Lawrence, 2016), *rstatix* V.0.5.0 for pairwise *t*-tests (Kassambra, 2020), *irr* V.0.84.1 for ICCs (Gamer et al., 2019), *psych* V.1.9.12.31 for Pearson correlations (Revelle, 2019) and *tidyverse* V.1.3.0 for general data management (Wickham et al., 2019).

The significance threshold for all analyses was $\alpha = 0.05$. Outliers were identified separately for each condition. Values were defined as outliers if they exceeded the mean plus three times the interquartile range (IQR) criterion or fell below the mean minus three times the IQR criterion. If the IQR was 0, outliers were not defined. Participants were excluded from analyses of variance if their scores were defined as outliers in more than half of the conditions. Participants were excluded from reliability analyses of those condition pairs, where at least one of two scores were defined as an outlier.

2.7.1. Test-retest reliability

To assess test-retest reliability, both Pearson and intraclass correlations (ICC) between T1 and T2 were calculated separately for the short (only block A) and long (blocks A and B combined) versions of the task. Additionally, they were also calculated for the background and target velocity effects. For ICCs, we used the two-way mixed-effect model for single measurements as a measure of absolute agreement (McGraw & Wong, 1996). ICCs have been widely used to assess test-retest reliabilities for a variety of outcomes (Bargary et al., 2017; Ettinger et al., 2003; Hedge et al., 2018).

To facilitate comparison, 95% confidence intervals were calculated. Reliability coefficients are interpreted according to the guidelines proposed by Cicchetti (1994), indicating that values less than 0.40 are poor, values between 0.40 and 0.59 are fair, values between 0.60 and 0.74 are good and values between 0.75 and 1.00 are excellent.

2.7.2. Split-half reliability

To assess split-half reliability, we calculated Pearson correlations and ICCs between block A and block B separately for T1 and T2. Additionally, they were also calculated for the background and target velocity effects.

2.7.3. Analyses of variance

To assess the effects of background, target velocity, block and time on velocity gain, we carried out a four-way repeated-measures ANOVA with the within-subjects factors background (present, absent), target velocity (0.2 Hz, 0.4 Hz, 0.6 Hz), block (A, B) and time (T1, T2) for pursuit gain as the dependent variable. Effect sizes were calculated as partial eta squared. If the sphericity assumption was violated, Greenhouse-Geisser correction was applied. Uncorrected degrees of freedom and Greenhouse-Geisser ε were calculated. Bonferroni-corrected *t*-tests were calculated as post hoc tests with d_{av} (Lakens, 2013) as effect size. Uncorrected *p*-values were obtained but significance was inferred from corrected alpha-thresholds.

Study data and the analysis code are available at https://osf.io/qbtcf.

3. Results

3.1. Participants

The final sample consisted of $N = 45$ participants (17 males, 28 females), aged $M = 23.00$ ($SD = 3.02$) years. Six additional participants completed T1 but did not return for T2. Those participants are not included in the analyses. Additionally, one participant (male) was excluded from the ANOVA because his scores were outliers in more than half of the conditions.

The mean absolute difference between T1 and T2 was 7.07 days ($SD = 0.33$ days, minimum = 7 days, maximum = 9 days). The mean absolute difference between the starting times of the two sessions was 7.78 min ($SD = 18.43$ min, minimum = 0 min, maximum = 110 min).

3.2. Descriptive results

Descriptive statistics of all dependent variables are shown in Table 1. As can be seen descriptively, both the presence of a stationary background and an increase in target velocity substantially affected performance, indicative of the expected background and target velocity effects (see Table 2; for detailed statistical analyses of these effects, see 3.4).

3.3. Reliability analyses

Results of the reliability analyses are shown in Supplementary Table 1 and Fig. 3 (ICCs only, Pearson correlations can be found in Supplementary Fig. 1). The number of outliers in each condition that were removed from the analyses can be found in Supplementary Table 4.

For the direct performance measures, Pearson correlations ranged from 0.51 to 0.94. ICCs were very similar to Pearson correlations and ranged from 0.50 to 0.92. Reliabilities were fair to good for the 0.2 Hz no background condition and good to excellent for all other conditions. Descriptively, in almost all conditions, reliability was higher in the presence of a stationary background and at higher target velocities.

Reliability indicators of the background and target velocity effects of velocity gain can be found in Supplementary Tables 2 and 3. For the background effect, reliability was good to excellent, ranging from 0.60 to 0.86 (Pearson correlations) and 0.59 and 0.85 (ICCs). For the target velocity effect, reliability was fair to excellent, ranging from 0.52 to 0.85 (Pearson correlations) and 0.51 to 0.86 (ICCs). Fig. 4 shows the correlations between T1 and T2 of the background effects of pursuit gain for the long version. Fig. 5 shows the correlations between T1 and T2 of the target velocity effects of pursuit gain for the long version.

For the direct performance measures, the longer task version always achieved higher test-retest Pearson correlations and ICCs than the shorter version except for the 0.4 Hz no background condition, where the opposite pattern was found. On average, the longer version was more reliable than the shorter version by 0.037 (Pearson correlation) and 0.042 (ICCs). The same pattern of results was found for the difference scores (background effect, target velocity effect). For the background effect, the longer version outperformed the shorter version on average by 0.08 (Pearson correlations) or 0.07 (ICCs). For the target velocity effect, the average difference between the short and long version was 0.07 (both for Pearson correlations and ICCs). For all conditions, confidence intervals of the short and long version of the task overlapped.

Split-half reliabilities reached results similar to test-retest reliabilities. In all conditions, split-half reliability was higher at T2 than at T1. The average difference between split-half reliabilities at T1 and T2 was 0.130 (Pearson correlations) and 0.135 (ICCs) for the direct performance measures. However, confidence intervals overlapped for all conditions except for the 0.2 Hz background condition. This pattern of results was similar for the difference scores. For the background effect, T2 split-half reliability outperformed T1 split-half reliability on average by 0.113 (Pearson) or 0.127 (ICCs). For the target velocity effect, T2 split-half reliability outperformed T1 split-half reliability on average by 0.195 (Pearson) or 0.210 (ICCs). All confidence intervals of T1 and T2 split-half reliability overlapped for the difference scores.

Table 1
Descriptive statistics of velocity gain.

Target velocity	Time	Block	Background		No background	
			M	*SD*	*M*	*SD*
0.2 Hz	T1	A	0.87	0.11	0.96	0.04
		B	0.84	0.14	0.96	0.04
		A + B	0.86	0.11	0.96	0.04
	T2	A	0.86	0.14	0.95	0.05
		B	0.87	0.13	0.96	0.05
		A + B	0.86	0.13	0.96	0.05
0.4 Hz	T1	A	0.75	0.17	0.90	0.08
		B	0.76	0.18	0.90	0.08
		A + B	0.75	0.17	0.90	0.07
	T2	A	0.77	0.18	0.90	0.07
		B	0.78	0.18	0.91	0.07
		A + B	0.77	0.17	0.90	0.07
0.6 Hz	T1	A	0.60	0.21	0.79	0.15
		B	0.61	0.23	0.81	0.13
		A + B	0.60	0.21	0.80	0.13
	T2	A	0.66	0.21	0.82	0.13
		B	0.68	0.21	0.83	0.12
		A + B	0.67	0.20	0.83	0.12

Descriptive statistics (*M* mean and *SD* standard deviation) of velocity gain of the background and no background conditions at three different target velocities of two sessions (T1, T2) one week apart, separately for blocks A and B and a joint version of the blocks (A + B) in a sample of $N = 44$ participants.

3.4. Task and time effects

Analyses of velocity gain revealed main effects of background ($F_{(1, 43)} = 69.87$, $p < .001$, $\eta_p^2 = 0.619$), target velocity ($F_{(2, 86)} = 114.69$, $p < .001$, $\eta_p^2 = 0.727$, $\epsilon = 0.62$) and time ($F_{(1, 43)} = 7.16$, $p = .011$, $\eta_p^2 = 0.143$). Gain was higher without a stationary background, at lower target velocities and at T2.

In addition, we found a significant two-way interaction between background and target velocity ($F_{(2, 86)} = 20.77$, $p < .001$, $\eta_p^2 = 0.326$). Bonferroni-corrected *t*-tests revealed significant differences between the background conditions at all target velocities (0.2 Hz: background vs. no background $t_{(43)} = -6.47$, $p < .001$, $d_{av} = -1.11$; 0.4 Hz: background vs. no background $t_{(43)} = -7.16$, $p < .001$, $d_{av} = -1.10$; 0.6 Hz: background vs. no background $t_{(43)} = -9.43$, $p < .001$, $d_{av} = -1.01$). Qualitatively, the interaction suggests that the effect of target velocity was stronger in the presence of a structured background.

We also found a significant two-way interaction between background and time ($F_{(1, 43)} = 8.44$, $p = .006$, $\eta_p^2 = 0.164$). Bonferroni-corrected *t*-tests showed that the improvement in gain from T1 to T2 was significant only in the background condition but not in the absence of a background (background: T1 vs. T2 $t_{(43)} = -3.49$, $p < .001$, $d_{av} = -0.15$; no background: T1 vs. T2 $t_{(43)} = -1.09$, $p = .28$, n.s. at the Bonferroni-corrected alpha-level, $d_{av} = -0.08$). The background effect was smaller at T2 than at T1, but achieved significance in both sessions (T1: background vs. no background $t_{(43)} = -9.09$, $p < .001$, $d_{av} = -0.92$; T2: background vs. no background $t_{(43)} = -7.25$, $p < .001$, $d_{av} = -0.86$).

Moreover, there was a two-way interaction between target velocity and time ($F_{(2, 86)} = 25.29$, $p < .001$, $\eta_p^2 = 0.370$, $\epsilon = 0.82$). Post hoc *t*-tests results showed that gain scores significantly increased from T1 to T2 only in the 0.6 Hz condition, but not in the lower target velocity conditions (0.2 Hz: T1 vs. T2 $t_{(43)} = 0.27$, $p = .79$, n.s. at the Bonferroni-corrected alpha-level, $d_{av} = 0.02$; 0.4 Hz: T1 vs. T2 $t_{(43)} = -1.37$, $p = .18$, n.s. at the Bonferroni-corrected alpha-level, $d_{av} = -0.08$; 0.6 Hz: T1 vs. T2 $t_{(43)} = -5.21$, $p < .001$, $d_{av} = -0.24$). Significant main effects of target velocity were found in both sessions, when analyzing them

Table 2
Descriptive statistics of the background and target velocity effects.

Time	Block	Background effect						Target velocity effect			
		0.2 Hz		0.4 Hz		0.6 Hz		Background		No background	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
T1	A	0.09	0.10	0.15	0.15	0.18	0.13	0.27	0.15	0.18	0.13
T1	B	0.12	0.12	0.14	0.14	0.20	0.16	0.24	0.17	0.16	0.12
T1	A + B	0.11	0.10	0.14	0.14	0.19	0.13	0.26	0.15	0.17	0.12
T2	A	0.09	0.12	0.13	0.14	0.16	0.14	0.20	0.15	0.13	0.11
T2	B	0.09	0.11	0.13	0.15	0.14	0.14	0.19	0.14	0.13	0.10
T2	A + B	0.09	0.11	0.13	0.13	0.15	0.13	0.19	0.13	0.13	0.10

Descriptive statistics (*M* mean and *SD* standard deviation) of velocity gain background effect (no background condition minus background condition) at three different target velocities and velocity gain target velocity effect (0.2 Hz condition minus 0.6 Hz condition) of the two background conditions of two sessions (T1, T2) one week apart, separately for blocks A and B and a joint version of the blocks (A + B) in a sample of $N = 44$ participants.

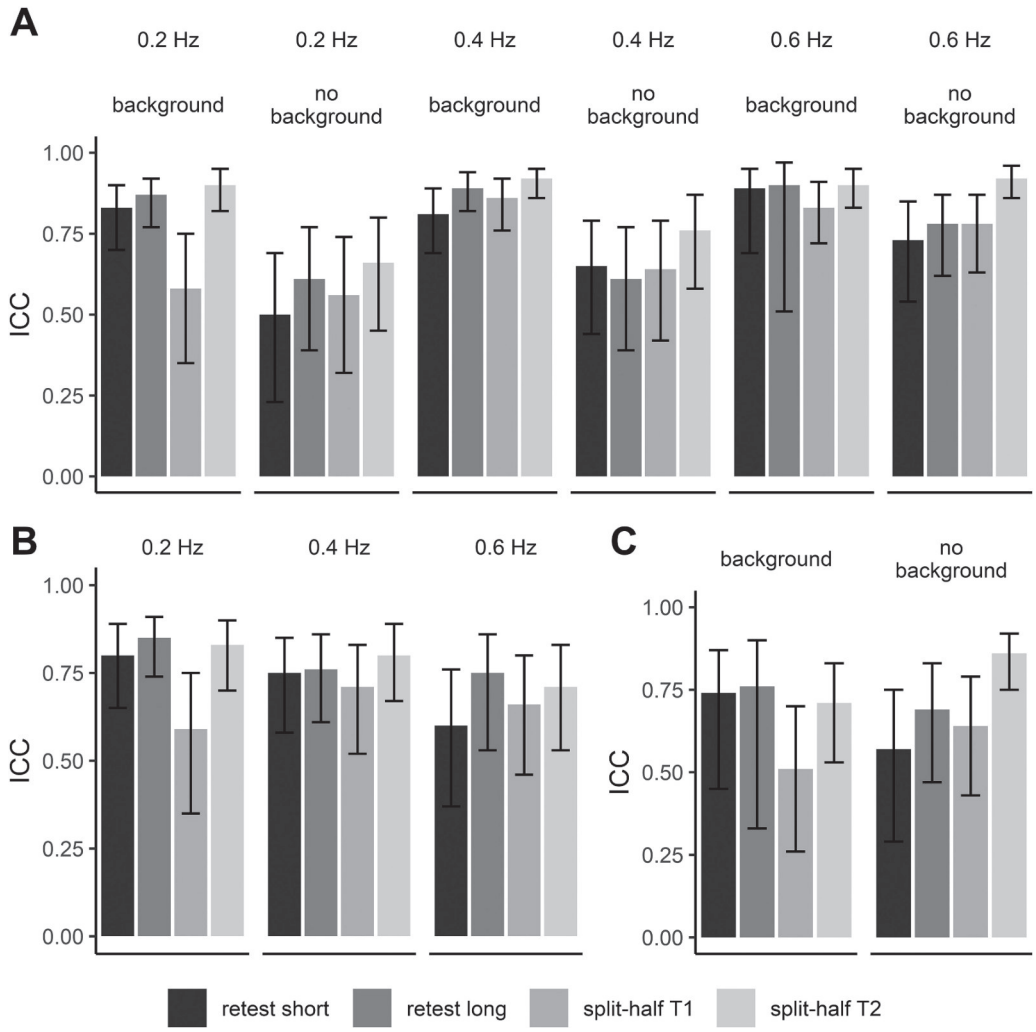

Fig. 3. Results of the reliability analyses (intraclass correlations).
Legend: Reliabilities for pursuit gain (Panel A) for the six background and target velocity conditions, pursuit gain background effect (Panel B; no background condition minus background condition) and pursuit gain target velocity effect (Panel C; 0.2 Hz condition minus 0.6 Hz condition). ICC = intraclass correlation. Error bars represent the upper and lower limit of the 95% confidence interval.

separately (T1: $F_{(2, 86)} = 124.75$, $p < .001$, $\eta_p^2 = 0.744$, $\epsilon = 0.62$; T2: $F_{(2, 86)} = 87.03$, $p < .001$, $\eta_p^2 = 0.669$, $\epsilon = 0.67$). However, the target velocity effect was smaller at T2.

There was no main effect of block and there were no further interactions (all $p > .05$). Supplementary Fig. 2 gives an overview of the task and time effects. Fig. 6 depicts the significant interactions.

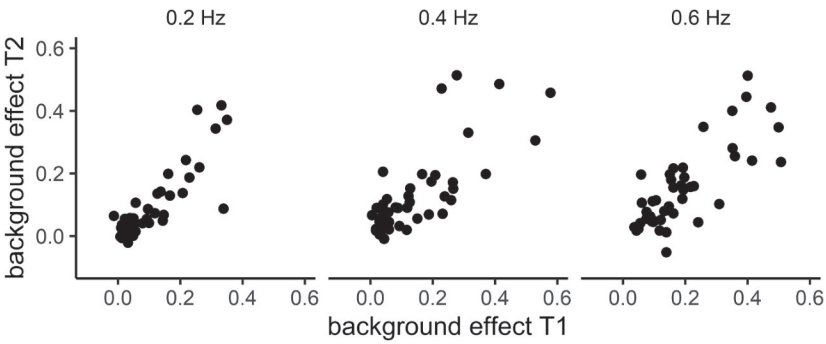

Fig. 4. Scatter plot of the background effect of velocity gain (long version) at T1 and T2 for the three target velocity conditions.

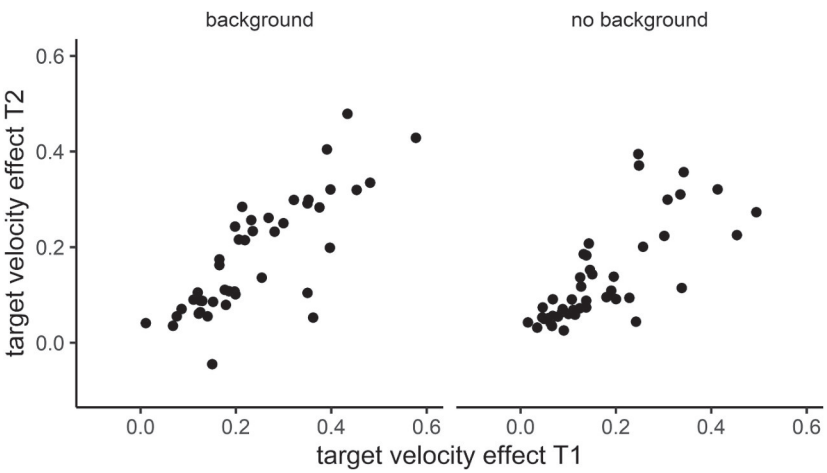

Fig. 5. Scatter plot of the target velocity effect of velocity gain (long version) at T1 and T2 for the two background conditions.

4. Discussion

The present study aimed to contribute to the controversial matter of the reliability of task effects in experimental psychology, termed the "reliability paradox" by Hedge et al. (2018). Specifically, we investigated the replicability and reliability of two well-established experimental effects in the domain of oculomotor control, viz. the detrimental effects of a stationary structured background and target velocity on smooth pursuit eye movement performance. To do so, healthy participants performed smooth pursuit tasks in a repeated-measures design in two sessions one week apart. The main results are as follows.

The presence of background distractors and higher target velocity impaired velocity gain, thereby replicating the background and target velocity effects, respectively.

Analyses of reliability revealed heterogeneous findings, with good to excellent reliabilities in the more challenging task conditions (higher target velocity and/or stationary background) and lower reliabilities in the absence of a stationary background or with lower target velocity. Importantly, the background effect revealed good to excellent reliability scores at all target velocities. Similarly, the target velocity effect reached predominantly good and excellent reliability scores.

Descriptively, the longer task version reached higher reliability than the shorter version, and split-half reliability was higher at T2 than at T1 for most task conditions and variables. However, differences were not significant and reliability scores fell in the same categories of interpretation (Cicchetti, 1994). Generally, Pearson correlations and ICCs reached converging results.

Repeated task exposure led to increased velocity gain at T2 compared to T1. However, this effect was driven by an increase in performance only in the presence of a structured background and at higher target velocities.

4.1. Reliability

The reliability indices obtained in this study were predominantly good or even excellent (Cicchetti, 1994).

For velocity gain, the primary measure of smooth pursuit performance, the study revealed excellent reliability scores in the presence of a stationary background and at higher target velocity. For slower targets and in the absence of a stationary background, however, reliability scores were lower, replicating earlier findings (Ettinger et al., 2003). The poorest reliability outcomes occurred in the putatively easiest version of the task, implying a correlation between task difficulty and reliability. As performance in those easier conditions was excellent and standard deviations were low, these results can be interpreted in terms of the reliability paradox (Hedge et al., 2018) since the sample was very homogenous in their responses in these conditions.

An interesting observation was that the decrease in performance (and increase in variance; Table 1) from the easier to the more difficult task conditions was comparably large for the target velocity and background manipulations. Strikingly, however, the improvement in reliability from the no background condition to the background condition was larger than from lowest to highest target velocity. This suggests that the higher reliability in the background condition was not merely due to

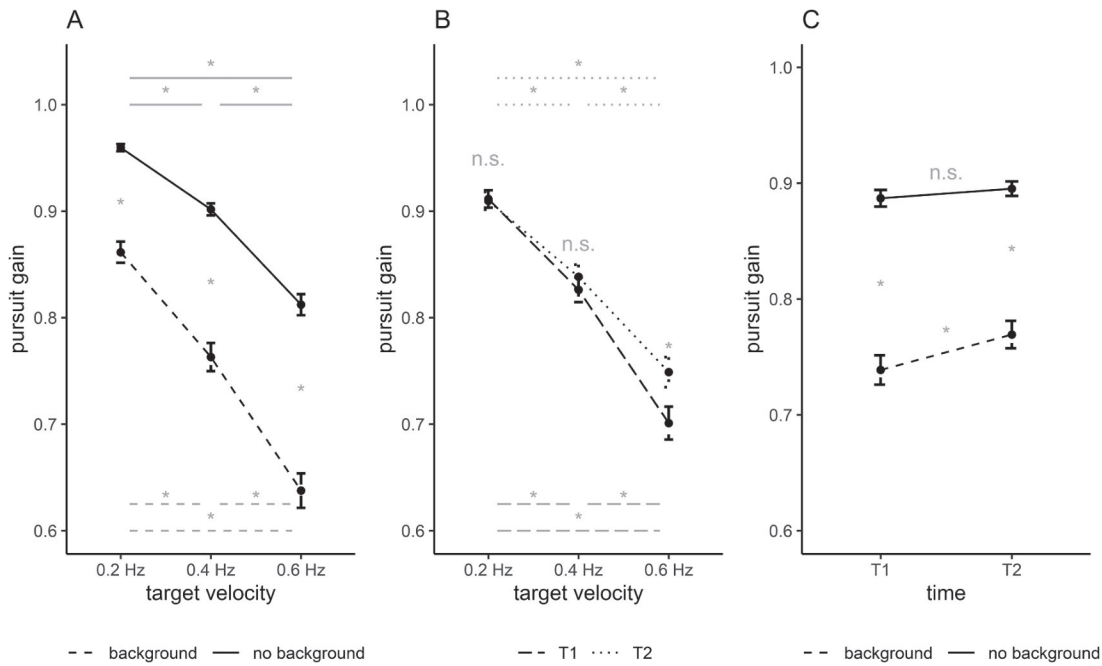

Fig. 6. Interactive effects of target velocity, background and time on pursuit velocity gain.
Legend: Two-way interaction of target velocity and background (Panel A), two-way interaction of target velocity and time (Panel B), two-way interaction of background and time (Panel C) on pursuit velocity gain. All interactions are significant at $\alpha = 0.05$. Significant *t*-tests after Bonferroni-correction are marked with an asterisk. Data are presented as mean ± standard errors.

greater variance in that condition compared to the no background condition. Instead, pursuing a target over a structured background appears to bring out inter-individual differences, possibly linked to enhanced recruitment of inhibitory processes (Lindner et al., 2001), that are highly reliable, and more so than in a high target velocity condition that yields comparable overall performance levels and variance.

For both the background and the target velocity effects, excellent reliability scores were obtained for the long version of the task for all levels of the other factor. These results, combined with the large magnitudes of the background and target velocity effect sizes at group level, are at odds with major claims of the reliability paradox. Specifically, in our study, between-subject variance was in fact so high (see Figs. 4 and 5) that excellent reliability scores could be ensured despite clear experimental effects at group level.

Earlier studies have revealed heterogeneous results for the reliability of difference measures depending on the specific task used (Hedge et al., 2018; Paap & Sawi, 2016; Soveri et al., 2018). Our results match the assumptions by Zimmerman and Williams (1998) concerning the circumstances under which difference scores can achieve good reliability. Specifically, variance and reliability were larger in the background condition than in the no background condition and at higher compared to lower target velocities (see Figs. 4 and 5, Table 1 and Supplementary Tables 1 to 3).

A potentially major conclusion from our findings is that oculomotor data might be better suited for individual difference research than outcomes from standard cognitive tasks focusing on manual-motor reaction times or error rates (Hedge et al., 2018). For instance, pursuit gain is less susceptible to common problems with reaction times or accuracy metrics such as speed-accuracy trade-offs or impurity of the measures (Draheim et al., 2019; Miller & Ulrich, 2013). Pursuit gain might therefore reflect the main function of smooth pursuit, the matching of eye velocity to target velocity, more accurately than reaction time measures reflect processes of inhibitory control, suggesting lower task impurity and higher ecological validity (Burgess et al., 2006; Miyake et al., 2000). In addition, smooth pursuit over a structured background is a behaviour shown regularly when exploring the environment, e.g., when looking at naturalistic scenes (Agtzidis et al., 2020; Startsev et al., 2019), indicative of a better match between the behaviour in the laboratory and in free viewing circumstances, compared to other inhibitory or visual tasks (Kristjánsson & Draschkow, 2021). Indeed, laboratory tasks of inhibitory control such as the Stroop task have been criticized for their lack of ecological validity (Burgess et al., 2006).

Castelhano and Henderson (2008) demonstrated that saccadic and fixational behaviour when viewing natural scenes is highly stable within participants across different stimuli. This might suggest that trial-to-trial variability in pursuit gain is smaller compared to classic inhibitory tasks, which in turn would facilitate higher reliability values as high trial variance has been identified as a major driver of low reliability in inhibition tasks (Rouder et al., 2019). Recently, de Haas and colleagues provided evidence not only for substantial interindividual differences in fixation pattern when viewing natural scenes but also for excellent test-retest and split-half reliabilities of these patterns in two independent samples (De Haas et al., 2019; Linka & de Haas, 2020), in line with the findings of the current study. However, the nature of smooth pursuit variability and its relation to reliability has to be explored in much more detail in future investigations. Still, our results suggest that robust experimental effects can indeed translate into reliable individual difference measures.

Interestingly, the reliability of the background effect declined at higher target velocities (especially when looking at the difference between the lowest and the intermediate and the lowest and highest target velocity, respectively). Conversely, reliability increased with higher target velocities for the direct performance measures. Possibly, reliability was poor for the lowest target velocity in the absence of a stationary background because of a ceiling effect of performance. At both sessions, participants were so accurate at pursuing the slow target that fluctuations between the sessions were random, resulting in low reliabilities. Higher target velocities decreased performance and

simultaneously increased between-subject variance, thereby facilitating higher reliabilities. Similarly, the presentation of a stationary background led to more between-subjects variance, enabling higher reliability values. The decrease in reliability of the background effect at higher target velocities might be due to the fact that the reliabilities mainly depend on variance in the background condition. As performance was quite homogeneous at 0.2 Hz in the absence of a stationary background and consequently the baseline was very similar between participants, the difference measures mainly reflect the background condition. A similar rationale has been argued by Hedge et al. (2018) for the explanation of the different reliabilities for reaction time and accuracy data.

The good reliabilities under the more difficult task conditions are promising, considering that in everyday life smooth pursuit occurs to more complex stimuli than in the present laboratory study. Future studies could therefore turn to investigating reliability of natural viewing behaviour (Agtzidis et al., 2020).

Descriptively, the longer version of the task reached higher reliability scores than the shorter version for almost all conditions, in accordance with previous investigations (Hedge et al., 2018; Wöstmann et al., 2013). However, for most variables, confidence intervals overlapped between the two versions, which consequently does not permit the conclusion of significant superiority of the longer task. In the future, therefore, the task length should be selected according to the specific study objectives, with the longer version recommended when individual differences are the main focus.

For most variables, split-half reliability scores for T2 were descriptively higher than for T1. The observed pattern of results can be interpreted as evidence of a reduction in error variance at T2, possibly due to better familiarity with the task. However, again, in most cases the confidence intervals overlapped, allowing for no firm conclusions to be drawn.

Pearson correlations and ICCs generally led to consistent or only slightly diverging results. Future investigations might therefore choose to report only one measure, preferably ICCs, as they not only rely on relative consistency but also contain additional information on absolute agreement (McGraw & Wong, 1996).

Our results extend previous studies on smooth pursuit reliability due to differences in the methodological approach. Firstly, in contrast to Bargary et al. (2017) and Ettinger et al. (2003), we did not use a triangular, constant-velocity target but a target following a sinusoidal velocity pattern, as is common in clinical smooth pursuit research (Barnes, 2008; Levy et al., 2010; Meyhöfer et al., 2015; Nkam et al., 2010; Ohlendorf et al., 2007). Secondly, we reported reliability scores separately for each of the target velocity and background conditions. This approach proved to be very valuable as our results suggest that reliability scores widely differed between different task configurations. Lastly, the present study was the first to directly assess the reliability of the background and target velocity effects, which had not yet been investigated despite these effects being well replicated experimental group-level findings in the pursuit literature.

The observed pattern of results speaks for the general stability and likely trait nature of eye movement performance, which has previously been shown for saccades using latent-state-trait modelling (Meyhöfer et al., 2016). Similar modelling approaches should also be adopted in the future to delineate the contribution of stable person effects and situational influences on smooth pursuit performance.

4.2. Task and time effects

4.2.1. Background

For all levels of target velocity, we found strong background effects, indicative of worse performance in the presence of background stimuli, in line with earlier findings (Barnes & Crombie, 1985; Collewijn & Tamminga, 1984; Hutton et al., 2000; Meyhöfer et al., 2019). This pattern of results can be explained by background induced optokinetic drive that slowed eye movements (Barnes, 2008; Lawden et al., 1995). The highly structured background stimuli provided a strong signal to the optokinetic reflex, interfering with the smooth pursuit tracking of the target. As a consequence, participants had to actively engage cognitive resources to selectively enhance processing of the target stimulus (Barnes & Crombie, 1985) or inhibit background processing in order to perform stable smooth pursuit. The latter might be achieved by attenuating sensitivity to global motion signals in the opposite direction of the pursuit target, which also corresponds to the direction of self-induced retinal motion (Lindner et al., 2001).

Lower pursuit performance in the presence of a structured background might depend on gradual attention shifts between target and background stimuli (Kerzel et al., 2008). These shifts may be modulated by feature similarity between target and background distractors (Störmer et al., 2011). For example, it has been shown that increased attention to the target due to a target-related secondary task may even improve smooth pursuit performance despite a general increase in demands due to the secondary task (Stubbs et al., 2018). Future studies should further explore the role of attention on target and distractor or background stimuli. In this context, partial processing of the background may even be beneficial in some cases, as it can also provide valuable information about future events such as target trajectory (Eggert et al., 2009; Ladda et al., 2007).

Results from a lesion study suggest that inhibition of irrelevant background distractors might depend on parietal cortex and frontoparietal white-matter connections (Lawden et al., 1995). Interestingly, the posterior parietal cortex has also been associated with divided attention between a SPEM target stimulus and an additional auditory target (Baumann & Greenlee, 2009) as well as the dissociation between the focus of attention and gaze (Ohlendorf et al., 2007). The specific role of this area in the context of smooth pursuit against a structured background might concern motion processing relative to a frame of reference (Ohlendorf et al., 2010) or attentional control (Baumann & Greenlee, 2009). However, the studies discussed above reported different peak locations in the parietal cortex, so further research is needed concerning the exact functions of the parietal cortex and its subregions during this complex sensorimotor process. In addition, it has been suggested that intact pathways of the basal ganglia are necessary for successful suppression of irrelevant stimuli during smooth pursuit (Henderson et al., 2011).

We also detected significant background × target velocity interactions, indicating that the adverse effects of a stationary background were particularly pronounced at higher target velocities, in line with previous findings (Howard & Marton, 1992; Hutton et al., 2000; Meyhöfer et al., 2019). Thus, if the pursuit system is challenged – by fast targets, structured backgrounds or the combination of both – performance deteriorates substantially. These effects might indicate that both factors rely on the same underlying process, for example spatial attention, which is important for both the matching of eye to target velocity and the inhibition of background processing. Interestingly, it has been shown that the focus of attention is modulated by target velocity (Van Donkelaar & Drew, 2002). The faster the target moves, the further ahead of the target attention shifts. If the target is no longer at the center of attention at high velocities, pursuit gain might be reduced as the matching of eye to target velocity is impeded. However, the assumed asymmetrical distribution of attention biased ahead of the target is not supported by all lines of evidence (Souto & Kerzel, 2021). The processing benefit at locations ahead of the target has been found in reaction time paradigms and with frequency-tagged steady-state visual evoked potentials (Chen et al., 2017; Van Donkelaar, 1999; Van Donkelaar & Drew, 2002) but not in perceptual discriminations tasks (Lovejoy et al., 2009; Watamaniuk & Heinen, 2015). It is debated whether these effects in fact represent spatial attention or rather visual processes such as the suppression of visual signals opposite of target direction (Souto & Kerzel, 2021). Therefore, more research is needed to investigate the relationship between smooth pursuit and attention and

how they relate to target velocity and the background the target is presented on.

Another important aspect to consider in explaining the background × target velocity interaction is velocity perception during pursuit, which has been shown to depend on the background the target is presented on (Raymond et al., 1984). However, this has been probed relative to a reference stimulus presented before the target and should be investigated in more detail.

4.2.2. Target velocity

Additionally, we aimed to replicate the effects of target velocity on pursuit performance. In line with previous research and our hypotheses, performance was affected by target velocity (Collewijn & Tamminga, 1984; Lisberger et al., 1981; Meyhöfer et al., 2019), with pursuit gain being lower at higher target velocity. Effect size measures indicated that target velocity accounted for a substantial part of pursuit gain variance. The manipulation of target velocity can therefore be regarded as a valuable tool to control overall task demands. Our results add to the literature by highlighting the importance of using more than a single level of target velocity since some task manipulations only become evident at a certain level of target velocity (e.g. background × target velocity interactions). As a consequence, studies that employ only a single level of target velocity might be limited in their explanatory power.

Although the effects of manipulating target velocity have been studied extensively, to our knowledge, target velocity effects as the difference in performance between two levels of target velocity are not typically reported. Therefore, here, we demonstrate the feasibility of this approach. Individual target velocity effects may prove to be particularly useful for later use in individual differences research to better understand between-subjects variance.

4.2.3. Block

In order to examine the course of performance over time, data were analyzed for within-session performance changes from the first to the second half of the experiment. However, no differences between the two blocks could be observed. This absence of effects suggests that performance is relatively stable over a duration of several minutes. This could be due to the fact that at the beginning of each session, participants had the opportunity to familiarize themselves with the task through a practice session. This way, understanding of instructions and familiarity with the study setup was ensured and did not have to be acquired during task performance, which may have led to differences between blocks.

4.2.4. Time

We found a significant main effect of time for pursuit gain, indicative of improvement of performance from the first (T1) to the second (T2) session day over a period of one week.

Interactions between time and background conditions as well as time and target velocity revealed that these effects only occurred in the more challenging conditions, namely in the presence of a stationary background and at higher target velocities. This pattern indicates that repetition or practice effects might depend on baseline performance, which is related to task difficulty. Performance in the easier task conditions may already be near ceiling at T1, with gain scores close to 1. Thus, the performance level could not improve any further. Performance improvements in the more difficult task conditions might be due to learning processes, which is consistent with previous results from healthy and neurological samples (Eibenberger et al., 2012; Kerkhoff et al., 2013). If the task is to be used in study designs with multiple assessments, the issue of performance changes due to multiple exposure to the task needs to be considered. Importantly, however, the background effect proved to be highly robust and could be observed in both sessions with large effect sizes. The same pattern of results was observed for the target velocity effect. Thus, time only influenced the size of the background or target velocity effect but not the effect as such.

Future investigations should further explore whether or at what point performance stabilizes over time by employing multiple assessments over several days.

We aimed to control the influence of previous exposure to the experimental stimulus sets by introducing a brief practice block at the beginning of each session. However, familiarity with the assessment setting might still influence performance, which is problematic especially in repeated-measures designs, where participants undergo experimental manipulations at different time points. In order to further reduce this influence in the future, the practice block could be presented for a longer time or participants could get familiarized with the task during an initial baseline measurement. The latter may also help to examine possible baseline effects on learning as stabilization might occur earlier or later dependent on initial performance levels.

4.3. Limitations

The study was limited in the number of sessions. In order to explore the effects of repeated exposure to the same task in more detail, more measurement sessions would have been informative. Also, latent state trait modelling (Geiser et al., 2015) of smooth pursuit data is called for to formally estimate trait and state components of variance as well as measurement error.

4.4. Conclusion

In this study, we have presented reliability scores and task effects for a smooth pursuit paradigm employing three target velocities and a background vs. no background condition in two sessions one week apart in a sample of 45 participants. Presenting background distractors and increasing target velocity impaired smooth pursuit performance consistent with previous investigations.

Background as well as target velocity effects were robustly replicated in both sessions. However, practice effects between the two sessions were observed in the more difficult task conditions and should be considered in future investigations using longitudinal designs.

Reliability results were good, especially at higher target velocities and/or in the presence of a stationary background. Reliability scores were largely in line with previous literature but also revealed interesting novel insights, especially concerning the role of task difficulty. Background as well as target velocity effects proved to be highly reliable. These findings demonstrate, in contrast to some other cognitive tasks (Hedge et al., 2018), that a task can produce both robust experimental effects and reliable individual difference outcomes.

Declaration of competing interest

None.

Acknowledgements

The PhD project of Rebekka Schröder is funded by the German Academic Scholarship Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.actpsy.2021.103364.

References

Agtzidis, I., Meyhöfer, I., Dorr, M., & Lencer, R. (2020). Following Forrest Gump: Smooth pursuit related brain activation during free movie viewing. *NeuroImage, 216*, Article 116491. https://doi.org/10.1016/j.neuroimage.2019.116491

Asendorpf, J. B., Conner, M., Fruyt, F.d., Houwer, J.d., Denissen, J. J. A., Fiedler, K., … Wicherts, J. M. (2013). Recommendations for increasing replicability in psychology. *European Journal of Personality, 27*(2), 108–119. https://doi.org/10.1002/per.1919

Bargary, G., Bosten, J. M., Goodbourn, P. T., Lawrance-Owen, A. J., Hogg, R. E., & Mollon, J. D. (2017). Individual differences in human eye movements: An oculomotor signature? *Vision Research, 141*, 157–169. https://doi.org/10.1016/j.visres.2017.03.001

Barnes, G. R. (2008). Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition, 68*(3), 309–326. https://doi.org/10.1016/j.bandc.2008.08.020

Barnes, G. R., & Asselman, P. T. (1991). The mechanism of prediction in human smooth pursuit eye movements. *The Journal of Physiology, 439*, 439–461. https://doi.org/10.1113/jphysiol.1991.sp018675

Barnes, G. R., & Crombie, J. W. (1985). The interaction of conflicting retinal motion stimuli in oculomotor control. *Experimental Brain Research, 59*(3), 548–558. https://doi.org/10.1007/BF00261346

Baumann, O., & Greenlee, M. W. (2009). Effects of attention to auditory motion on cortical activations during smooth pursuit eye tracking. *PLoS One, 4*(9), Article e7110. https://doi.org/10.1371/journal.pone.0007110

Buizza, A., & Schmid, R. (1986). Velocity characteristics of smooth pursuit eye movements to different patterns of target motion. *Experimental Brain Research, 63*(2), 395–401. https://doi.org/10.1007/BF00236858

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M.-A., Dawson, D. R., … Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society : JINS, 12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Calkins, M. E., Iacono, W. G., & Curtis, C. E. (2003). Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology, 49*(2), 139–146. https://doi.org/10.1016/S0167-8760(03)00101-6

Castelhano, M. S., & Henderson, J. M. (2008). Stable individual differences across images in human saccadic eye movements. *Canadian Journal of Experimental Psychology = Revue Canadienne De Psychologie Experimentale, 62*(1), 1–14. https://doi.org/10.1037/1196-1961.62.1.1

Censor, N., Sagi, D., & Cohen, L. G. (2012). Common mechanisms of human perceptual and motor learning. *Nature Reviews Neuroscience, 13*(9), 658–664. https://doi.org/10.1038/nrn3315

Chen, J., Valsecchi, M., & Gegenfurtner, K. R. (2017). Attention is allocated closely ahead of the target during smooth pursuit eye movements: Evidence from EEG frequency tagging. *Neuropsychologia, 102*, 206–216. https://doi.org/10.1016/j.neuropsychologia.2017.06.024

Cicchetti, D. V. (1994). Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment, 6*(4), 284–290. https://doi.org/10.1037/1040-3590.6.4.284

Collewijn, H., & Tamminga, E. P. (1984). Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *The Journal of Physiology, 351*, 217–250. https://doi.org/10.1113/jphysiol.1984.sp015242

De Haas, B., Iakovidis, A. L., Schwarzkopf, D. S., & Gegenfurtner, K. R. (2019). Individual differences in visual salience vary along semantic dimensions. *Proceedings of the National Academy of Sciences of the United States of America, 116*(24), 11687–11692. https://doi.org/10.1073/pnas.1820553116

Draheim, C., Mashburn, C. A., Martin, J. D., & Engle, R. W. (2019). Reaction time in differential and developmental research: A review and commentary on the problems and alternatives. *Psychological Bulletin, 145*(5), 508–535. https://doi.org/10.1037/bul0000192

Eggert, T., Ladda, J., & Straube, A. (2009). Inferring the future target trajectory from visual context: Is visual background structure used for anticipatory smooth pursuit? *Experimental Brain Research, 196*(2), 205–215. https://doi.org/10.1007/s00221-009-1840-3

Eibenberger, K., Ring, M., & Haslwanter, T. (2012). Sustained effects for training of smooth pursuit plasticity. *Experimental Brain Research, 218*(1), 81–89. https://doi.org/10.1007/s00221-012-3009-8

Ettinger, U., Kumari, V., Crawford, T. J., Davis, R. E., Sharma, T., & Corr, P. J. (2003). Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology, 40*(4), 620–628. https://doi.org/10.1111/1469-8986.00063

Ettinger, U., Meyhöfer, I., Steffens, M., Wagner, M., & Koutsouleris, N. (2014). Genetics, cognition, and neurobiology of schizotypal personality: A review of the overlap with schizophrenia. *Frontiers in Psychiatry, 5*, 18. https://doi.org/10.3389/fpsyt.2014.00018

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175–191. https://doi.org/10.3758/bf03193146

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: A latent-variable analysis. *Journal of Experimental Psychology. General, 133*(1), 101–135. https://doi.org/10.1037/0096-3445.133.1.101

Gamer, M., Lemon, J., & Puspendra Singh, I. F. (2019). irr: Various coefficients of interrater reliability and agreement. Retrieved from https://CRAN.R-project.org/package=irr.

Geiser, C., Litson, K., Bishop, J., Keller, B. T., Burns, G. L., Servera, M., & Shiffman, S. (2015). Analyzing person, situation and person × situation interaction effects: Latent state-trait models for the combination of random and fixed situations. *Psychological Methods, 20*(2), 165–192. https://doi.org/10.1037/met0000026

Haraldsson, H. M., Ettinger, U., Magnusdottir, B. B., Sigmundsson, T., Sigurdsson, E., & Petursson, H. (2008). Eye movement deficits in schizophrenia: Investigation of a genetically homogenous Icelandic sample. *European Archives of Psychiatry and Clinical Neuroscience, 258*(6), 373–383. https://doi.org/10.1007/s00406-008-0806-y

Haslam, N., McGrath, M. J., Viechtbauer, W., & Kuppens, P. (2020). Dimensions over categories: A meta-analysis of taxometric research. *Psychological Medicine*, 1–15. https://doi.org/10.1017/S003329172000183X

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods, 50*(3), 1166–1186. https://doi.org/10.3758/s13428-017-0935-1

Henderson, T., Georgiou-Karistianis, N., White, O., Millist, L., Williams, D. R., Churchyard, A., & Fielding, J. (2011). Inhibitory control during smooth pursuit in Parkinson's disease and Huntington's disease. *Movement Disorders : Official Journal of the Movement Disorder Society, 26*(10), 1893–1899. https://doi.org/10.1002/mds.23757

Holzman, P. S., Proctor, L. R., & Hughes, D. W. (1973). Eye-tracking patterns in schizophrenia. *Science (New York, N.Y.), 181*(4095), 179–181. https://doi.org/10.1126/science.181.4095.179

Howard, I. P., & Marton, C. (1992). Visual pursuit over textured backgrounds in different depth planes. *Experimental Brain Research, 90*(3), 625–629. https://doi.org/10.1007/BF00230947

Hutton, S. B., Crawford, T. J., Kennard, C., Barnes, T. R., & Joyce, E. M. (2000). Smooth pursuit eye tracking over a structured background in first-episode schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience, 250*(5), 221–225. https://doi.org/10.1007/s004060070011

Kassambra, A. (2020). Rstatix: Pipe-friendly framework for basic statistical tests. Retrieved from https://CRAN.R-project.org/package=rstatix.

Kaufman, S. R., & Abel, L. A. (1986). The effects of distraction on smooth pursuit in normal subjects. *Acta Oto-Laryngologica, 102*(1–2), 57–64. https://doi.org/10.3109/00016488609108647

Kerkhoff, G., Reinhart, S., Ziegler, W., Artinger, F., Marquardt, C., & Keller, I. (2013). Smooth pursuit eye movement training promotes recovery from auditory and visual neglect: A randomized controlled study. *Neurorehabilitation and Neural Repair, 27*(9), 789–798. https://doi.org/10.1177/1545968313491012

Kerzel, D., Souto, D., & Ziegler, N. E. (2008). Effects of attention shifts to stationary objects during steady-state smooth pursuit eye movements. *Vision Research, 48*(7), 958–969. https://doi.org/10.1016/j.visres.2008.01.015

Kristjánsson, Á., & Draschkow, D. (2021). Keeping it real: Looking beyond capacity limits in visual cognition. *Attention, Perception, & Psychophysics, 83*, 1375–1390. https://doi.org/10.3758/s13414-021-02256-7

Ladda, J., Eggert, T., Glasauer, S., & Straube, A. (2007). Velocity scaling of cue-induced smooth pursuit acceleration obeys constraints of natural motion. *Experimental Brain Research, 182*(3), 343–356. https://doi.org/10.1007/s00221-007-0988-y

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Lawden, M. C., Bagelmann, H., Crawford, T. J., Matthews, T. D., & Kennard, C. (1995). An effect of structured backgrounds on smooth pursuit eye movements in patients with cerebral lesions. *Brain: A Journal of Neurology, 118*(Pt 1), 37–48. https://doi.org/10.1093/brain/118.1.37

Lawrence, M. A. (2016). ez: Easy analysis and visualization of factorial experiments. Retrieved from https://CRAN.R-project.org/package=ez.

Leigh, R. J., & Zee, D. S. (2015). *The neurology of eye movements* (5 ed.). New York: Oxford University Press. https://doi.org/10.1093/med/9780199969289.001.0001

Lencer, R., & Trillenberg, P. (2008). Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition, 68*(3), 219–228. https://doi.org/10.1016/j.bandc.2008.08.013

Lenzenweger, M. F., & O'Driscoll, G. A. (2006). Smooth pursuit eye movement and schizotypy in the community. *Journal of Abnormal Psychology, 115*(4), 779–786. https://doi.org/10.1037/0021-843X.115.4.779

Levy, D. L., Sereno, A. B., Gooding, D. C., & O'Driscoll, G. A. (2010). Eye tracking dysfunction in schizophrenia: Characterization and pathophysiology. *Current Topics in Behavioral Neurosciences, 4*, 311–347. https://doi.org/10.1007/7854_2010_60

Lindner, A., Schwarz, U., & Ilg, U. J. (2001). Cancellation of self-induced retinal image motion during smooth pursuit eye movements. *Vision Research, 41*(13), 1685–1694. https://doi.org/10.1016/S0042-6989(01)00050-5

Linka, M., & de Haas, B. (2020). Osieshort: A small stimulus set can reliably estimate individual differences in semantic salience. *Journal of Vision, 20*(9), 13. https://doi.org/10.1167/jov.20.9.13

Lisberger, S. G. (2015). Visual guidance of smooth pursuit eye movements. *Annual Review of Vision Science, 1*, 447–468. https://doi.org/10.1146/annurev-vision-082114-035349

Lisberger, S. G., Evinger, C., Johanson, G. W., & Fuchs, A. F. (1981). Relationship between eye acceleration and retinal image velocity during foveal smooth pursuit in man and monkey. *Journal of Neurophysiology, 46*(2), 229–249. https://doi.org/10.1152/jn.1981.46.2.229

Lisberger, S. G., Morris, E. J., & Tychsen, L. (1987). Visual motion processing and sensory-motor integration for smooth pursuit eye movements. *Annual Review of Neuroscience, 10*, 97–129. https://doi.org/10.1146/annurev.ne.10.030187.000525

Lovejoy, L. P., Fowler, G. A., & Krauzlis, R. J. (2009). Spatial allocation of attention during smooth pursuit eye movements. *Vision Research, 49*(10), 1275–1285. https://doi.org/10.1016/j.visres.2009.01.011

McGraw, K. O., & Wong, S. P. (1996). Forming inferences about some intraclass correlation coefficients. *Psychological Methods, 1*(1), 30–46. https://doi.org/10.1037/1082-989X.1.1.30

Meyhöfer, I., Bertsch, K., Esser, M., & Ettinger, U. (2016). Variance in saccadic eye movements reflects stable traits. *Psychophysiology, 53*(4), 566–578. https://doi.org/10.1111/psyp.12592

Meyhöfer, I., Kasparbauer, A.-M., Steffens, M., & Ettinger, U. (2019). Effects of nicotine on smooth pursuit eye movements in healthy non-smokers. *Psychopharmacology, 236*, 2259–2271. https://doi.org/10.1007/s00213-019-05223-1

Meyhöfer, I., Steffens, M., Kasparbauer, A.-M., Grant, P., Weber, B., & Ettinger, U. (2015). Neural mechanisms of smooth pursuit eye movements in schizotypy. *Human Brain Mapping, 36*(1), 340–353. https://doi.org/10.1002/hbm.22632

Miller, J., & Ulrich, R. (2013). Mental chronometry and individual differences: Modeling reliabilities and correlations of reaction time means and effect sizes. *Psychonomic Bulletin & Review, 20*(5), 819–858. https://doi.org/10.3758/s13423-013-0404-5

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Mohrmann, H., & Thier, P. (1995). The influence of structured visual backgrounds on smooth-pursuit initiation, steady-state pursuit and smooth-pursuit termination. *Biological Cybernetics, 73*(1), 83–93. https://doi.org/10.1007/BF00199058

Niemann, T., & Hoffmann, K.-P. (1997). The influence of stationary and moving textured backgrounds on smooth-pursuit initiation and steady state pursuit in humans. *Experimental Brain Research, 115*(3), 531–540. https://doi.org/10.1007/PL00005723

Nkam, I., Bocca, M.-L., Denise, P., Paoletti, X., Dollfus, S., Levillain, D., & Thibaut, F. (2010). Impaired smooth pursuit in schizophrenia results from prediction impairment only. *Biological Psychiatry, 67*(10), 992–997. https://doi.org/10.1016/j.biopsych.2009.11.029

Ohlendorf, S., Kimmig, H., Glauche, V., & Haller, S. (2007). Gaze pursuit, 'attention pursuit' and their effects on cortical activations. *The European Journal of Neuroscience, 26*(7), 2096–2108. https://doi.org/10.1111/j.1460-9568.2007.05824.x

Ohlendorf, S., Sprenger, A., Speck, O., Glauche, V., Haller, S., & Kimmig, H. (2010). Visual motion, eye motion, and relative motion: A parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. *Journal of Vision, 10*(14), 21. https://doi.org/10.1167/10.14.21

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Orban de Xivry, J.-J., & Lefèvre, P. (2007). Saccades and pursuit: Two outcomes of a single sensorimotor process. The Journal of Physiology, 584(Pt 1), 11–23. doi:https://doi.org/10.1113/jphysiol.2007.139881.

Ostry, D. J., & Gribble, P. L. (2016). Sensory plasticity in human motor learning. *Trends in Neurosciences, 39*(2), 114–123. https://doi.org/10.1016/j.tins.2015.12.006

Paap, K. R., & Sawi, O. (2016). The role of test-retest reliability in measuring individual and group differences in executive functioning. *Journal of Neuroscience Methods, 274*, 81–93. https://doi.org/10.1016/j.jneumeth.2016.10.002

Raymond, J. E., Shapiro, K. L., & Rose, D. J. (1984). Optokinetic backgrounds affect perceived velocity during ocular tracking. *Perception & Psychophysics, 36*(3), 221–224. https://doi.org/10.3758/BF03206362

Revelle, W. (2019). *psych: Procedures for Psychological, Psychometric, and Personality Research*. Evanston, Illinois. Retrieved from https://CRAN.R-project.org/package=psych.

Rouder, J., Kumar, A., & Haaf, J. M. (2019). *Why most studies of individual differences with inhibition tasks are bound to fail*. PsyArXiv. Advance online publication. https://doi.org/10.31234/osf.io/3cjr5.

Roy-Byrne, P., Radant, A., Wingerson, D., & Cowley, D. S. (1995). Human oculomotor function: Reliability and diurnal variation. *Biological Psychiatry, 38*(2), 92–97. https://doi.org/10.1016/0006-3223(94)00225-R

Smyrnis, N. (2008). Metric issues in the study of eye movements in psychiatry. *Brain and Cognition, 68*(3), 341–358. https://doi.org/10.1016/j.bandc.2008.08.022

Smyrnis, N., Evdokimidis, I., Mantas, A., Kattoulas, E., Stefanis, N. C., Constantinidis, T. S., … Stefanis, C. N. (2007). Smooth pursuit eye movements in 1,087 men: Effects of schizotypy, anxiety, and depression. *Experimental Brain Research, 179*(3), 397–408. https://doi.org/10.1007/s00221-006-0797-8

Souto, D., & Kerzel, D. (2021). Visual selective attention and the control of tracking eye movements: A critical review. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00145.2019. Advance online publication.

Soveri, A., Lehtonen, M., Karlsson, L. C., Lukasik, K., Antfolk, J., & Laine, M. (2018). Test-retest reliability of five frequently used executive tasks in healthy adults. *Applied Neuropsychology. Adult, 25*(2), 155–165. https://doi.org/10.1080/23279095.2016.1263795

Spering, M., Gegenfurtner, K. R., & Kerzel, D. (2006). Distractor interference during smooth pursuit eye movements. *Journal of Experimental Psychology. Human Perception and Performance, 32*(5), 1136–1154. https://doi.org/10.1037/0096-1523.32.5.1136

Spering, M., & Montagnini, A. (2011). Do we track what we see? Common versus independent processing for motion perception and smooth pursuit eye movements: A review. *Vision Research, 51*(8), 836–852. https://doi.org/10.1016/j.visres.2010.10.017

Startsev, M., Agtzidis, I., & Dorr, M. (2019). Characterizing and automatically detecting smooth pursuit in a large-scale ground-truth data set of dynamic natural scenes. *Journal of Vision, 19*(14), 10. https://doi.org/10.1167/19.14.10

Störmer, V. S., Li, S.-C., Heekeren, H. R., & Lindenberger, U. (2011). Feature-based interference from unattended visual field during attentional tracking in younger and older adults. *Journal of Vision, 11*(2). https://doi.org/10.1167/11.2.1

Stubbs, J. L., Corrow, S. L., Kiang, B., Panenka, W. J., & Barton, J. J. S. (2018). The effects of enhanced attention and working memory on smooth pursuit eye movement. *Experimental Brain Research, 236*(2), 485–495. https://doi.org/10.1007/s00221-017-5146-6

Van Donkelaar, P. (1999). Spatiotemporal modulation of attention during smooth pursuit eye movements. *Neuroreport, 10*(12), 2523–2526. https://doi.org/10.1097/00001756-199908200-00016

Van Donkelaar, P., & Drew, A. S. (2002). The allocation of attention during smooth pursuit eye movements. In *, Vol. 140. Progress in brain research. The brain's eye: Neurobiological and clinical aspects of oculomotor research* (pp. 267–277). Elsevier. https://doi.org/10.1016/S0079-6123(02)40056-8.

Versino, M., Castelnovo, G., Bergamaschi, R., Romani, A., Beltrami, G., Zambarbieri, D., & Cosi, V. (1993). Quantitative evaluation of saccadic and smooth pursuit eye movements. Is it reliable? *Investigative Ophthalmology & Visual Science, 34*(5), 1702–1709.

Walter, S. D., Eliasziw, M., & Donner, A. (1998). Sample size and optimal designs for reliability studies. *Statistics in Medicine, 17*(1), 101–110. https://doi.org/10.1002/(SICI)1097-0258(19980115)17:1<101::AID-SIM727>3.0.CO;2-E

Watamaniuk, S. N. J., & Heinen, S. J. (2015). Allocation of attention during pursuit of large objects is no different than during fixation. *Journal of Vision, 15*(9), 9. https://doi.org/10.1167/15.9.9

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L. D., François, R., … Yutani, H. (2019). Welcome to the tidyverse. *Journal of Open Source Software, 4*(43), 1686. https://doi.org/10.21105/joss.01686

Wöstmann, N. M., Aichert, D. S., Costa, A., Rubia, K., Möller, H.-J., & Ettinger, U. (2013). Reliability and plasticity of response inhibition and interference control. *Brain and Cognition, 81*(1), 82–94. https://doi.org/10.1016/j.bandc.2012.09.010

Zimmerman, D. W., & Williams, R. H. (1998). Reliability of gain scores under realistic assumptions about properties of pre-test and post-test scores. *British Journal of Mathematical and Statistical Psychology, 51*(2), 343–351. https://doi.org/10.1111/j.2044-8317.1998.tb00685.x

Appendix B | Study II

Schröder, R., Reuter, M., Faßbender, K., Plieger, T., Poulsen, J., Lui, S. S., Chan, R. C. K., & Ettinger, U. (2021). The role of the *SLC6A3* 3'UTR VNTR in nicotine effects on cognitive, affective, and motor function. *Psychopharmacology*, *239*(2), 489–507. https://doi.org/10.1007/s00213-021-06028-x

Licensed under CC BY 4.0.

Psychopharmacology
https://doi.org/10.1007/s00213-021-06028-x

ORIGINAL INVESTIGATION

The role of the *SLC6A3* 3′ UTR VNTR in nicotine effects on cognitive, affective, and motor function

Rebekka Schröder[1] · Martin Reuter[1] · Kaja Faßbender[1] · Thomas Plieger[1] · Jessie Poulsen[2] · Simon S. Y. Lui[3] · Raymond C. K. Chan[4,5] · Ulrich Ettinger[1]

Received: 26 May 2021 / Accepted: 11 November 2021
© The Author(s) 2021

Abstract

Rationale Nicotine has been widely studied for its pro-dopaminergic effects. However, at the behavioural level, past investigations have yielded heterogeneous results concerning effects on cognitive, affective, and motor outcomes, possibly linked to individual differences at the level of genetics. A candidate polymorphism is the 40-base-pair variable number of tandem repeats polymorphism (rs28363170) in the *SLC6A3* gene coding for the dopamine transporter (DAT). The polymorphism has been associated with striatal DAT availability (9R-carriers > 10R-homozygotes), and 9R-carriers have been shown to react more strongly to dopamine agonistic pharmacological challenges than 10R-homozygotes.

Objectives In this preregistered study, we hypothesized that 9R-carriers would be more responsive to nicotine due to genotype-related differences in DAT availability and resulting dopamine activity.

Methods *N*=194 non-smokers were grouped according to their genotype (9R-carriers, 10R-homozygotes) and received either 2-mg nicotine or placebo gum in a between-subject design. Spontaneous blink rate (SBR) was obtained as an indirect measure of striatal dopamine activity and smooth pursuit, stop signal, simple choice and affective processing tasks were carried out in randomized order.

Results Reaction times were decreased under nicotine compared to placebo in the simple choice and stop signal tasks, but nicotine and genotype had no effects on any of the other task outcomes. Conditional process analyses testing the mediating effect of SBR on performance and how this is affected by genotype yielded no significant results.

Conclusions Overall, we could not confirm our main hypothesis. Individual differences in nicotine response could not be explained by rs28363170 genotype.

Keywords Nicotine · SLC6A3 · DAT · Smooth pursuit · Inhibition · Spontaneous blink rate · Proactive inhibition · Stop signal task · Individual differences

Introduction

Nicotine is a non-selective agonist of the nicotinic acetylcholine receptors (nAChr; de Kloet et al. 2015; Wonnacott et al. 2005) that stimulate dopamine release in the nucleus accumbens (and striatum in general) through activation of dopamine neurons in ventral tegmental area (VTA; Bonci et al. 2003; Cachope et al. 2012; de Kloet et al. 2015; Nisell et al. 1994; Threlfell et al. 2012; Wonnacott et al. 2005).

Nicotine has been widely studied for its potential pro-cognitive effects (Hahn 2015; Heishman et al. 2010), especially in groups with attentional dysfunction such as patients with neurodegenerative diseases, schizophrenia and ADHD (Barr et al. 2008b; Barreto et al. 2014; D'Souza and Markou, 2012; Levin et al. 1996; Rezvani

✉ Ulrich Ettinger
ulrich.ettinger@uni-bonn.de

1 Department of Psychology, University of Bonn, Bonn, Germany

2 Nicotine Science Center, Fertin Pharma A/S, Vejle, Denmark

3 Department of Psychiatry, The University of Hong Kong, Hong Kong Special Administrative Region, China

4 Neuropsychology and Applied Cognitive Neuroscience (NACN) Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China

5 Department of Psychology, University of Chinese Academy of Sciences, Beijing, China

Published online: 02 December 2021

and Levin 2001). However, nicotine effects on cognitive performance in healthy individuals are heterogeneous, with some studies providing evidence for beneficial effects, specifically in the domain of attention, yet others suggest detrimental effects (Almeida et al. 2020; Ettinger et al. 2017; Hahn 2015; Heishman et al. 2010; Niemegeers et al. 2014; Wignall and de Wit 2011).

Generally, nicotine effects appear to depend on factors such as baseline performance, dosage and smoking status (Almeida et al. 2020; Niemegeers et al. 2014; Wignall and de Wit 2011), suggesting substantial interindividual variance in dopamine-related function.

There is also evidence that such interindividual variability may be linked to differences at the level of genetics (Hariri 2009; Siebner et al. 2009). Here, to explain variability in nicotine response, we focus on a 40-base pair variable number of tandem repeats (VNTR) polymorphism (rs28363170) in the 3' untranslated region of the gene (*SLC6A3*) coding for the dopamine transporter (DAT). The DAT plays a major role in dopamine neurotransmission by controlling re-uptake of dopamine into the presynaptic neuron, thereby regulating synaptic dopamine availability (Piccini 2003; Salatino-Oliveira et al. 2018). DAT density is particularly high in striatum, a structure known to play a crucial role in dopamine response to nicotine (Cachope et al. 2012; Piccini 2003; Threlfell et al. 2012).

In humans, the most common alleles of the VNTR are the 9 (9R) and 10 repeat (10R) forms (Kang et al. 1999). At the behavioural level, there is no evidence of rs28363170 as a significant predictor of cognitive function in healthy adults (Gurvich and Rossell 2014; Rincón-Pérez et al. 2018). For outcomes both at the level of brain function and subjective experience, however, differences between genotypes have been identified in response to dopamine agonistic interventions (Brewer et al. 2015; Franklin et al. 2009, 2011; Gelernter et al. 1994; Kambeitz et al. 2014; Lott et al. 2005; Millar et al. 2011). These studies suggest that 9R-carriers are more responsive to challenges or interventions known to increase extracellular dopamine availability than 10R-homozygotes. However, the mechanisms of this effect are unclear. Here, we argue that differences in response between 9R carriers and 10R-homozygotes stem from differences in baseline DAT availability. Specifically, there is evidence for 9R carriers to have higher DAT availability (for meta-analysis, see Faraone et al. 2014), although this relationship was not significant in all studies (Kasparbauer et al. 2015; Wagner et al. 2014). This may be expected to result in lower baseline levels of extracellular dopamine in striatum.

In this preregistered study, we challenged the dopamine system by administering nicotine to rs28363170 9R carriers and 10R homozyogtes. We recorded spontaneous blink rate (SBR) as an indirect measure of striatal dopamine activity (Depue et al. 1994; Jongkees and Colzato 2016) to better understand possible genotype-related between-group differences in dopamine activity.

In order to characterise the interactive effects of nicotine and *SLC6A3*-genotype on cognitive, motor and affective functioning, we selected four paradigms that have been shown to be sensitive to dopaminergic influences. Specifically, we assessed smooth pursuit eye movements (SPEM; Meyhöfer et al. 2019), reactive inhibition in the stop signal task (Logemann et al. 2014a; Logan and Cowan 1984), proactive inhibition by comparing reaction times to go stimuli in the stop signal task and in a simple choice task where no stop signals are presented and effortful behaviour associated with affective processing in the Anticipatory and Consummatory Pleasure task (ACP; Heerey and Gold 2007; Lui et al. 2016).

In line with previous research, we expected 9R carrier to respond more strongly to nicotine administration than 10R homozygotes. We further hypothesized that drug effects on task performance are mediated by effects on SBR and that this relationship is moderated by genotype.

Materials and methods

The study was approved by the ethics committee of the Faculty of Medicine at the University of Bonn (registration number 215/18). The study was preregistered at https://osf.io/6wux4. This preregistration entails that our research questions and analysis plans were defined and time-stamped prior to data collection (Nosek et al. 2018).

Participants and screening procedure

We aimed for 200 participants to complete the study. This sample size yields at least 90% power to detect an effect of $f = 0.25$ with an alpha-level of .05 (G*Power 3.1.9.2; Faul et al. 2007).

We included healthy female and male non-smokers (at most 10 cigarettes in a lifetime, or equivalents such as e-vaping, nicotine gums etc.), aged 18-40 years, with normal or corrected to normal vision and carriers of 9R/9R, 9R/10R or 10R/10R genotypes. For statistical analyses, 9R-carriers (9R/9R, 9R/10R) were compared to 10R-homozygotes. A full list of exclusion criteria is available in Table 1.

Participants were recruited via advertisements on the campus of the University of Bonn, circular emails and social media. They were invited to fill in a short online questionnaire to confirm basic inclusion criteria. Suitable participants were invited to an in-person screening at the Department of Psychology at the University of Bonn. In the screening, participants confirmed their willingness to participate in the study and provided written, informed consent. Then, a semi-structured interview was conducted

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
-Healthy	-Known allergic reaction to nicotine
-Male or female	-Known heart disease
-18–40 years of age	-Known brain circulatory disorder (e.g., stroke)
-Non-smoker (less than 10 cigarettes in lifetime)	-Hypertension (systolic ≥140 and diastolic ≥90)
-Carrier of the 9R/9R, 9R/10R or 10R/10R genotype	-Hypotension (systolic <100 and diastolic <60)
-Normal or corrected-to-normal vision	-Bradycardia (resting pulse <60 per minute)
-Good German skills	-Tachycardia (resting pulse >100 per minute)
	-Known circulatory disorder
	-Known diabetes mellitus
	-Known hyperthyreosis
	-Known tumour in the adrenal gland
	-Known kidney or liver disease
	-Known oesophagitis, infections in mouth or throat, gastritis or stomach ulcers
	-Known fructose intolerance
	-Body mass index (BMI) <18 or >29 for men or <19 or >30 for women
	-For women: not using effective contraceptives for at least one cycle, pregnant or breastfeeding
	-Current drug abuse
	-Current medical or CNS disease
	-Current psychiatric or neurological diagnoses
	-Current medication intake (except oral contraceptives or vitamin preparations)
	-Current participation in a medication trial

to screen for psychiatric (Ackenheil et al. 1999), neurological or physical disorders and further exclusion criteria (Table 1). Handedness (Oldfield 1971), verbal intelligence (Lehrl 1999), blood pressure, heart rate, height and weight were obtained and body mass index (BMI) was calculated. Finally, participants provided a DNA sample (see below).

Suitable participants were then invited to the experimental assessment. They were asked to arrive well rested at the laboratory and to abstain from alcohol and medication at least 24 hours before the assessment and from citrus fruits on the day of the assessment. In addition, they were asked to maintain their usual caffeine intake and to have a light meal before the assessment.

Study design and procedure

The study followed a double-blind, placebo-controlled randomized between-subjects design, with separate randomization for females and males. The study team carrying out the assessments were involved neither in generating the randomisation list nor in the preparation of the nicotine and placebo gums.

At the beginning of each assessment, inclusion and exclusion criteria were reconfirmed. Then, participants were asked to provide a urine sample for analyses of current use of nicotine (qualitative cotinine tests with a 200 ng/ml cut-off, nal von minden GmbH, Moers, Germany) and pregnancy (Runbio Biotech Co., Guangdong, China; female participants only). Positive results led to study exclusion.

Participants were then given a chewing gum containing either 2 mg nicotine (Nicotinell®, spearmint) or placebo (Fertin Pharma, Vejle, Denmark). The placebo gums were customized to match the taste, mouth feel and appearance of the nicotine gums as accurately as possible. The gum was chewed following a standardized protocol (Meyhöfer et al. 2019). Voice-recorded instructions presented via headphones asked participants to alternate between chewing and keeping the gum between upper front teeth and lips for 30 minutes (12 short periods of each). Immediately after completion of the chewing protocol, participants filled in computerised visual analogue rating scales (VAS; Bond and Lader 1974) to assess subjective feelings. Blood pressure and heart rate were measured.

Then, SBR was assessed. Subsequently, the SPEM, ACP, stop signal and simple choice tasks were carried out in randomized order. However, the stop signal and simple choice tasks were always presented as a block, starting with the stop signal task for half of the participants and the simple choice task for the other half. At the end of each assessment, participants were asked to guess whether they had received nicotine or placebo.

Participants received course credits or €30 for participating. The experimental session took approximately 2 hours 30 minutes. An overview of the study procedure is depicted in Figure 1.

DNA extraction and genotyping

All participants provided buccal mucosa cell samples for DAT genotyping. DNA was extracted using commercial

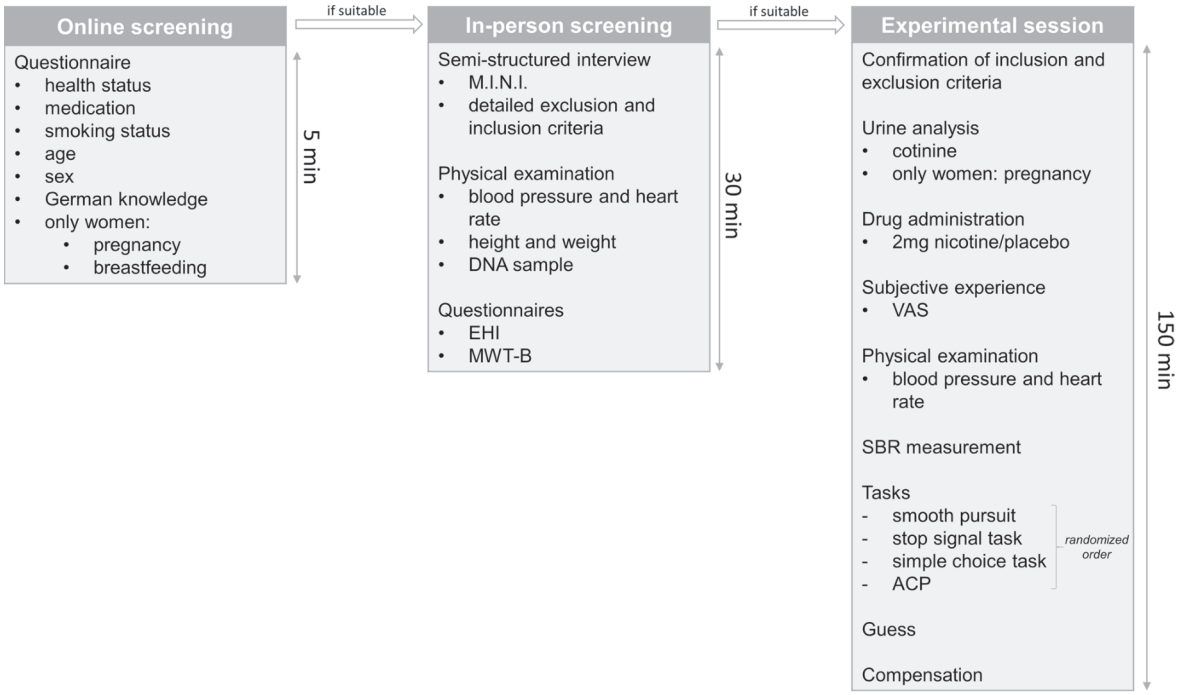

Fig. 1 Study procedure. M.I.N.I: Mini International Neuropsychiatric Interview (Ackenheil et al., 1999), EHI: Edinburgh Handedness Inventory (Oldfield, 1971), MWT-B: Mehrfachwahl-Wortschatz-Intelligenztest, version B (Lehrl, 1999), VAS: visual analogue scales (Bond & Lader, 1974), SBR: spontaneous blink rate, ACP: Anticipatory and Consummatory Pleasure Task.

MagNA Pure extraction kits (MagNA Pure LC DNA isolation kit; Roche Diagnostics; Mannheim, Germany).

Amplification of the DAT VNTR was conducted by means of polymerase chain reaction (PCR). Primer sequences for amplification were 5'-TGTGGTGTAGGG AACGGCCTGAG-3' and

5'-CTTCCTGGAGGTCACGGCTCAAGG-3'. The PCR protocol started with 3 minutes of initial denaturation at 94°C followed by 39 cycles of 45 seconds denaturation at 94°C, 30 seconds annealing at 62°C, and 30 seconds extension at 72°C. The final elongation at 72°C lasted 5 minutes. PCR products were genotyped by electrophoresis on a 2% agarose gel in a TBE solution and subsequent visualization under UV light.

Genotype frequencies of the DAT VNTR (9R/9R: N =14; 9R/10R: $N = 80$; 10R /10R: $N = 100$) were in Hardy Weinberg equilibrium ($\chi^2 = 0.14$, $p = .713$).

Tasks

The fixation and SPEM tasks were built in Experiment-Builder (SR Research Ltd., Ontario, Canada, version 1.10) and presented on a 24-inch BenQ LCD monitor (resolution 1920×1080 px; 120 Hz refresh rate). To record eye movements and blink rate, a desktop-mounted video-based combined pupil and corneal reflection eye-tracker (EyeLink 1000, SR Research Ltd.) was used. A centroid pupil-tracking algorithm was employed to detect pupil and corneal reflection of the right eye at 1000 Hz sampling rate. Prior to each task, a five-point horizontal-vertical calibration was performed. During the tasks, participants rested their head on a chin-rest.

The ACP, stop signal and simple choice tasks were presented on a 19-inch Hyundai LCD monitor (resolution 1440×900 px, 60 Hz refresh rate).

Distance from eye to monitor was approximately 70 cm for all tasks and instructions and stimuli were presented on a black (0, 0, 0) screen.

Fixation

The fixation target was a grey (128, 128, 128) circle (diameter = 15px/0.27°, stroke width = 5px/0.09°) presented at the centre (0°, 0°) of the screen for 180 seconds. Participants were instructed to fixate on the target as accurately as possible with their eyes while keeping their head still.

SBR (N/s) was obtained using DataViewer (SR Research Ltd.).

Smooth pursuit

The smooth pursuit task (Supplementary Figure 1) was the same as the one used by Meyhöfer et al. (2019). The task was presented on the inner 1680×1050 px of the monitor. Surrounding pixels were black. The smooth pursuit target was a grey (128, 128, 128) circle (diameter = 15px/0.27°, stroke width = 5px/0.09°) moving horizontally between ±432px (7.89°) across the screen in a sinusoidal velocity waveform at three target velocities (or frequencies: 0.2 Hz, 0.4 Hz, 0.6 Hz). The sinusoidal pattern indicates that target velocity constantly changed over time, accelerating towards the center of the screen, and decelerating towards the turning points. Peak and average velocities were 9.91°/s and 6.31°/s for the 0.2 Hz target, 19.83°/s and 12.62°/s for the 0.4 Hz target and 29.74°/s and 18.94°/s for the 0.6 Hz target. Each target velocity was presented twice, once with and once without a stationary structured background, resulting in a total of 6 blocks. The structured background consisted of a symmetrical six-by-six grid of white (255, 255, 255) circles (diameter = 15px/0.27°, stroke width = 5px/0.09°) with the following corner coordinates in pixels: 408, 310; 408, 740; 1272, 310; 1272, 740 (in inner 1680×1050 px of the monitor). Each block was presented for 30 seconds in randomized order. Participants were instructed to follow the target as accurately as possible with their eyes while keeping their head still. A brief practice task was presented prior to the task, consisting of four blocks (0.4 Hz without background, 0.2 Hz with background, 0.4 Hz with background, 0.6 Hz without background), each lasting five seconds.

Eye movement data were preprocessed in Matlab R2016A (Natick, Massachusetts: The MathWorks Inc.). First, the first excursion of the target from the centre, blinks and saccades were excluded. Then, segments of pursuit in the middle 50% of each half-cycle lasting 50 ms or longer were identified. Velocity gain was the primary outcome measure of pursuit performance, calculated as the time-weighted average of the ratio of mean eye velocity to mean target velocity for these segments. Optimal performance corresponds to a gain value of one.

For both eye-tracking tasks, data quality was first individually assessed. Participants with poor eye-tracking data quality were excluded from analyses.

Stop signal task

The stop signal task (Supplementary Figure 2) was written using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA). It was adapted from the stop signal task provided in the Cognitive Experiment III v3 pack provided by Neurobehavioral Systems (www.neurobs.com). The task consisted of 150 go trials and 50 stop trials. In go trials, participants had to indicate the direction of a centrally presented arrow (go stimulus, "<" or ">") by pressing a key on a 'qwertz' keyboard ("x" and ";", respectively). In stop trials, a stop stimulus ("⋀") was presented immediately after the go stimulus. In these trials, participants had to inhibit their responses.

Each trial started with a fixation cross presented centrally for 500 ms. Then, the go-stimulus appeared at the same position for 100 ms followed by a blank screen. In stop trials, the stop stimulus appeared after the current stop signal delay (SSD) for 500 ms. In go trials, a black screen was presented until the next trial was initiated (current SSD-100ms+500ms). The intertrial interval was 1000 ms (black screen). The initial SSD of 400 ms was adjusted to the participant's performance (maximum 500 ms, minimum 50 ms) in 16 ms steps using a tracking procedure (Verbruggen et al. 2019). Thus, SSD was increased by 16 ms after successful stop trials and decreased by 16 ms after unsuccessful stop trials, converging on a 50% probability of successful stop trials. If the SSD was shorter than 100 ms, the go stimulus was presented for the duration of the SSD. Stop trials occurred equally often after right and left arrows, respectively. Trial order was randomized.

All cues were presented in Helvetica font in white (255, 255, 255) on black (0, 0, 0) background. Font sizes were 7.5% of screen height for the fixation cross, 10% for go stimuli and 12.5% for stop stimuli.

Participants were instructed to leave their index fingers on the response keys throughout the entire task. They were asked to respond as fast and accurately as possible and not to wait for the stop signal.

Prior to the task a practice block (20 trials) was presented. If the accuracy in this block was less than 50%, it was repeated until an accuracy of more than 50% was achieved.

Stop signal reaction time (SSRT) was obtained as the primary outcome measure. It was calculated using the integration method with replacement of go-omissions (Verbruggen et al. 2019).

Participants were excluded if go trial accuracy was less than 80%, and/or if they had more than 75% or less than 25% successful stop-trials and/or in case of negative SSRT (Congdon et al. 2012; Verbruggen et al. 2019).

Simple choice task

The simple choice task (Supplementary Figure 3) was identical to the stop signal task with the difference that no stop trials were presented. Hence, participants had to respond to left and right arrows with the "x" and ";" keys, respectively, in 150 trials (75 right, 75 left). After each go stimulus a black

screen was presented for 900 ms followed by the intertrial interval of 1000 ms. Instructions were to respond as fast and accurately as possible and to leave the index fingers on the response keys throughout. Again, 20 practice trials were presented before the task and repeated until accuracy exceeded 50%.

To assess proactive inhibition, reaction times of correct go responses were obtained both for the stop signal task and the simple choice task.

Participants were excluded if their go-accuracy in either task was less than 80%.

ACP

The ACP task (Supplementary Figure 4) was written using E-Prime Software (Version 2.0, Psychology Software Tools, Sharpsburg, PA, USA). It was adapted from Lui et al. (2016) and comprised an anticipatory phase followed by a consummatory phase.

In the anticipatory phase, participants saw 42 slides showing three pictures each. The pictures were drawn from the International Affective Pictures System (Lang et al. 1997). Three types of slides were used (14 positive, 14 negative and 14 neutral). All pictures on one slide were from the same category. The slides were presented consecutively. First, participants were asked to rate valence and arousal evoked by each slide on a nine-point Likert scale, ranging from *very unpleasant* to *very pleasant* and *very calm* to *very arousing*, respectively. Ratings were obtained by the number keys at the top of the keyboard. Rating time was not limited, but slides were removed from the screen after rating. Second, participants were asked to indicate whether they wanted to see a particular slide again later or not. They were told they could alter the probability of the later reappearance of a slide by rapidly and alternately pressing two keys on the keyboard. Half of the participants were instructed to press "m" and "n" on the keyboard to increase the probability of seeing the current slide again and "x" and "y" to decrease the probability. For the other half of the participants, the key assignment was reversed. The response window for the key presses was two seconds. During this time, participants saw an instruction to press the keys and a reminder of the key allocation. Each trial started with a 500 ms fixation dot and ended on a 2000 ms rest period. Participants were instructed to use the index and middle fingers of their left and right hands. In addition, they were asked to only press the keys if they in fact wanted (or not wanted) to see a particular slide again and to not press the keys if they were indifferent to whether they wanted to see the slide again or not.

In the consummatory phase, participants saw 30 slides (10 positive, 10 negative, 10 neutral) from the anticipatory phase. They could alter the presentation time of the slides by rapidly and alternately pressing the same keys as in the anticipatory phase. Presentation times were prolonged if they pressed the keys used in phase 1 to increase slide probability (e.g., "m" and "n"). Presentation times were shortened if they pressed the keys used in phase 1 to decrease slide probability (e.g., "x" and "y"). Presentation times ranged from two to ten seconds depending on participants' key press response. If no keys were pressed, presentation time was five seconds. Participants had no influence on total task duration as intertrial intervals (black screen) were adjusted to slide presentation durations so that total trial duration and intertrial interval were always the same.

A practice block was carried out prior to each phase.

The primary outcome measure was key pressing speed, i.e., the number of key presses per second (N/s), to account for differences in target presentation duration in the second task phase. Importantly, the factor valence was determined individually according to each participant's valence ratings. Ratings of 1-3 were considered negative, 4-6 neutral and 7-9 positive.

A trial was considered invalid if a participant's Likert rating of a slide did not match their key press response, e.g., if a participant gave a positive rating but pressed keys (> 4 key presses) to decrease probability of later stimulus reappearance or to shorten presentation duration, and vice versa for negative ratings. However, slides with neutral ratings were always valid. Trials with invalid responses were excluded from analysis. To account for individual differences in key pressing speed, results from a calibration block at the beginning of the task were applied in the consummatory phase in order to adjust presentation durations similarly between participants.

Visual analogue scales

Subjective feelings after drug administration were assessed with computerised visual analogue scales (VAS; Bond and Lader 1974), yielding alertness (9 scales), calmness (2 scales) and contentedness (5 scales) factors. VAS scales were 100 mm long and ratings are reported as average values for each factor with higher values indicating higher expressions on the factors.

Statistical analyses

For the primary outcome of each task, analysis of variance (ANOVA) and conditional process analysis were carried out. For subjective and cardiovascular outcomes, *t*-tests were carried out. Significance threshold for all analyses was $\alpha = .05$. Departing from our preregistration, outliers were not winsorized following recent recommendations (Leys et al. 2019).

Analyses of variance

For each dependent variable (SBR, SPEM velocity gain, SSRT, go RT, key press speed), a between-subjects ANOVA with the factors drug (nicotine, placebo) and genotype (9R, 10/10) was carried out. Some analyses had additional within-subject factors, depending on the task analysed. For SPEM, the additional within-subjects factors were target velocity (0.2 Hz, 0.4 Hz and 0.6 Hz) and background (present, absent). For ACP, the additional within-subjects factors were valence (determined individually according to ratings; positive, negative and neutral) and phase (anticipatory, consummatory). The proactive inhibition analysis had the additional within-subjects factor task (stop signal, simple choice task).

Effect sizes were calculated as partial eta squared. If the sphericity assumption was violated, Greenhouse-Geisser correction was applied. Uncorrected degrees of freedom and Greenhouse-Geisser ε were obtained. Bonferroni-corrected *t*-tests were calculated as post hoc tests with d_{av} (Lakens 2013) as effect size for repeated-measures factors. Uncorrected *p*-values were obtained but significance was inferred from corrected alpha-thresholds.

Conditional process analyses

Based on our preregistered hypotheses, a conditional process analysis was performed for the primary outcome measures of each task (averaged across within-subject conditions for key press speed and SPEM velocity gain; difference between go and stop signal task for go reaction times) with the R *process* package (Hayes 2015). Specifically, model 8 was tested with four different outcome variables (Y; SPEM velocity gain, SSRT, go RT, key press speed). Drug was the independent variable (X), SBR was the mediator (M) and genotype was the moderator (W) on the paths between drug and SBR and drug and outcome measures, respectively. Bootstrap 95%-confidence intervals were calculated with 5000 bootstrap iterations. Participants were excluded according to above criteria. Specifically, a participant was not included in the conditional process analysis if fixation data quality was poor. Unstandardized regression coefficients are reported. Drug and genotype were coded as uncentered dichotomous variables (placebo = 0, nicotine = 1; 10/10 = 0, 9R = 1).

Conceptual and statistical diagrams of the conditional process model are depicted in Figure 2.

Additional analyses

Two-sample *t*-tests were carried out in order to test drug effects on heart rate, blood pressure and the three VAS scales. Cohen's *d* was calculated to determine effect sizes. A χ^2-test of independence was calculated to assess whether participants guessed correctly if they had received nicotine or placebo.

Bayesian analyses

In addition to the preregistered analyses described above, Bayesian ANOVAs were calculated using JASP software (Version 0.14.1, JASP Team [2020]). Dependent and independent variables were selected as described in "Analyses of variance". JASP default priors were used, i.e. Cauchy priors centered on zero with a fixed effects scale factor of $r = 0.5$ and random effects scale factor of $r = 1$.

Bayes factors (BF) are interpreted according to Wagenmakers et al. (2018) with BF > 100 suggesting extreme evidence, 30-100 very strong evidence, 10-30 strong evidence, 3-10 moderate evidence, 1-3 anecdotal evidence and 1 no evidence. Bayesian model averaging (across all models) yielded BF quantifying the evidence for including or excluding a specific main or interaction effect (van den Bergh et al. 2020).

Data and code availability

Anonymized data and analysis code are available at https://osf.io/bg3c6/.

Results

Participants

A total of 739 participants filled in the online questionnaire, 507 of whom met initial criteria and were invited to a face-to-face screening. Of those, 271 followed the invitation and 227 of them were considered suitable for participation. After genotyping, 18 participants had to be excluded because DNA analyses were inconclusive or revealed rare genotypes (not 9R/9R, 9R/10R or 10R/10R). Of the remaining participants, seven did not follow the invitation, four had positive cotinine tests, two consumed alcohol or took medication prior to testing and two had to discontinue participation due to adverse nicotine side effects.

The final sample consisted of $N = 194$ participants (153 females, 41 males), aged $M = 22.82$ years ($SD = 3.33$ years). Ninety-nine participants received nicotine (44 9R-carriers and 55 10R-homozygotes) and ninety-five participants received placebo (50 9R-carriers and 45 10R-homozygotes). Further demographic information is in Table 2.

Data collection took place between December 2018 and February 2020. It was discontinued before the targeted sample size of 200 was reached due to a nationwide

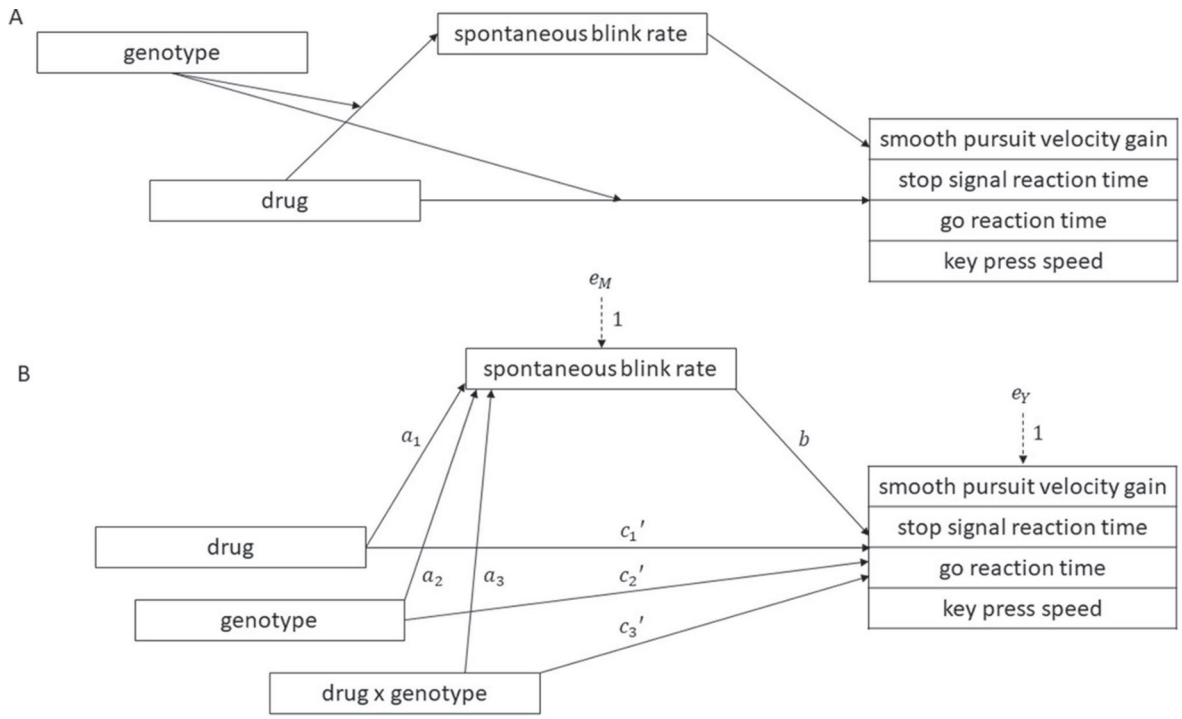

Fig. 2 Conceptual (panel A) and statistical (panel B) diagram of the conditional process models. Spontaneous blink rate is considered a mediator of the drug effects on the four performance outcomes (smooth pursuit velocity gain, stop signal reaction time, go reaction time and key press speed). For each performance outcome, a separate analysis was carried out. Genotype acts as a moderator of the drug effect on spontaneous blink rate and performance.

lockdown related to the Sars-CoV-2 pandemic. However, we believe that the deviation is so minor that it does not have a significant impact on the statistical power in this study.

Due to poor eye-tracking data quality, two participants were excluded from SBR analyses and seven participants from SPEM analyses. Thirty-three participants were excluded from stop signal task and twelve participants from simple choice task analyses for fulfilling above exclusion criteria. Three participants were excluded from ACP analyses due to technical errors or failure to understand instructions.

Fixation

ANOVA on SBR yielded no significant main effects for drug or genotype and no interaction of the two factors (all $p > .05$; Table 2; Figure 3).

Table 2: Demographic information and blink rates of the experimental groups

	Nicotine		Placebo	
	9R	10/10	9R	10/10
N	44	55	50	45
Age				
(mean, SD)	22.05 (2.53)	22.89 (3.30)	23.1 (3.76)	23.18 (3.52)
Gender (*N* females/ males)	37/7	40/15	40/10	36/9
Handedness (*N* right/left/ambidextrous)	35/7/2	47/6/2	44/6/0	35/7/3
Years spent in formal education (mean, SD)	15.39 (2.16)	15.98 (2.45)	15.82 (3.42)	15.98 (3.49)
MWT-B sum score (mean, SD)	25.18 (4.13)	26.18 (4.33)	25.24 (3.86)	25.13 (4.2)
SBR (N/s; mean, SD)	0.22 (0.43)	0.18 (0.18)	0.16 (0.14)	0.17 (0.19)

Legend: Demographic information and blink rates of the four experimental groups. MWT-B: Mehrfachwahl-Wortschatz-Intelligenz Test (Version B). Handedness was assessed with the Edinburgh Handedness Inventory. SBR: spontaneous blink rate.

The Bayesian ANOVA suggested that the data were best represented by a null model (see Supplementary Table 1). There was moderate evidence to exclude drug (BF_{excl} = 8.34) and genotype (BF_{excl} = 7.62) and very strong evidence to exclude their interaction (BF_{excl} = 52.98) (see Supplementary Table 2).

SPEM

Analyses of velocity gain revealed main effects of background ($F_{(1, 183)} = 286.44$, $p < .001$, $\eta_p^2 = .610$) and velocity ($F_{(2, 366)} = 391.69$, $p < .001$, $\eta_p^2 = .682$, $\epsilon = .74$) and a two-way interaction of background and target velocity ($F_{(2, 366)} = 56.85$, $p < .001$, $\eta_p^2 = .237$, $\epsilon = .94$; Figure 4). Bonferroni-corrected *t*-tests revealed significant differences between the background conditions at all target velocities (0.2 Hz: background vs. no background $t_{(186)} = -10.75$, $p < .001$, $d_{av} = -.76$; 0.4 Hz: background vs. no background $t_{(186)} = -13.62$, $p < .001$, $d_{av} = -.78$; 0.6 Hz: background vs. no background $t_{(186)} = -17.77$, $p < .001$, $d_{av} = -.89$). However, background effects were larger at higher target velocities. Differences between all target velocity conditions were significant at each background level (background: 0.2 Hz vs. 0.4 Hz $t_{(186)} = 13.80$, $p < .001$, $d_{av} = .64$; background: 0.2 Hz vs. 0.6 Hz $t_{(186)} = 21.58$, $p < .001$, $d_{av} = 1.31$; background: 0.4 Hz vs. 0.6 Hz $t_{(186)} = 15.27$, $p < .001$, $d_{av} = .63$; no background: 0.2 Hz vs. 0.4 Hz $t_{(186)} = 12.86$, $p < .001$, $d_{av} = .74$; no background: 0.2 Hz vs. 0.6 Hz $t_{(186)} = 17.97$, $p < .001$, $d_{av} = 1.33$; no background: 0.4 Hz vs. 0.6 Hz $t_{(186)} = 13.95$, $p < .001$, $d_{av} = .62$). There were no main effects of drug or genotype and no further interactions (all $p > .05$).

Conditional process analysis yielded no significant paths (Supplementary Tables 3 and 4). The index of moderated mediation was 0.015 (SE = 0.472) [-1.296; 0.702]. The bootstrap confidence interval included zero, suggesting a nonsignificant effect.

The Bayesian ANOVA suggested that the data were best represented by a model including the factor target velocity, background and their interaction (see Supplementary Table 5). There was extreme evidence to include the main effects of target velocity (BF_{incl} = 7.460e+12) and

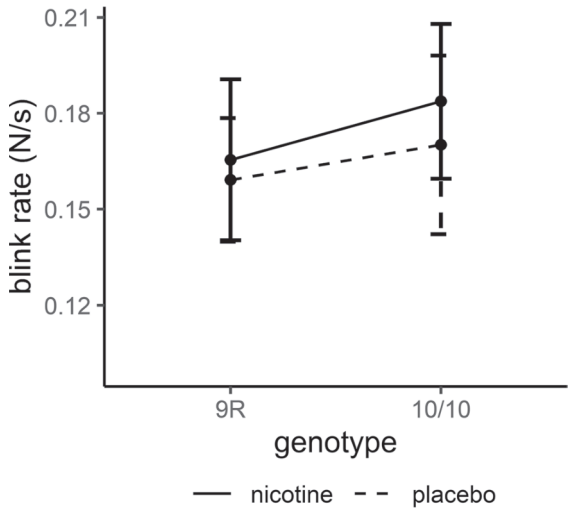

Fig. 3 Effects of drug and genotype on spontaneous blink rate. Data are presented as mean ± standard errors. $N = 192$.

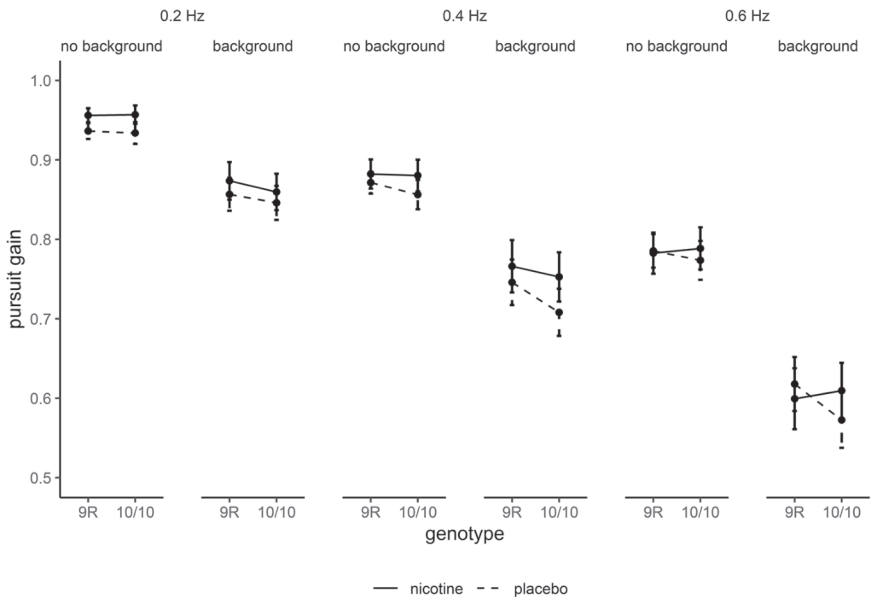

Fig. 4 Effects of drug, genotype, target velocity and background on smooth pursuit velocity gain. Data are presented as mean ± standard errors. $N = 187$

background (BF_{incl} = 7.460e+12) as well as their interaction (BF_{incl} = 5.359e+7) and strong evidence to exclude the main effects of drug (BF_{excl} = 18.51) and genotype (BF_{excl} = 21.99) as well as strong to extreme evidence to exclude all other interactions (all BF_{excl} >= 21.74; see Supplementary Table 6).

Stop signal

In line with assumptions of the race model (Verbruggen et al. 2019), reaction times in go trials were significantly larger than in incorrect stop trials ($t_{(160)} = 19.20$, $p < .001$, $d_{av} = .68$).

ANOVA on SSRT did not result in any main or interaction effects of drug and genotype (all $p > .05$; Figure 5).

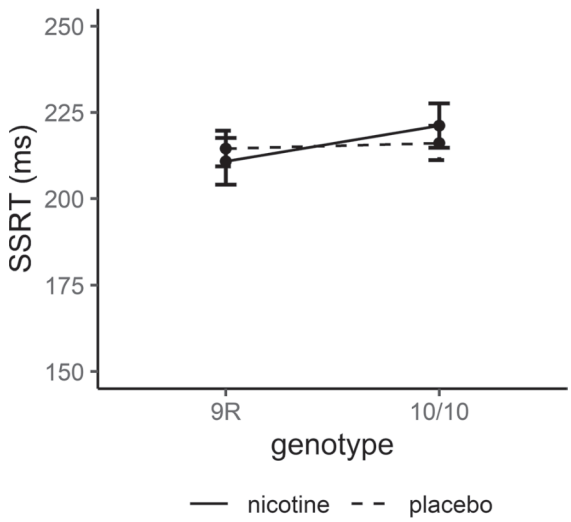

Fig. 5 Effects of drug and genotype on stop signal reaction time. Data are presented as mean ± standard errors. SSRT: stop signal reaction time. $N = 161$.

Conditional process analysis yielded no significant paths (Supplementary Tables 7 and 8). The index of moderated mediation was -0.012 (SE = 1.473) [-3.94; 2.234]. The bootstrap confidence interval included zero, suggesting a nonsignificant effect.

The Bayesian ANOVA suggested that the data were best represented by a null model (see Supplementary Table 9). There was moderate evidence to exclude drug (BF_{excl} = 8.21) and genotype (BF_{excl} = 5.15) and strong evidence to exclude their interaction (BF_{excl} = 27.19) (see Supplementary Table 10).

Proactive inhibition

ANOVA on go reaction times revealed significant main effects of drug ($F_{(1, 178)} = 3.90$, $p = .0499$, $\eta_p^2 = .021$) and task ($F_{(1, 178)} = 270.45$, $p < .001$, $\eta_p^2 = .603$; Figure 6). Reaction times were shorter under nicotine vs. placebo and in the simple choice task compared to the stop signal task. There were no interactions and no main effect of genotype (all $p > .05$).

Conditional process analysis yielded no significant paths (Supplementary Tables 11 and 12). The index of moderated mediation was 0.451 (SE = 3.464) [-7.056; 8.097]. The bootstrap confidence interval included zero, suggesting a nonsignificant effect.

The Bayesian ANOVA suggested that the data were best represented by a model including only the factor task (see Supplementary Table 13). There was extreme evidence for the inclusion of task (BF_{incl} = 2.924e+14), anecdotal evidence for the exclusion of drug (BF_{excl} = 2.30) and moderate evidence to exclude genotype (BF_{excl} = 6.65). There was moderate evidence for the exclusion of the task × drug (BF_{excl} = 3.07) and task × genotype (BF_{excl} = 5.67) interactions, strong evidence for the exclusion of drug × genotype (BF_{excl} = 16.43) and extreme evidence for the exclusion of the task × drug × genotype (BF_{excl} = 116.31) interactions (see Supplementary Table 14).

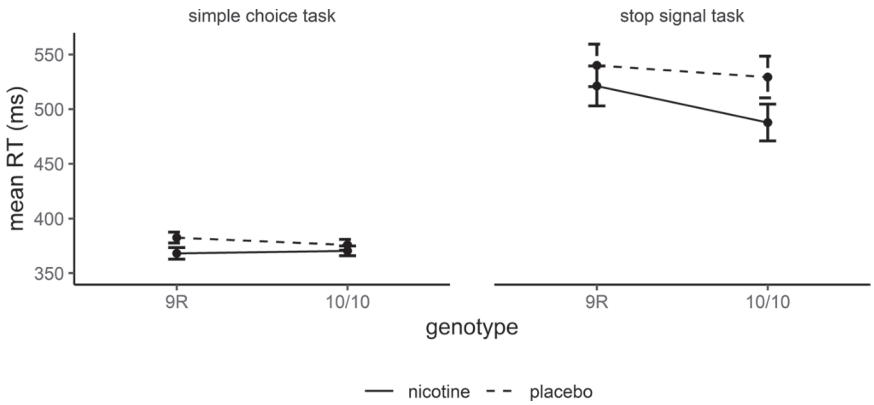

Fig. 6 Effects of drug and genotype on go reaction times in the simple choice and stop signal tasks. Data are presented as mean ± standard errors. RT: reaction time. $N = 182$.

ACP

ANOVA on key press speed revealed significant main effects of valence ($F_{(2, 374)} = 564.36$, $p < .001$, $\eta_p^2 = .751$, $\epsilon = .96$) and phase ($F_{(1, 187)} = 78.53$, $p < .001$, $\eta_p^2 = .296$; Figure 7). Key press speed was higher for negative and positive compared to neutral slides (negative vs. neutral $t_{(190)} = 31.00$, $p < .001$, $d_{av} = 2.35$; negative vs. positive $t_{(190)} = 11.60$, $p < .001$, $d_{av} = .57$; neutral vs. positive $t_{(190)} = -22.04$, $p < .001$, $d_{av} = -1.63$) and higher for the anticipatory compared to the consummatory phase. In addition, there was a significant interaction of valence and phase ($F_{(2, 374)} = 15.06$, $p < .001$, $\eta_p^2 = .075$, $\epsilon = .93$) suggesting that differences between the two phases were bigger for positive and negative slides than for neutral slides. However, all differences were significant (negative: anticipatory vs. consummatory $t_{(190)} = 8.22$, $p < .001$, $d_{av} = .41$; neutral: anticipatory vs. consummatory $t_{(190)} = 5.00$, $p < .001$, $d_{av} = .32$; positive: anticipatory vs. consummatory $t_{(190)} = 7.52$, $p < .001$, $d_{av} = .46$). There were no further main effects or interactions (all $p > .05$).

Conditional process analysis yielded no significant paths (Supplementary Tables 15 and 16). The index of moderated mediation was 0.092 (SE = 0.072) [-0.128; 0.179]. The bootstrap confidence interval included zero, suggesting a nonsignificant effect.

The Bayesian ANOVA suggested that the data were best represented by a model including the factors phase and valence as well as their interaction (see Supplementary Table 17). There was extreme evidence for the inclusion of valence (BF_{incl} = 9.883e+12) and phase (BF_{incl} = 9.883e+12) main effects and their interaction (BF_{incl} = 7.607e+13). There was very strong to extreme evidence to exclude the main effects of drug and genotype and all other interactions (all BF_{excl} >= 35.27; see Supplementary Table 18).

Descriptive statistics of all task effects are summarized in Supplementary Table 19.

Cardiovascular effects

Heart rate was higher under nicotine compared to placebo ($t_{(192)} = 2.53$, $p = .01$, $d = 0.36$), but nicotine had no effect on blood pressure (all $p > .05$; Table 3).

Visual analogue scales

T-tests of nicotine influence on subjective feelings revealed significant effects on alertness ($t_{(192)} = -2.60$, $p = .01$, $d = -0.37$) and calmness ($t_{(192)} = -2.61$, $p = .01$, $d = -0.37$), but not on contentedness ($t_{(192)} = -1.08$, $p = .28$, $d = -0.16$). Participants receiving nicotine reported to be less alert and less calm than participants receiving placebo. Table 3 shows the descriptive statistics of heart rate, blood pressure and VAS.

Individual substance identification

On average, participants guessed correctly which substance they had received ($\chi_1^2 = 18.48$, $p < .001$).

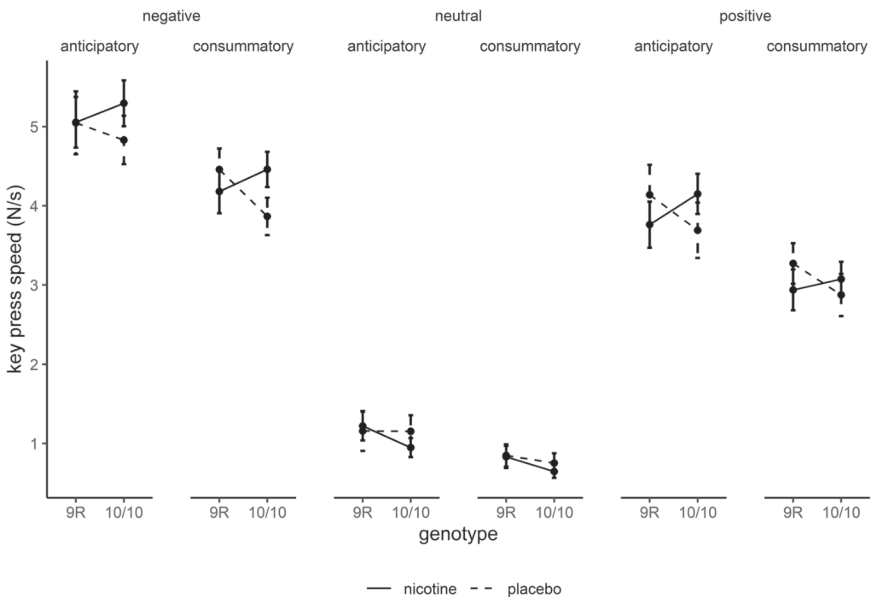

Fig. 7 Effects of drug and genotype on key press speed in the ACP task. Data are presented as mean ± standard errors. *N* = 191.

Table 3: Descriptive statistics of cardiovascular parameters and subjective experience in the nicotine and placebo groups

	Nicotine	Placebo
Heart rate	75.06 (11.58)	71.21 (9.49)
Systolic blood pressure	112.99 (12.33)	110.80 (11.91)
Diastolic blood pressure	74.42 (7.63)	72.34 (7.50)
VAS alertness	59.69 (16.81)	65.82 (16.06)
VAS contentedness	70.37 (14.76)	72.47 (12.15)
VAS calmness	67.66 (20.10)	74.69 (17.32)

Legend: Numbers indicate mean and standard deviations (in brackets). VAS: visual analogue scales. Heart rate is given in contractions per minute, systolic and diastolic blood pressure are given in millimetres of mercury, VAS values are average scale values with higher values indicating higher expression on the factors (range 0-100).

$N = 194$.

Discussion

Nicotine is a widely used substance with pro-dopaminergic effects. However, studies examining nicotine effects on cognitive, motor and affective functioning in healthy non-smokers yield heterogenous results suggesting substantial between-subject variance, possibly related to genetic variations.

This preregistered study focused on a candidate polymorphism in a gene related to dopaminergic functioning, the *SLC6A3* 3' UTR VNTR. 194 participants were grouped according to genotype and received either nicotine or placebo in a randomized 2×2-between-subjects design. In order to test whether the assumed nicotine × genotype interactions depend on striatal dopamine activity, SBR was obtained and conditional process analyses testing the mediating effect of SBR on task performance were conducted.

In the frequentist analysis approach, nicotine reduced go reaction times in simple choice and stop signal tasks but had no effect on smooth pursuit performance, reactive and proactive inhibition and affective processing. Bayesian ANOVA, however, revealed anecdotal evidence against nicotine effects on reaction times, but confirmed the null effects on all other tasks. In addition, in frequentist and Bayesian analyses, no interactions with genotype were observed. Conditional process analyses showed no significant results of substance or genotype. Nicotine increased heart rate and decreased subjective ratings of alertness and calmness. Participants guessed above chance-level, which substance they had received.

Nicotine effects

Fixation

Contrary to our hypothesis, no modulatory effect of nicotine on SBR could be observed despite the well-established role of the nicotinic acetylcholine receptor in striatal dopamine functioning and prior evidence of nicotine effects on SBR (Klein et al. 1993; de Kloet et al. 2015). Importantly, in the past, pharmacological enhancement of dopamine functioning has not consistently increased SBR (Jongkees and Colzato 2016). For example, Cavanagh et al. (2014) showed that administration of the dopamine-D2-receptor agonist cabergoline enhanced SBR only in participants with low placebo SBR and decreased it in participants with high placebo SBR. Unfortunately, baseline dependency effects cannot be investigated in our between-subjects study but should be considered in future work.

In a recent study, no relationship between SBR and striatal D2 availability and, more importantly, no drug-related SBR modulation following dopamine agonist bromocriptine administration was observed in healthy participants (Dang et al. 2017). This result along with our null finding suggests that the relationship between SBR and pharmacologically challenged dopamine activity in healthy humans is less straight-forward than expected. Importantly, as suggested by Dang et al. (2017) correlations between SBR and dopamine functioning might only become apparent under more extreme circumstances, such as dopamine-related clinical diseases, but not in healthy participants.

An additional line of argument is that nicotine influences dopamine neurotransmission indirectly via the cholinergic system (de Kloet et al. 2015), but also via activation of γ-aminobutyric acid (GABA) and glutamate (Wonnacott et al. 2005). Consequently, it can be argued that nicotine may not be specific enough to induce the hypothesized effects on SBR.

SPEM

In contrast to our previous study (Meyhöfer et al. 2019) we could not find any nicotine effect on SPEM. This result is surprising given the large effect size in Meyhöfer et al. (2019), who used the same paradigm, application protocol and dose. The reason for this rather contradictory result is not entirely clear, but the most striking difference between the studies is the use of between- vs. within-subject drug administration. We addressed this matter by using a much larger sample with sufficient power to detect the effects observed by Meyhöfer et al. (2019), but still failed to replicate them in our study.

It is worth noting that other studies too have been unsuccessful in showing improved SPEM performance in response to nicotine in healthy non-smokers (Kasparbauer et al. 2016; Olincy et al. 1998; Sibony et al. 1988). Crucially, however, results are more consistent in groups with impaired dopamine neurotransmission, such as patients with schizophrenia. Here, mostly beneficial effects of nicotine have been reported (Olincy et al. 1998; Sherr et al. 2002; Tregellas et al. 2005). This suggests that nicotine may positively influence SPEM only when performance is at a suboptimal level.

Unfortunately, our between-subjects approach does not allow analysis of baseline dependent drug effects that have been revealed in the past for other oculomotor tasks (Babin et al. 2011). Low-dose nicotine effects on SPEM might be so subtle that they only emerge in participants with lower-than-average performance or in study designs with better control of interindividual variability.

Reactive inhibition

Beneficial effects of nicotine on SSRT have been found in samples with lower-than-average inhibition performance such as deprived smokers or highly impulsive individuals (Potter and Newhouse 2004; Tsaur et al. 2015). In healthy non-smokers, however, results are less consistent. While one study found weak effects (Logemann et al. 2014b), others have failed to do so (Ettinger et al. 2017; Logemann et al. 2014a; Wignall and de Wit 2011). Our results are in line with the latter, confirming that nicotine does not show inhibition enhancing effects in the stop signal task in healthy, non-smoking individuals.

Proactive inhibition

The only task-related measure where nicotine effects were found in frequentist analyses, were go reaction times in the stop signal and simple choice tasks. Reaction times were significantly reduced by nicotine, indicative of enhanced motor responses under nicotine, consistent with meta-analytic findings of improved fine motor performance and decreased alerting attention reaction times under nicotine (Heishman et al. 2010). This finding may, at least in part, be attributed to nicotinic action at peripheral, striatal and motor cortex sites (Dani and Bertrand 2007; Heishman et al. 2010; Mansvelder et al. 2006). Importantly, however, Bayesian analyses provided anecdotal (or inconclusive) evidence against nicotine effects on reaction times. This points to the need for more research to better understand the exact effects of nicotine on reaction times.

Nicotine did not differentially affect reaction times in the stop signal and simple choice tasks, suggesting no specific drug effect on proactive inhibition.

ACP

Nicotine did not affect key press speed in the ACP task implying that affective processing is not altered by drug administration. This is in contrast to previous investigations describing nicotine-induced effects on incentive motivation, reward processing and affective responses to film clips (Barr et al. 2008a; Dawkins et al. 2006; Dawkins and Powell 2011). Our data suggest that motivated behaviour to alter probability or presentation times of emotional stimulus displays is unaffected by nicotine administration. In contrast to the simple choice and stop signal tasks, no general facilitation of motor responses could be observed. This may be the results of differences in task instructions. While participants were instructed to react as fast and accurately as possible with a single key press to the stimuli in the simple choice and stop signal tasks, instructions in the ACP required sustained responses over a period of several seconds as a result of in-depth processing of the stimulus and evaluation of one's own motivational state. Thus, simple reaction times are the result of fast visuomotor transformations as a consequence of simple stimulus-response associations while ACP reactions reflect more complex, self-generated effortful behaviour in anticipation of or in direct response to an affective stimulus.

Genotype

Overall, our results show that nicotine might facilitate motor responses, as indicated by the decrease in reaction times in the simple choice and stop signal tasks which – of note – was not confirmed in Bayesian analyses but has no effects on other outcomes. Importantly, considering the level of genetics (*SLC6A3* 3' UTR VNTR 9R-carriers vs. 10R-homozygotes) with a view to tapping differences in DAT-related dopamine neurotransmission did not help to explain interindividual differences in nicotine response in healthy non-smokers and thus cannot contribute to resolving inconsistencies in the literature. While this is in contrast to the majority of previous investigations (Brewer et al. 2015; Franklin et al. 2009, 2011; Gelernter et al. 1994; Millar et al. 2011), it is not the first study that failed to observe differences in response to pro-dopaminergic pharmacological manipulations between the genotype groups (Hart et al. 2013; Kambeitz et al. 2014). Accordingly, previous findings might reflect false positive results of poorly-powered studies (Hart et al. 2013) or only apply to specific substances or tasks.

Of note, DAT availability is not static and can change, e.g. with smoking status or drug administration (Newberg et al. 2007; Schmitt and Reith, 2010; Yang et al. 2008). Here, we only included healthy, young non-smokers who did not regularly consume other drugs, while smoking and drug administration status might have been less well controlled in previous investigations

Task effects

SPEM

SPEM velocity gain decreased with higher target velocities and in the presence of a structured background. In addition, we showed a significant interaction between the target

velocity and background factors, indicating that negative background effects are larger at higher target velocities. These results are in excellent agreement with our earlier investigations employing the same paradigm, closely replicating previously observed effect sizes (Meyhöfer et al. 2019; Schröder et al. 2021). Increasing task demands due to higher velocity targets or stationary background could challenge processes inherent to pursuit performance, such as spatial attention and motion perception (Kerzel et al. 2008; Ohlendorf et al. 2010), leading to the observed decreases in velocity gain. Along with the recent finding of high test-retest and split-half reliability in this task (Schröder et al. 2021) the replication of these task effects at group level underlines the robustness of this paradigm for both the current and future investigations of SPEM.

Stop signal

The race model underlying stop signal task performance is based on the assumption that go and stop responses are triggered by the presentation of go and stop stimuli, respectively. The first of these two processes to finish, determines whether a response is executed or stopped (Logan and Cowan 1984). The SSRT is a measure of the duration of the stop process (Logan and Cowan 1984). In the present study, the stop signal task was carried out in accordance with recommendations of a recently published consensus guide (Verbruggen et al. 2019). To make sure that race model assumptions were met, we excluded participants according to strict criteria (described in "Stop signal task"). Moreover, reaction times in go trials were higher than in incorrect stop trials, confirming the independence of the stop and go processes. The high number of excluded participants was possibly due to the relatively small step size (16 ms) in the tracking procedure combined with only 50 stop trials. However, after exclusion, the sample size was still so large, that drug effects of medium size could have been detected. Taken together, it may be concluded that stop signal reaction time was validly assessed in this study although no evidence for a modulation by nicotine could be uncovered.

Proactive inhibition

In agreement with the literature, reaction times to go stimuli were significantly higher in the stop signal task than the simple choice task (Chikazoe et al. 2009; Verbruggen and Logan 2009; Vink et al. 2015). This pattern of results suggests that participants proactively slowed their responses in the stop signal task in anticipation of the requirement to inhibit the motor response. This is probably achieved by adjusting the individual response strategy by trading speed in the simple choice task for success in the stop signal task despite the explicit instruction not to wait for the stop signal (Verbruggen and Logan 2009). Although the increase in response time in the stop signal task can be the result of two different processes, proactive adjustment and dual-task requirements, the former is considered to play a larger role (Verbruggen and Logan 2009). Overall, our results confirm the validity of the approach to compare tasks with and without stop trials in order to study proactive inhibition although no nicotine effect could be observed.

ACP

So far, the ACP task has mainly been used to study clinical groups, such as patients with schizophrenia, where decreased coupling of subjective experience and behaviour was observed (Heerey and Gold 2007; Lui et al. 2016). In the present study, we replicated valence and phase effects indicating increased key press speed to negative and positive compared to neutral slides and in the anticipatory compared to the consummatory phase. The fact that participants engaged in more effortful behaviour in anticipation than in direct response to an emotional stimulus display is in line with the notion that behavioural responses are more tightly linked to wanting than to liking of stimuli (Berridge 2007; Pool et al. 2016). Key press speed was higher to negative than positive slides, indicative of negativity bias in affective processing (Ito et al. 1998).

The replicability of these task effects indicates that the ACP is an adequate method for quantifying motivational behaviour.

Cardiovascular and subjective effects

The finding of increased heart rate with nicotine (Benowitz et al. 1982, 1988; Logemann et al. 2014a) is likely due to excitatory nicotinic effects on the sympathetic nervous system (Adamopoulos et al. 2008). Significant effects on other cardiovascular measures could not be observed, possibly due to the low dose applied here.

At the level of subjective experience, we observed negative nicotine effects on alertness and calmness, but no effect on contentedness. The calmness effect is consistent with a meta-analysis suggesting decreased subjective relaxation levels after nicotine administration in both smokers and non-smokers (Kalman and Smith 2005). Similarly, the effect on alertness matches the decreased vigour ratings found under nicotine in the same meta-analysis (Kalman and Smith 2005). In light of the attention-enhancing effects of nicotine (Hahn 2015; Heishman et al. 2010), decreased alertness ratings seem surprising at first sight. However, negative subjective effects along with decreased reaction times have also been reported in previous studies (Ettinger et al. 2017; Heishman and Henningfield, 2000). Importantly, subjective ratings of alertness covered a broad range of feelings

compared to the relatively specific measure of reaction times in response to a stimulus following task instructions. This may suggest that in non-smokers objective improvements in performance are overshadowed by negative subjective nicotine effects or that nicotine can improve some aspects of cognition without the concomitant subjective experience of this improvement. This may lead to the conclusion that subjective and behavioural outcomes are differentially affected by nicotine. It should also be noted, however, that some studies did not observe any subjective nicotine effects (Meyhöfer et al. 2019; Thiel and Fink 2007) or effects opposite to ours (Griesar et al. 2002; Warburton and Mancuso 1998). The heterogeneity in subjective nicotine effects might be attributed to different approaches in assessing subjective experience, dosage, smoking status and baseline subjective state (Griesar et al. 2002; Kalman and Smith 2005; Perkins et al. 1992).

General limitations

Our results should be considered in the light of some limitations.

First, we did not collect baseline data on SBR prior to drug administration. Therefore, potential baseline dependency effects could not be explored (Jongkees and Colzato 2016; Unsworth et al. 2019). This may be critical as there is substantial variability in SBR (Unsworth et al. 2019) and nicotine administration might exert non-linear effects (Cavanagh et al. 2014; Cools and D'Esposito 2011) that could not be captured with our approach. Similarly, baseline data for other dependent variables such as task performance and subjective feelings may also have helped to qualify the observed results (Ettinger et al. 2017; Perkins et al. 1992).

Second, every participant received the same nicotine dose and nicotine plasma levels were not monitored. However, we tried to control nicotine intake as accurately as possible by presenting a standardized chewing protocol and we restricted the sample to participants with normal body weight according to BMI criteria.

Third, a 2 mg nicotine dose might have been too low to induce the expected effects. Notably, however, participants were selected according to strict non-smoking criteria and the same dose has yielded positive effects on a broad range of outcomes in non-smokers in the past (Almeida et al. 2020; Meinke et al. 2006; Meyhöfer et al. 2019). Also, even with this relatively low dose, two participants had to discontinue their study participation because of adverse side effects. Presumably, this number would have been even higher with higher dosage (Nyberg et al. 1982).

Fourth, we did not directly measure dopamine turnover via single photon emission computed tomography (SPECT) or positron emission tomography (PET) due to the invasiveness and costs of such methods. Instead, we decided to rely on indirect measures of striatal dopamine activity, i.e. SBR, that might have been too imprecise for our purposes.

Conclusion

To conclude, across a number of a priori selected oculomotor, cognitive and affective outcomes, beneficial effects of nicotine were observed in a large sample of healthy non-smokers only for reaction times to go stimuli in stop signal and simple choice tasks. Of note, this effect was small and not supported – but also not conclusively ruled out - by Bayesian analyses. Against our preregistered hypothesis - but confirmed by Bayesian analyses - *SLC6A3* 3' UTR VNTR genotype (9R-carriers and 10R-homozygotes) did not interact with nicotine administration. SBR as a measure of striatal dopamine activity was not affected by nicotine and unrelated to performance. Nicotine had negative effects on subjective ratings on alertness and calmness and increased heart rate, in accordance with previous investigations. Taken together, our results highlight the need for more well-powered research to characterize the association between dopaminergic genes and response to pharmacological challenges.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-06028-x .

Acknowledgments We would like to thank Joana Abondo, Laura Augsburg, Philine Baumert, Susen Fischer, Hanna Lehr, Sharon Sahler, Eva Schönenborn, Alena Senger, and Tatyana Yovcheva for their invaluable help in data collection.

Funding Open Access funding enabled and organized by Projekt DEAL. The PhD project of Rebekka Schröder is funded by the German Academic Scholarship Foundation. The PhD project of Jessie Poulsen is funded by Innovation Fund Denmark (grant no. 7038-00043B).

Raymond Chan was supported by the CAS Key Laboratory of Mental Health, Institute of Psychology.

Declaration

Conflicting of interest The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

Ackenheil M, Stotz-Ingenlath G, Dietz-Bauer R, Vossen A (1999) MINI Mini International Neuropsychiatric Interview, German version 5.0.0 DSM IV. Psychiatrische Universitätsklinik München, Germany

Adamopoulos D, Borne van de P, Argacha JF (2008) New insights into the sympathetic, endothelial and coronary effects of nicotine. Clin Exp Pharmacol Physiol 35:458–463 https://doi.org/10.1111/j.1440-1681.2008.04896.x

Almeida NL, Rodrigues SJ, Gonçalves LM, Silverstein SM, Sousa IC, Gomes GH, Butler PD, Fernandes TP, Santos NA (2020) Opposite effects of smoking and nicotine intake on cognition. Psychiatry Res 293:113357. https://doi.org/10.1016/j.psychres.2020.113357

Babin SL, Hood AJ, Wassef AA, Williams NG, Patel SS, Sereno AB (2011) Effects of haloperidol on cognition in schizophrenia patients depend on baseline performance: a saccadic eye movement study. Prog Neuropsychopharmacol Biol Psychiatry 35:1753–1764. https://doi.org/10.1016/j.pnpbp.2011.06.004

Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE (2008a) A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. Biol Psychiatry 63:1061–1065. https://doi.org/10.1016/j.biopsych.2007.09.015

Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, Deckersbach T, Kelly JF, Freudenreich O, Goff DC, Evins AE (2008b) The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology 33:480–490. https://doi.org/10.1038/sj.npp.1301423

Barreto GE, Iarkov A, Moran VE (2014) Beneficial effects of nicotine, cotinine and its metabolites as potential agents for Parkinson's disease. Front Aging Neurosci 6:340. https://doi.org/10.3389/fnagi.2014.00340

Benowitz NL, Jacob P, Jones RT, Rosenberg J (1982) Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. J Pharmacol Exp Ther 221:368–372

Benowitz NL, Porchet H, Sheiner L, Jacob P (1988) Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 44:23–28. https://doi.org/10.1038/clpt.1988.107

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience Psychopharmacology 191:391–431. https://doi.org/10.1007/s00213-006-0578-x

Bonci A, Bernardi G, Grillner P, Mercuri NB (2003) The dopamine-containing neuron: maestro or simple musician in the orchestra of addiction? Trends Pharmacol Sci 24:172–177 https://doi.org/10.1016/S0165-6147(03)00068-3

Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings Psychol Psychother 47:211–218. https://doi.org/10.1111/j.2044-8341.1974.tb02285.x

Brewer AJ , Nielsen DA, Spellicy CJ, Hamon SC, Gingrich J, Thompson-Lake DG, Nielsen EM, Mahoney JJ, Kosten TR, Newton TF, La Garza R de (2015) Genetic variation of the dopamine transporter (DAT1) influences the acute subjective responses to cocaine in volunteers with cocaine use disorders. Pharmacogenetics and Genomics:296–304. https://doi.org/10.1097/FPC.0000000000000137

Cachope R, Mateo Y, Mathur BN, Irving J, Wang H-L, Morales M, Lovinger DM, Cheer JF (2012) Selective activation of cholinergic interneurons enhances accumbal phasic dopamine release: setting the tone for reward processing. Cell Rep 2:33–41. https://doi.org/10.1016/j.celrep.2012.05.011

Cavanagh JF, Masters SE, Bath K, Frank MJ (2014) Conflict acts as an implicit cost in reinforcement learning. Nat Commun 5:5394. https://doi.org/10.1038/ncomms6394

Chikazoe J, Jimura K, Hirose S, Yamashita K, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci 29:15870–15877. https://doi.org/10.1523/JNEUROSCI.3645-09.2009

Congdon E, Mumford JA, Cohen JR, Galvan A, Canli T, Poldrack RA (2012) Measurement and reliability of response inhibition. Front Psychol 3:37. https://doi.org/10.3389/fpsyg.2012.00037

Cools R, D'Esposito M (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69:e113–e125 https://doi.org/10.1016/j.biopsych.2011.03.028

D'Souza MS, Markou A (2012) Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. Neuropharmacology 62:1564–1573. https://doi.org/10.1016/j.neuropharm.2011.01.044

Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Newhouse PA, Zald DH (2017) Spontaneous Eye Blink Rate (EBR) Is Uncorrelated with Dopamine D2 Receptor Availability and Unmodulated by Dopamine Agonism in Healthy Adults. eNeuro 4. https://doi.org/10.1523/ENEURO.0211-17.2017

Dani JA, Bertrand D (2007) Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annu Rev Pharmacol Toxicol 47:699–729. https://doi.org/10.1146/annurev.pharmtox.47.120505.105214

Dawkins L, Powell J (2011) Effects of nicotine and alcohol on affective responses to emotionally toned film clips. Psychopharmacology 216:197–205. https://doi.org/10.1007/s00213-011-2197-4

Dawkins L, Powell JH, West R, Powell J, Pickering A (2006) A double-blind placebo controlled experimental study of nicotine: I—effects on incentive motivation. Psychopharmacology 189:355–367. https://doi.org/10.1007/s00213-006-0588-8

de Kloet SF, Mansvelder HD, de Vries TJ (2015) Cholinergic modulation of dopamine pathways through nicotinic acetylcholine receptors. Biochem Pharmacol 97:425–438. https://doi.org/10.1016/j.bcp.2015.07.014

Depue RA, Luciana M, Arbisi P, Collins P, Leon A (1994) Dopamine and the structure of personality: Relation of agonist-induced dopamine activity to positive emotionality. J Pers Soc Psychol 67:485–498. https://doi.org/10.1037/0022-3514.67.3.485

Ettinger U, Faiola E, Kasparbauer A-M, Petrovsky N, Chan RCK, Liepelt R, Kumari V (2017) Effects of nicotine on response inhibition and interference control. Psychopharmacology 234:1093–1111. https://doi.org/10.1007/s00213-017-4542-8

Faraone SV, Spencer TJ, Madras BK, Zhang-James Y, Biederman J (2014) Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: a meta-analysis. Mol Psychiatry 19:880–889. https://doi.org/10.1038/mp.2013.126

Faul F, Erdfelder E, Lang A-G, Buchner A (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175–191. https://doi.org/10.3758/bf03193146

Franklin TR, Lohoff FW, Wang Z, Sciortino N, Harper D, Li Y, Jens W, Cruz J, Kampman K, Ehrman R, Berrettini W, Detre JA, O'Brien CP, Childress AR (2009) DAT genotype modulates brain and behavioral responses eliicited by cigarette cues. Neuropsychopharmacology 34:717–728. https://doi.org/10.1038/npp.2008.124

Franklin TR, Wang Z, Li Y, Suh JJ, Goldman M, Lohoff FW, Cruz J, Hazan R, Jens W, Detre JA, Berrettini W, O'Brien CP, Childress AR (2011) Dopamine transporter genotype modulation of neural responses to smoking cues: confirmation in a new cohort: DAT genotype effects on SCs. Addict Biol 16:308–322. https://doi.org/10.1111/j.1369-1600.2010.00277.x

Gelernter J, Kranzler HR, Satel SL, Rao PA (1994) Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacology 11:195–200. https://doi.org/10.1038/sj.npp.1380106

Griesar WS, Zajdel DP, Oken BS (2002) Nicotine effects on alertness and spatial attention in non-smokers. Nicotine Tob Res 4:185–194. https://doi.org/10.1080/14622200210123617

Gurvich CT, Rossell SL (2014) Genetic variations in dopamine and inhibitory control: lack of influence on action restraint. Behav Brain Res 267:12–16. https://doi.org/10.1016/j.bbr.2014.03.015

Hahn B (2015) Nicotinic receptors and attention. In: Balfour DJK, Munafò MR (eds) The neurobiology and genetics of nicotine and tobacco. Springer International Publishing Cham 23:103–135

Hariri AR (2009) The neurobiology of individual differences in complex behavioral traits. Annu Rev Neurosci 32:225–247. https://doi.org/10.1146/annurev.neuro.051508.135335

Hart AB, de Wit H, Palmer AA (2013) Candidate gene studies of a promising intermediate phenotype: failure to replicate. Neuropsychopharmacology 38:802–816. https://doi.org/10.1038/npp.2012.245

Hayes AF (2015) An index and test of linear moderated mediation Multivar Behav Res 50:1–22. https://doi.org/10.1080/00273171.2014.962683

Heerey EA, Gold JM (2007) Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. J Abnorm Psychol 116:268. https://doi.org/10.1037/0021-843X.116.2.268

Heishman SJ, Henningfield JE (2000) Tolerance to repeated nicotine administration on performance, subjective, and physiological responses in nonsmokers. Psychopharmacology 152:321–333. https://doi.org/10.1007/s002130000541

Heishman SJ, Kleykamp BA, Singleton EG (2010) Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology 210:453–469. https://doi.org/10.1007/s00213-010-1848-1

Ito TA, Larsen JT, Smith NK, Cacioppo JT (1998) Negative information weighs more heavily on the brain: The negativity bias in evaluative categorizations. J Pers Soc Psychol 75:887–900. https://doi.org/10.1037/0022-3514.75.4.887

Jongkees BJ, Colzato LS (2016) Spontaneous eye blink rate as predictor of dopamine-related cognitive function—A review. Neurosci Biobehav Rev 71:58–82. https://doi.org/10.1016/j.neubiorev.2016.08.020

Kalman D, Smith SS (2005) Does nicotine do what we think it does? A meta-analytic review of the subjective effects of nicotine in nasal spray and intravenous studies with smokers and nonsmokers. Nicotine Tob Res 7:317–333. https://doi.org/10.1080/14622200500125385

Kambeitz J, Romanos M, Ettinger U (2014) Meta-analysis of the association between dopamine transporter genotype and response to methylphenidate treatment in ADHD. Pharmacogenomics J 14:77–84. https://doi.org/10.1038/tpj.2013.9

Kang A, Palmatier MA, Kidd KK (1999) Global variation of a 40-bp VNTR in the 3′-untranslated region of the dopamine transporter gene (SLC6A3). Biol Psychiatry 46:151–160. https://doi.org/10.1016/S0006-3223(99)00101-8

Kasparbauer A-M, Rujescu D, Riedel M, Pogarell O, Costa A, Meindl T, La Fougère C, Ettinger U (2015) Methylphenidate effects on brain activity as a function of SLC6A3 genotype and striatal dopamine transporter availability. Neuropsychopharmacology 40:736–745. https://doi.org/10.1038/npp.2014.240

Kasparbauer A-M, Meyhöfer I, Steffens M, Weber B, Aydin M, Kumari V, Hurlemann R, Ettinger U (2016) Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. Neuroimage 141:52–59. https://doi.org/10.1016/j.neuroimage.2016.07.012

Kerzel D, Souto D, Ziegler NE (2008) Effects of attention shifts to stationary objects during steady-state smooth pursuit eye movements. Vision Res 48:958–969. https://doi.org/10.1016/j.visres.2008.01.015

Klein C, Andresen B, Thom E (1993) Blinking, alpha brain waves and smoking in schizophrenia. Acta Psychiatr Scand 87:172–178. https://doi.org/10.1111/j.1600-0447.1993.tb03351.x

Lakens D (2013) Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 4:863. https://doi.org/10.3389/fpsyg.2013.00863

Lang PJ, Bradley MM, Cuthbert BN (1997) International affective picture system (IAPS): Technical manual and affective ratings

Lehrl S (1999) Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B. Spitta

Levin ED, Wilson W, Rose JE, McEvoy J (1996) Nicotine-Haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 15:429–436. https://doi.org/10.1016/S0893-133X(96)00018-8

Leys C, Delacre M, Mora YL, Lakens D, Ley C (2019) How to Classify, Detect, and Manage Univariate and Multivariate Outliers, With Emphasis on Pre-Registration. International Review of Social Psychology 32. https://doi.org/10.5334/irsp.289

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:295–327. https://doi.org/10.1037/0033-295X.91.3.295

Logemann HNA, Böcker KBE, Deschamps PKH, Kemner C, Kenemans JL (2014a) Differences between nicotine-abstinent smokers and non-smokers in terms of visuospatial attention and inhibition before and after single-blind nicotine administration. Neuroscience 277:375–382. https://doi.org/10.1016/j.neuroscience.2014.07.016

Logemann HNA, Böcker KBE, Deschamps PKH, Kemner C, Kenemans JL (2014b) The effect of enhancing cholinergic neurotransmission by nicotine on EEG indices of inhibition in the human brain. Pharmacol Biochem Behav 122:89–96. https://doi.org/10.1016/j.pbb.2014.03.019

Lott DC, Kim S-J, Cook EH, de Wit H (2005) Dopamine transporter gene associated with diminished subjective response to amphetamine. Neuropsychopharmacology 30:602–609. https://doi.org/10.1038/sj.npp.1300637

Lui SSY, Shi Y, Au ACW, Li Z, Tsui CF, Chan CKY, Leung MMW, Wong PTY, Wang Y, Yan C, Heerey EA, Cheung EFC, Chan RCK (2016) Affective experience and motivated behavior in schizophrenia spectrum disorders: Evidence from clinical and nonclinical samples. Neuropsychology 30:673–684. https://doi.org/10.1037/neu0000278

Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB (2006) Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology 184:292–305. https://doi.org/10.1007/s00213-005-0070-z

Meinke A, Thiel CM, Fink GR (2006) Effects of nicotine on visuospatial selective attention as indexed by event-related potentials. Neuroscience 141:201–212. https://doi.org/10.1016/j.neuroscience.2006.03.072

Meyhöfer I, Kasparbauer A-M, Steffens M, Ettinger U (2019) Effects of nicotine on smooth pursuit eye movements in healthy nonsmokers. Psychopharmacology 236:2259–2271. https://doi.org/10.1007/s00213-019-05223-1

Millar A, Smith D, Choueiry J, Fisher D, Albert P, Knott V (2011) The moderating role of the dopamine transporter 1 gene on P50 sensory gating and its modulation by nicotine. Neuroscience 180:148–156. https://doi.org/10.1016/j.neuroscience.2011.02.008

Newberg A, Lerman C, Wintering N, Ploessl K, Mozley PD (2007) Dopamine transporter binding in smokers and nonsmokers. Clin

Nucl Med 32:452–455. https://doi.org/10.1097/01.rlu.0000262980.98342.dd

Niemegeers P, Dumont GJH, Quisenaerts C, Morrens M, Boonzaier J, Fransen E, de Bruijn ERA, Hulstijn W, Sabbe BGC (2014) The effects of nicotine on cognition are dependent on baseline performance. Eur Neuropsychopharmacol 24:1015–1023. https://doi.org/10.1016/j.euroneuro.2014.03.011

Nisell M, Nomikos GG, Svensson TH (1994) Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 16:36–44. https://doi.org/10.1002/syn.890160105

Nosek BA, Ebersole CR, DeHaven AC, Mellor DT (2018) The preregistration revolution. Proc Natl Acad Sci U S A 115:2600–2606. https://doi.org/10.1073/pnas.1708274114

Nyberg G, Panfilov V, Sivertsson R, Wilhelmsen L (1982) Cardiovascular effect of nicotine chewing gum in healthy non-smokers. Eur J Clin Pharmacol 23:303–307. https://doi.org/10.1007/BF00613610

Ohlendorf S, Sprenger A, Speck O, Glauche V, Haller S, Kimmig H (2010) Visual motion, eye motion, and relative motion: A parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. J Vis 10:21. https://doi.org/10.1167/10.14.21

Oldfield RC (1971) The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Olincy A, Ross RG, Young DA, Roath M, Freedman R (1998) Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. Neuropsychopharmacology 18:175–185. https://doi.org/10.1016/S0893-133X(97)00095-X

Perkins KA, Grobe JE, Epstein LH, Caggiula AR, Stiller RL (1992) Effects of nicotine on subjective arousal may be dependent on baseline subjective state. J Subst Abuse 4:131–141. https://doi.org/10.1016/0899-3289(92)90013-N

Piccini PP (2003) Dopamine transporter: Basic aspects and neuroimaging. Mov Disord 18:S3–S8. https://doi.org/10.1002/mds.10571

Pool E, Sennwald V, Delplanque S, Brosch T, Sander D (2016) Measuring wanting and liking from animals to humans: A systematic review. Neurosci Biobehav Rev 63:124–142. https://doi.org/10.1016/j.neubiorev.2016.01.006

Potter AS, Newhouse PA (2004) Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. Psychopharmacology 176:183–194. https://doi.org/10.1007/s00213-004-1874-y

Rezvani AH, Levin ED (2001) Cognitive effects of nicotine. Biol Psychiat 49:258–267. https://doi.org/10.1016/S0006-3223(00)01094-5

Rincón-Pérez I, Sánchez-Carmona AJ, Albert J, Hinojosa JA (2018) The association of monoamine-related gene polymorphisms with behavioural correlates of response inhibition: A meta-analytic review. Neurosci Biobehav Rev 84:49–62. https://doi.org/10.1016/j.neubiorev.2017.11.009

Salatino-Oliveira A, Rohde LA, Hutz MH (2018) The dopamine transporter role in psychiatric phenotypes. Am J Med Genet B Neuropsychiatr Genet 177:211–231. https://doi.org/10.1002/ajmg.b.32578

Schmitt KC, Reith MEA (2010) Regulation of the dopamine transporter: aspects relevant to psychostimulant drugs of abuse. Ann N Y Acad Sci 1187:316–340. https://doi.org/10.1111/j.1749-6632.2009.05148.x

Schröder R, Baumert PM, Ettinger U (2021) Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements. Acta Psychol 219:103364. https://doi.org/10.1016/j.actpsy.2021.103364

Sherr JD, Myers C, Avila MT, Elliott A, Blaxton TA, Thaker GK (2002) The effects of nicotine on specific eye tracking measures in schizophrenia. Biol Psychiatry 52:721– 728. https://doi.org/10.1016/S0006-3223(02)01342-2

Sibony PA, Evinger C, Manning KA (1988) The effects of tobacco smoking on smooth pursuit eye movements. Ann Neurol 23:238–241. https://doi.org/10.1002/ana.410230305

Siebner HR, Callicott JH, Sommer T, Mattay VS (2009) From the genome to the phenome and back: linking genes with human brain function and structure using genetically informed neuroimaging using genetically informed neuroimaging. Neuroscience 164:1–6. https://doi.org/10.1016/j.neuroscience.2009.09.009

Thiel CM, Fink GR (2007) Visual and auditory alertness: modality-specific and supramodal neural mechanisms and their modulation by nicotine. J Neurophysiol 97:2758–2768. https://doi.org/10.1152/jn.00017.2007

Threlfell S, Lalic T, Platt NJ, Jennings KA, Deisseroth K, Cragg SJ (2012) Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. Neuron 75:58–64. https://doi.org/10.1016/j.neuron.2012.04.038

Tregellas JR, Tanabe JL, Martin LF, Freedman R (2005) FMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. Am J Psychiatry 162:391–393. https://doi.org/10.1176/appi.ajp.162.2.391

Tsaur S, Strasser AA, Souprountchouk V, Evans GC, Ashare RL (2015) Time dependency of craving and response inhibition during nicotine abstinence. Addict Res Theory 23:205–212. https://doi.org/10.3109/16066359.2014.953940

Unsworth N, Robison MK, Miller AL (2019) Individual differences in baseline oculometrics: Examining variation in baseline pupil diameter, spontaneous eye blink rate, and fixation stability. Cogn Affect Behav Neurosci 19:1074–1093. https://doi.org/10.3758/s13415-019-00709-z

van den Bergh D, van Doorn J, Marsman M, Draws T, van Kesteren E-J, Derks K, Dablander F, Gronau QF, Kucharský Š, Gupta ARKN, Sarafoglou A, Voelkel JG, Stefan A, Ly A, Hinne M, Matzke D, Wagenmakers E-J (2020) A Tutorial on Conducting and Interpreting a Bayesian ANOVA in JASP. L'année Psychologique 120:73. https://doi.org/10.3917/anpsy1.201.0073

Verbruggen F, Logan GD (2009) Proactive adjustments of response strategies in the stop-signal paradigm. J Exp Psychol Hum Percept Perform 35:835–854. https://doi.org/10.1037/a0012726

Verbruggen F, Aron AR, Band G, Beste C, Bissett P, Brockett AT, Brown JW, Chamberlain S, Chambers C, Colonius H, Colzato L, Corneil BD, Coxon JP, Eagle DM, Dupuis A, Garavan H, Greenhouse I, Heathcote A, Huster RJ, Jahfari S, Kenemans L, Leunissen I, Logan GD, Matzke D, Morein-Zamir S, Murthy A, Li C-SR, Paré M, Poldrack RA, Ridderinkhof R, Robbins TW, Roesch MR, Rubia K, Schachar R, Schall J, Stock A-K, Swann NC, Thakkar KN, van der Molen M, Vermeylen L, Vink M, Wessel J, Whelan R, Zandbelt B, Boehler CN (2019) A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. eLife 8:e46323. https://doi.org/10.7554/eLife.46323

Vink M, Kaldewaij R, Zandbelt BB, Pas P, Du Plessis S (2015) The role of stop-signal probability and expectation in proactive inhibition. Eur J Neurosci 41:1086–1094. https://doi.org/10.1111/ejn.12879

WagenmakersE-J, Love J, Marsman M, Jamil T, Ly A, Verhagen J, Selker R, Gronau QF, Dropmann D, Boutin B, Meerhoff F, Knight P, Raj A, van Kesteren E-J, van Doorn J, Šmíra M, Epskamp S, Etz A, Matzke D, de Jong T, van den Bergh D, Sarafoglou A,

Steingroever H, Derks K, Rouder JN, Morey RD (2018) Bayesian inference for psychology. Part II: Example applications with JASP. Psychon Bull Rev 25:58–76. https://doi.org/10.3758/s13423-017-1323-7

Wagner AK, Scanion JM, Becker CR, Ritter AC, Niyonkuru C, Dixon CE, Conley YP, Price JC (2014) The influence of genetic variants on striatal dopamine transporter and D2 receptor binding after TB. J Cereb Blood Flow Metab 34:1328–1339. https://doi.org/10.1038/jcbfm.2014.87

Warburton DM, Mancuso G (1998) Evaluation of the information processing and mood effects of a transdermal nicotine patch. Psychopharmacology 135:305–310. https://doi.org/10.1007/s002130050514

Wignall ND, Wit de H (2011) Effects of nicotine on attention and inhibitory control in healthy nonsmokers. Exp Clin Psychopharmacol 19:183–191. https://doi.org/10.1037/a0023292

Wonnacott S, Sidhpura N, Balfour DJK (2005) Nicotine: from molecular mechanisms to behaviour. Curr Opin Pharmacol 5:53–59. https://doi.org/10.1016/j.coph.2004.12.002

Yang YK, Yao WJ, Yeh TL, Lee IH, Chen PS, Lu RB, Chiu NT (2008) Decreased dopamine transporter availability in male smokers – a dual isotope SPECT study. Prog Neuropsychopharmacol Biol Psychiatry 32:274–279. https://doi.org/10.1016/j.pnpbp.2007.08.018

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Appendix C | Study III

Schröder, R., Kasparbauer, A. M., Meyhöfer, I., Steffens, M., Trautner, P., & Ettinger, U. (2020). Functional connectivity during smooth pursuit eye movements. *Journal of Neurophysiology*, *124*(6), 1839–1856. https://doi.org/10.1152/jn.00317.2020

J Neurophysiol 124: 1839–1856, 2020.
First published September 30, 2020; doi:10.1152/jn.00317.2020.

RESEARCH ARTICLE | *Control of Movement*

Functional connectivity during smooth pursuit eye movements

Rebekka Schröder,[1] Anna-Maria Kasparbauer,[1] Inga Meyhöfer,[1] Maria Steffens,[1] Peter Trautner,[2,3] and Ulrich Ettinger[1]

[1]*Department of Psychology, University of Bonn, Bonn, Germany;* [2]*Institute for Experimental Epileptology and Cognition Research, University of Bonn, Bonn, Germany; and* [3]*Core Facility MRI, Bonn Technology Campus, University of Bonn, Bonn, Germany*

Submitted 29 May 2020; accepted in final form 25 September 2020

Schröder R, Kasparbauer AM, Meyhöfer I, Steffens M, Trautner P, Ettinger U. Functional connectivity during smooth pursuit eye movements. *J Neurophysiol* 124: 1839–1856, 2020. First published September 30, 2020; doi:10.1152/jn.00317.2020.—Smooth pursuit eye movements (SPEM) hold the image of a slowly moving stimulus on the fovea. The neural system underlying SPEM primarily includes visual, parietal, and frontal areas. In the present study, we investigated how these areas are functionally coupled and how these couplings are influenced by target motion frequency. To this end, healthy participants (n = 57) were instructed to follow a sinusoidal target stimulus moving horizontally at two different frequencies (0.2 Hz, 0.4 Hz). Eye movements and blood oxygen level-dependent (BOLD) activity were recorded simultaneously. Functional connectivity of the key areas of the SPEM network was investigated with a psychophysiological interaction (PPI) approach. How activity in five eye movement-related seed regions (lateral geniculate nucleus, V1, V5, posterior parietal cortex, frontal eye fields) relates to activity in other parts of the brain during SPEM was analyzed. The behavioral results showed clear deterioration of SPEM performance at higher target frequency. BOLD activity during SPEM versus fixation occurred in a geniculo-occipito-parieto-frontal network, replicating previous findings. PPI analysis yielded widespread, partially overlapping networks. In particular, frontal eye fields and posterior parietal cortex showed task-dependent connectivity to large parts of the entire cortex, whereas other seed regions demonstrated more regionally focused connectivity. Higher target frequency was associated with stronger activations in visual areas but had no effect on functional connectivity. In summary, the results confirm and extend previous knowledge regarding the neural mechanisms underlying SPEM and provide a valuable basis for further investigations such as in patients with SPEM impairments and known alterations in brain connectivity.

NEW & NOTEWORTHY This study provides a comprehensive investigation of blood oxygen level-dependent (BOLD) functional connectivity during smooth pursuit eye movements. Results from a large sample of healthy participants suggest that key oculomotor regions interact closely with each other but also with regions not primarily associated with eye movements. Understanding functional connectivity during smooth pursuit is important, given its potential role as an endophenotype of psychoses.

eye movements; fMRI; functional connectivity; psychophysiological interactions; smooth pursuit

Correspondence: U. Ettinger (ulrich.ettinger@uni-bonn.de).

INTRODUCTION

Smooth pursuit eye movements (SPEM) support vision by holding the image of a small moving target on the fovea (Leigh and Zee 2015). In general, SPEM help to achieve two goals, reducing motion of an object's image on the retina and maintaining an object's image close to the fovea, the area of highest acuity on the retina (Barnes 2008), while entailing both open- and closed-loop processes (Lisberger et al. 1987). Important parameters in SPEM research include global measures such as root mean square error (RMSE) or pursuit gain (ratio of eye velocity to target velocity) as well as more specific measures such as the number of catch-up saccades (Barnes 2008; Lencer and Trillenberg 2008; Smyrnis 2008). SPEM performance is impaired in a number of psychiatric and neurological conditions (see, e.g., Ivleva et al. 2014; Lencer et al. 2015; O'Driscoll and Callahan 2008; Shakespeare et al. 2015) and has been intensely studied as a biomarker and potential endophenotype of psychoses (Calkins et al. 2008).

A considerable body of evidence concerning the neural system underlying pursuit has already been accumulated in human and nonhuman animals (Ilg and Thier 2008; Leigh and Zee 2015; Lencer and Trillenberg 2008; Sharpe 2008). Visual information is projected from the retina to primary visual cortex (V1) through lateral geniculate nucleus (LGN; Lencer and Trillenberg 2008). From there, projections lead to visual area V5, also known as middle temporal area (Leigh and Zee 2015). This region encompasses the human analogs of areas MT and MST (Dukelow et al. 2001) and includes neurons selective for stimulus direction, speed, and orientation (Maunsell and Van Essen 1983a). However, V5 neurons not only respond to motion signals but are strongly connected to other cortical areas (Zeki 2015) and receive extraretinal input (Newsome et al. 1988). From V5, signals are propagated to other cortical areas including posterior parietal cortex (PPC), frontal eye fields (FEF), and supplementary eye fields (SEF), all of which interact closely (Leigh and Zee 2015; Lencer and Trillenberg 2008). The PPC is considered to play an important role in the allocation of attention during smooth pursuit (Drew and van Donkelaar 2007b; Ohlendorf et al. 2007). The FEF control the gain of the transformation of visual and predictive signals into motor commands (Gagnon et al. 2006; Tanaka and Lisberger 2001). Eye movement information and visual information are integrated in the pontine nuclei and projected from there to the cerebellum. Finally, signals are sent to the motoneurons of the extraocular muscles via the vestibular and oculomotor

 0022-3077/20 Copyright © 2020 the American Physiological Society

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

nuclei in the midbrain (Ilg and Thier 2008; Leigh and Zee 2015; Lencer and Trillenberg 2008). Elaborate models have been developed to map the complex cooperation of different systems during the generation of SPEM incorporating intricate feedback loops and the notion of active inference (Adams et al. 2012; Krauzlis and Lisberger 1994; Robinson et al. 1986).

Despite the well-established blood oxygen level-dependent (BOLD) correlates of smooth pursuit in humans (Berman et al. 1999; Dukelow et al. 2001; Lencer et al. 2004; Nagel et al. 2008; Petit and Haxby 1999; Tanabe et al. 2002), a number of questions remain unanswered. These include *1*) fundamental aspects of brain-behavior relationships such as the effects of target motion frequency not only on performance but also on underlying neural activity, *2*) the characterization of functional connectivity among pursuit-related areas during task performance, and *3*) brain-behavior relationships at the level of individual differences.

Regarding the first question, the deterioration of pursuit performance with increasing target motion frequency (as an indicator of peak target velocity) for sinusoidal movement patterns is a well-established effect at the behavioral level (Collewijn and Tamminga 1984; Lisberger et al. 1981; Meyhöfer et al. 2019). However, less is known about effects of target velocity on BOLD signal (Lebranchu et al. 2010; Nagel et al. 2008, 2012). Investigations of the parametric influence of target velocity on brain activity can help to identify those regions of the pursuit network that increase their activity in response to higher external demands and those regions that do not show such sensitivity to increasing demands. This can help to characterize the different roles of the individual components of the pursuit network.

Using a whole brain approach, Nagel et al. (2008) observed increases in BOLD in primary visual cortex, angular gyrus, cerebellum, and basal ganglia with increasing target velocity. Additionally, a less conservative small-volume corrected regression analysis yielded neural activity increases with increasing velocity in large parts of the oculomotor network including primary visual cortex, V5, lateral intraparietal area, FEF, SEF, cerebellum, putamen, and thalamus. Nagel et al. (2012) partly replicated these findings and additionally showed that target velocity was processed at the neural level differently in patients with schizophrenia than in healthy control subjects. To better understand these deficits in patient populations, it is crucial to comprehensively investigate the underlying processes in healthy subjects. However, the studies by Nagel et al. (2008, 2012) used a step-ramp task in which pursuit occurs to individual ramps for a duration of only a few seconds, which is best suited to study the early phases of pursuit, including initiation. The effects of target frequency on BOLD during sustained pursuit maintenance, as required in the more frequently used block designs, thus remain unclear.

With regard to the second question, in recent years, neuroimaging research has evolved from studying functionally segregated areas to the assessment of their integration (Friston 2011). In this context, functional connectivity refers to the statistical dependence among remote neurophysiological events (Friston 2011). Although resting-state functional connectivity of visual and oculomotor networks has already been studied in humans and nonhuman animals (Genç et al. 2016; Heinzle et al. 2011; Hutchison et al. 2013; Vincent et al. 2007), the functional interactions among areas supporting smooth pursuit are still poorly understood. Advanced approaches to functional MRI (fMRI) data analysis over the last years have yielded methods to delineate the connectivity between task-related activation peaks (Friston et al. 1997; McLaren et al. 2012). In an early study, Acs and Greenlee (2008) investigated effective connectivity during eye movements with a dynamic causal modeling (DCM) approach. Their results showed that attention modulates the bottom-up connection between V1 and V5. Although important, that study was limited both in sample size (n = 8) and because only a small number of pursuit-related areas were investigated, i.e., V1, V5, and PPC. To further our understanding of functional connectivity during smooth pursuit, the present study employed comprehensive psychophysiological interaction (PPI) analysis (Friston et al. 1997; McLaren et al. 2012) in a considerably larger sample.

The third issue raised above concerns individual differences in smooth pursuit performance and their underlying neural manifestation. The study of interindividual differences marks a unique opportunity for testing brain-behavior relationships as well as for theory development and testing (Seghier and Price 2018; Underwood 1975; Vogel and Awh 2008). Treating neural differences between individuals as a source of information rather than noise may help to identify reasons for variance in performance (Seghier and Price 2018). For example, people might differ in how much they rely on retinal or extraretinal signals during pursuit, or it might be possible to identify regions that are crucial for excellent performance, which could also reveal candidate regions for clinical research in populations with known SPEM deficits.

Furthermore, the convergence of behavioral and neural data may help to elucidate the dynamics of the sensorimotor pursuit system. Studying convergence between behavioral and neural data can be useful to address questions such as how increasing demands on the system are expressed in both behavior and neural activity. Specifically, how are differences in performance related to the underlying neural system? Do they reflect changes in processing efficiency or in allocation of neural resources? Consequently, this study aims at better understanding the neural foundations of SPEM and their correlations with behavioral outcomes.

Therefore, the specific aims of the present study were to replicate the pursuit network components in a large sample of healthy participants, to investigate frequency effects on pursuit performance and BOLD, to investigate functional connectivity during pursuit and its sensitivity to target motion frequency, and to explore correlations between individual differences in task performance and BOLD response. We hypothesized to find higher BOLD-activations in key components of the pursuit network (including V1, V5, FEF, SEF, PPC) during pursuit compared with fixation. Additionally, we expected a decrease in pursuit performance and higher activations in the pursuit network at higher compared with lower target velocities. Because of the novelty of the connectivity approach in eye movement research, the PPI analyses were exploratory. Concerning individual differences, we expected to find correlations between behavioral outcomes and BOLD in visual and oculomotor brain regions.

MATERIALS AND METHODS

Participants

A total of 57 participants took part in the study. Participants were recruited via ads placed around the University of Bonn and in local

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

newspapers as well as online and via circular e-mails. Exclusion criteria were determined before data analysis and included any prescription or over-the-counter medication, any personal history of head injuries with loss of consciousness, impairment of vision, and any current Axis I disorder diagnosis as assessed by the Mini International Neuropsychiatric Interview (Ackenheil et al. 1999). All participants were suitable for MRI and video-based combined pupil and corneal reflection eye tracking. This is a secondary analysis of previously published data (Kasparbauer et al. 2016: placebo group; Meyhöfer et al. 2015: low-schizotypy group; Steffens et al. 2016: placebo condition in participants receiving placebo during first scan). Therefore, sample size was not determined for this analysis but for the primary studies. The present reanalysis benefits from pooling those previous samples together, and the overall sample size thus clearly exceeds those of relevant previous studies (e.g., Acs and Greenlee 2008; Berman et al. 1999; Nagel et al. 2008; Petit and Haxby 1999). Ethical permission was granted from the local ethics committee and written informed consent obtained from all participants.

SPEM Task and Eye Movement Data Acquisition

The SPEM task was presented in a block design. The target stimulus was a white circle (width and height 15 pixels, no filling, stroke width 5 pixels, 0.35° visual angle) moving horizontally in a sinusoidal waveform on a black background at two different frequencies (low frequency: 0.2 Hz, 5 blocks; high frequency: 0.4 Hz, 5 blocks) starting in the central position and subtending a visual angle of ±5.8°. Additionally, there were nine fixation blocks, where the target remained stationary in the center of the screen. The order of blocks was randomized but identical for each subject: 0.2 Hz/FIX/0.4 Hz/FIX/0.4 Hz/FIX/0.2 Hz/FIX/0.4 Hz/FIX/0.2 Hz/FIX/0.4 Hz/FIX/0.4 Hz/FIX/0.2 Hz/FIX/0.2 Hz. Each block lasted 30 s. Before scanning, participants received written and verbal instructions to follow the target with their eyes as accurately as possible during the SPEM blocks and fixate on the stationary target during fixation blocks, while keeping their head still.

To record eye movements, an MRI-compatible video-based combined pupil and corneal reflection EyeLink 1000 (SR Research Ltd., Ottawa, ON, Canada) eye tracker was used. A central pupil-tracking algorithm was used to detect pupil and corneal reflection of the right eye at a sampling rate of 1,000 Hz (for 38 participants) or 500 Hz (for 19 participants). Before the task, a five-point horizontal-vertical (38 participants) or three-point horizontal (19 participants) calibration was performed. Distance from eye to camera was ~172 cm. The stimuli were presented on a NordicNeuroLab LCD monitor (resolution 1,024 × 768 pixels, refresh rate 120 Hz).

SPEM Data Analysis

Eye movement data were analyzed with DataViewer software and LabVIEW. The first and last half-ramp of each pursuit block were excluded from further analysis. Time-weighted average maintenance gain was calculated for sections of pursuit in the middle 50% of each ramp by dividing mean eye frequency by mean target frequency for sections without saccades and blinks. Saccade rate (N/s) was computed using minimum amplitude (1°) and velocity (30°/s) criteria for detection of saccades. Mean RMSE scores (in pixels) as a measure of the position error between eye and target were computed for all included ramps, excluding blinks. All SPEM variables were calculated separately for the two conditions. Legal privacy restrictions do not permit us to publicly archive the study materials and preprocessing code. Readers seeking access to this code are advised to contact the corresponding author (U. Ettinger). Access to named individuals will be granted in consultation with the copyright holder.

Image Acquisition

Scanning was conducted with a 3-T Siemens (Erlangen, Germany) Trio Scanner at the Life&Brain Center Bonn. Participants wore earplugs or headphones to reduce the impact of scanner noise, and foam paddings were used to minimize head motion. During the smooth pursuit task, a total of 239 functional images of the brain were acquired with a T2-weighted gradient-echo planar image (EPI) sequence. Slices were oriented parallel to the intercommissural plane (AC-PC line). Scanning parameters were as follows: repetition time (TR) = 2,500 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 192 mm, 37 slices, slice thickness = 3 mm; sequential slice order with interslice gap of 0.3 mm. For 19 participants a standard 8-channel head coil was used for radio frequency transmission and reception, the matrix size was 64 × 64, and the voxel size was 3 × 3 × 3.3; for the remaining 38 participants a 12-channel head coil was used, the matrix size was 96 × 96, and the voxel size was 2 × 2 × 3.3.

Additionally, for each participant a T1-weighted high-resolution structural scan was acquired for image coregistration. Scanning parameters were as follows: TR = 1,660 ms, TE = 2.54 ms, flip angle = 9°, matrix = 320 × 320, FOV = 256 × 256 mm^2, slice thickness = 0.8 mm for 27 participants; TR = 1,570 ms, TE = 3.42 ms, flip angle = 15°, matrix = 256 × 256, FOV = 256 × 256 mm^2, slice thickness = 1 mm for 19 participants; and TR = 1,660 ms, TE = 2.75 ms, flip angle = 9°, matrix = 320 × 320, FOV = 256 × 256 mm^2, slice thickness = 0.8 mm for 11 participants.

Analyses

Behavioral data. Statistical analyses of eye movement data were run with R and the stats (v3.6.2) package (R Core Team 2020). To analyze frequency effects on smooth pursuit gain, saccade rate, and RMSE, pairwise *t* tests with target frequency as within-subject factor were conducted for each of the three dependent variables. Effect sizes are given as Cohen's d_{av} (Lakens 2013).

fMRI data. fMRI data were analyzed with SPM12 implemented in MATLAB (R2016a) except for the functional connectivity analyses, which ran in SPM8. Anatomical labels were defined with the *bspmview* toolbox and the SPM Anatomy toolbox atlas (Eickhoff et al. 2005; Spunt 2016). Functional localizations were identified from previous literature (Amunts et al. 2000; Berman et al. 1999; Lencer et al. 2004; Tanabe et al. 2002; Wilms et al. 2005). Coordinates are reported in Montreal Neurological Institute (MNI) space.

First, origins were set manually to anterior commissure to facilitate coregistration. Then, functional images were realigned to the first image, coregistered to the individual structural image, normalized, and smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian filter.

Task effects. At the single-subject level (first level), data were modeled with a hemodynamic response function (HRF)-convolved 30-s boxcar function, using the general linear model in SPM12. To account for low-frequency fluctuations in the BOLD signal, a 128-s high-pass filter was applied. The two frequency conditions were modeled independently, while the fixation blocks served as an implicit baseline that was not entered as a separate regressor. Individual motion regressors from the realignment preprocessing step were entered as regressors of no interest to decrease error variance.

At the second level, one-sample *t* tests (random effects) were performed for the low frequency versus fixation, high frequency versus fixation, and high versus low frequency contrasts, respectively. Results are reported whole brain family-wise error rate (FWE) corrected ($P <$ 0.001, peak level) for clusters of at least 25 voxels.

PPI. To assess task-dependent connectivity changes, we performed psychophysiological interaction (PPI) analyses. PPI investigate how the contribution of one brain region to another changes with experimental manipulation (Friston et al. 1997). Thus, they provide information on regions that change their activity depending on the interaction between a psychological (e.g., the task condition) and a physiological factor (e.g., the time course in a chosen seed region) (O'Reilly et al. 2012). PPI analysis is based on a general linear model (GLM) approach in which an interaction term is formed as the element-by-element product of the psychological and physiological variables. This interaction vector is

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

entered in a GLM along with the psychological and physiological variables as covariates of no interest to assess what the interaction can explain in addition to what is explained by the psychological and physiological variables alone. Thus, PPI analysis is a powerful tool to explore context-dependent functional connectivity without a priori defining possible models (O'Reilly et al. 2012). With the task and design used in the present study, PPI analyses are employed to reveal which regions show significant coactivations with the chosen seed regions during pursuit of a given frequency versus fixation and during higher- versus lower-frequency pursuit.

We used the generalized form of PPI (gPPI) with the help of the automated gPPI SPM toolbox (McLaren et al. 2012) running in SPM8. The gPPI approach offers more flexibility and better model fit than the standard PPI approach implemented in SPM, especially for tasks with multiple conditions (McLaren et al. 2012). It also proved to be a particularly powerful tool for analyzing fMRI data in block designs (Cisler et al. 2014).

Seed regions were selected based on previous literature describing the SPEM network (e.g., Berman et al. 1999; Tanabe et al. 2002). In total, 30 gPPI analyses were carried out for the following regions: LGN, V1, V5, PPC, and FEF, for each region separately for left and right hemisphere and the low frequency versus fixation, high frequency versus fixation, and high versus low frequency contrasts.

Coordinates of regions of interest (ROIs) were selected based on previous literature if available and, if necessary, converted to MNI space. LGN coordinates (−24, −26, −4; 22, −26, 0) were taken from an independent sample of healthy participants performing the same task in the same scanner (control group data from Faiola E, Urquijo MF, Bey K, Meyhöfer I, Steffens M, Kasparbauer AM, Ruef A, Högenauer H, Hurlemann R, Kambeitz J, Philipsen A, Wagner M, Koutsouleris N, Ettinger U, unpublished observations). V1 (−11, −80, −1; 20, −75, −3; Amunts et al. 2000) and V5 (−44, −76, 2; 43, −73, 5; Wilms et al. 2005) coordinates were selected from relevant publications. For FEF (−30, −6, 55; 30, −9, 50) and PPC (−25, −60, 56; 24, −56, 47), coordinates of all available papers presenting fMRI data of healthy participants performing a SPEM task were reviewed, coordinates were converted to MNI space (if necessary), and the weighted mean coordinates were calculated (see Supplemental Table S1; all Supplemental Material is available at https://osf.io/jc8su).

To account for interindividual anatomical variability, individual seed voxels were identified for each participant for the V1, V5, PPC, and FEF regions. Based on the coordinates described above, the nearest local maximum was selected in the omnibus F test first-level contrast image (uncorrected, thresholded at $P < 0.001$) for each of the regions in both hemispheres and contrasts. If the distance between the individual seed voxel and the anatomically expected voxel exceeded the mean plus two standard deviations, the participant was excluded from the analyses for this seed voxel because it could no longer be assumed that the individual seed voxel was within the targeted region. This exclusion criterion was determined after initial data inspection. For LGN, distances between the anatomically expected LGN coordinates and the nearest local maximum were generally large (mean = 9.55 mm, SD = 7.32 mm left hemisphere; mean = 9.91 mm, SD = 5.98 mm right hemisphere). Therefore, and as the LGN is a small structure (Andrews et al. 1997), we decided not to select individual coordinates as seed voxels but instead used identical coordinates for each participant.

A 4-mm sphere was drawn around the seed voxels for each participant, and the first eigenvariate of the time series from all voxels within the ROI was extracted. The PPI regressors were calculated as the interaction terms between the deconvolved physiological variable and task regressors. These interaction terms were then convolved with the HRF and entered into a generalized PPI (gPPI) first-level GLM along with the task vectors, the seed region time series, and motion regressors as covariates of no interest as well as a constant. Three contrasts (PPI low frequency versus fixation, PPI high frequency versus fixation, PPI high frequency versus PPI low frequency) on these models were then calculated and entered into random-effects one-sample t tests for second-level analyses for each of the regions and hemispheres. Results are reported whole brain FWE corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels.

Correlations. To identify correlations between BOLD response and behavioral outcomes, multiple-regression analyses were run in SPM12. The first-level task contrasts (low frequency versus fixation, high frequency versus fixation) were entered into separate random-effects multiple-regression models for second-level analysis along with the behavioral outcome variable (pursuit gain, RMSE, saccade rate) of the corresponding task condition (low or high frequency), resulting in a total of six regression models. Additionally, multiple-regression models were run for the 10 PPI maps and the behavioral outcome variables to identify correlations between functional connectivity and performance, resulting in a total of 60 regression models. To this end, the first-level PPI contrasts were entered into separate random-effects multiple-regression models for second-level analysis along with the behavioral outcome variable (pursuit gain, RMSE, saccade rate) of the corresponding task condition (low or high frequency).

To more specifically explore the relationships between ROIs and behavioral outcomes, Pearson correlations between behavioral outcomes and mean extracted beta values in the corresponding seed voxel spheres were run in R with the Hmisc (v4.4-0) package (Harrell 2020). Mean activity was extracted with the help of the MarsBar MATLAB toolbox (Brett et al. 2002).

RESULTS

Participants

The sample consisted of 57 participants (49 men, 8 women) aged 19–34 yr (mean = 24.70, SD = 3.77). Because of poor eye tracking data quality, pursuit gain, RMSE, and saccade rate could not be calculated for 13 participants (11 men, 2 women). fMRI analyses are based on a sample of 54 participants, as 3 participants (all male) had to be excluded because of failed preprocessing. Additionally, for the PPI analyses the following number of participants had to be excluded because the distance between their individual seed voxel and the anatomically expected voxel exceeded the mean plus two standard deviations: V1 left: 1 (female); V1 right: none; V5 left: 1 (female); V5 right: 2 (both male); PPC left: 2 (1 male, 1 female); PPC right: 2 (both male); FEF left: 3 (2 male, 1 female); FEF right: 2 (both male). Behavioral data and the corresponding analysis code can be found online (https://osf.io/jc8su). The conditions of our ethics approval do not permit public archiving of anonymized fMRI data. Readers seeking access to the data should contact the corresponding author (U. Ettinger) at the Department of Psychology, University of Bonn. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement to obtain the data.

Behavioral Results

There were significant effects of target frequency on pursuit gain [$t(43) = 8.09$, $P < 0.001$, $d = 0.82$], RMSE [$t(43) = -12.51$, $P < 0.001$, $d = -1.19$], and saccade rate [$t(43) = -12.26$, $P < 0.001$, $d = -1.54$], with lower gain, higher RMSE, and higher saccade rate for higher target frequency. Descriptive results are summarized in Table 1.

Task and Frequency Effects

Table 2 and Fig. 1 display areas with significant BOLD response during low-frequency pursuit, high-frequency pursuit, and high- versus low-frequency pursuit.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

Table 1. *Descriptive statistics of SPEM variables*

	Pursuit Gain	Saccade Rate, N/s	RMSE
Low frequency	0.93 (0.07)	0.51 (0.37)	48.91 (21.15)
High frequency	0.86 (0.11)	1.29 (0.64)	75.89 (24.35)

Values are means (standard deviation). RMSE, root mean square error; SPEM, smooth pursuit eye movements.

At both frequencies, SPEM elicited higher BOLD activation than fixation in large occipito-temporal clusters (including calcarine gyrus, lingual gyrus, inferior, middle, and superior occipital gyrus, cuneus, middle temporal gyrus, fusiform gyrus, extending into cerebellum), precentral and superior frontal gyrus including FEF, posterior-medial frontal cortex including SEF, middle cingulate cortex, inferior and superior parietal lobule, and thalamus including LGN. There were no significant clusters showing higher activation in the fixation > SPEM contrasts.

For the frequency contrast (high > low frequency), a significant cluster in visual cortex (including lingual gyrus, calcarine gyrus, cuneus, and superior occipital gyrus) was found. No significant clusters were found for the opposite contrast.

PPI Results

The 10 seed regions (right and left LGN, V1, V5, PPC, and FEF) showed significant increases in coupling to widespread, partially overlapping regions during SPEM at both target frequencies compared with fixation (see Figs. 2, 3, 4, and 5 and Supplemental Tables S3–S22).

All four LGN contrasts showed significant task-dependent connectivity to occipital cortex (lingual gyrus, calcarine gyrus), cingulate gyrus, thalamus, caudate, putamen, and inferior frontal gyrus. All except for the right high frequency versus fixation contrast also included fusiform gyrus. The two low frequency versus fixation contrasts also showed connectivity to precentral gyrus and cerebellum, whereas clusters from both high frequency contrasts also included insula lobe and superior temporal gyrus. In both right contrasts, additional connectivity to cuneus and middle temporal gyrus was found. In both left contrasts, connectivity also extended into precuneus. Descriptively, the left contrasts showed more and larger connectivity clusters than the right contrasts.

All four V1 contrasts showed significant task-dependent connectivity to large occipital clusters (lingual gyrus, calcarine gyrus, inferior occipital gyrus, cuneus), cerebellum, and striatum (all of which included caudate; all except for the right high frequency versus fixation contrast included putamen). All except for the left low frequency versus fixation contrast also included superior occipital gyrus and precuneus. All except for the left high frequency versus fixation contrast also included fusiform gyrus. In both right contrasts, additional thalamic connectivity could be observed.

All four V5 contrasts showed significant task-dependent connectivity to two large occipital-temporal clusters encompassing lingual gyrus, inferior, middle, and superior occipital gyrus, calcarine gyrus, fusiform gyrus, as well as middle and inferior temporal gyrus. Moreover, there was connectivity to thalamus, superior parietal lobule, and cerebellum. All contrasts except for the right high frequency versus fixation contrast also showed connectivity to precentral and/or middle frontal gyrus (FEF) and caudate and/or putamen. All except for the right low frequency versus fixation contrast also showed connectivity to precuneus. In both low frequency contrasts connectivity to inferior frontal gyrus was observed. Both high frequency contrasts also showed connectivity to supramarginal gyrus.

All four PPC contrasts showed significant task-dependent connectivity to superior and inferior parietal lobule, precuneus, inferior and middle temporal gyrus, middle and superior occipital gyrus, calcarine, fusiform and supramarginal gyrus, postcentral gyrus, middle and inferior frontal gyrus, precentral gyrus (FEF), and cerebellum. All contrasts except for the right low frequency versus fixation contrast also showed connectivity to thalamus and lingual gyrus. In all contrasts except for the right high frequency versus fixation contrast, additional connectivity to paracentral lobule and putamen and/or caudate could be detected. All but the left high frequency versus fixation contrast showed connectivity to angular gyrus. In all contrasts except for the right low frequency versus fixation contrast connectivity also extended into Rolandic operculum and inferior occipital gyrus. In both low frequency versus fixation contrasts, the significant clusters also encompassed posterior-medial frontal cortex (SEF). Only for the left hemispheric seeds was connectivity to cuneus and superior-medial gyrus observed.

All four FEF contrasts showed large-spread connectivity with regions including frontal [precentral gyrus, inferior, middle and superior frontal gyrus, posterior-medial frontal (SEF)], parietal (postcentral gyrus, inferior and superior parietal lobule, precuneus, supramarginal gyrus), occipital (inferior, middle and superior occipital, lingual gyrus), temporal (inferior and middle temporal, fusiform gyrus), insular and cingulate areas, Rolandic operculum, and subcortical structures (putamen and thalamus). In all contrasts except for the right low frequency versus fixation contrast, connectivity also extended into superior-medial gyrus, superior temporal gyrus, and temporal pole. All contrasts but the left high frequency versus fixation contrast showed connectivity to cerebellum. The two right contrasts and the left high frequency versus fixation contrast showed additional connectivity to paracentral lobule. Both low frequency contrasts shared connectivity to the calcarine gyrus. Only for the two high frequency versus fixation contrasts did significant clusters also encompass Heschl's gyrus.

There were no significant connectivity results for the comparisons between the two frequencies or for any of the fixation versus pursuit contrasts (all $P > 0.001$, FWE corrected). These results did not change with a less conservative correction threshold (all $P > 0.05$, FWE corrected).

A synthesis of the connections of the five seed regions to each other can be found in Supplemental Fig. S1.

Brain-Behavior Relationships: Individual Differences

None of the six behavioral regressors showed any significant correlations with task-related BOLD response or PPI maps (all $P > 0.001$, FWE corrected). The same nonsignificant results were obtained at a more liberal correction threshold (all $P > 0.05$, FWE corrected). There were also no significant correlations between activity in the ROIs and the behavioral outcome variables (all $P > 0.05$; see Supplemental Table S2).

DISCUSSION

This study provides a comprehensive investigation of functional connectivity during smooth pursuit eye movements.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

Table 2. *BOLD response during low-frequency pursuit vs. fixation, high-frequency pursuit vs. fixation, and high-frequency pursuit vs. low-frequency pursuit*

Anatomical Label [functional label]	Cluster Size	*t* Value	MNI Coordinates *x*	*y*	*z*
Low frequency vs. fixation					
R calcarine gyrus [including V1]	12,893	18.41	10	−80	6
L calcarine gyrus [including V1]		18.11	−8	−86	0
L lingual gyrus		17.32	−10	−84	−6
L superior occipital gyrus		15.00	−14	−90	12
L cuneus		14.40	0	−84	16
R superior occipital gyrus		11.80	24	−80	30
R lingual gyrus		11.78	12	−68	−6
L middle occipital gyrus		11.20	−40	−80	2
R middle temporal gyrus [including V5]		9.36	44	−66	4
Cerebellar vermis (7)		8.94	−2	−72	−26
R precuneus		8.04	6	−80	46
L inferior occipital gyrus [including V5]		7.58	−40	−74	−12
L fusiform gyrus		7.23	−36	−80	−16
L thalamus [including LGN]	161	11.28	−20	−28	−2
R thalamus [including LGN]	111	11.25	22	−26	−2
L MCC	87	11.19	−14	−22	44
R superior frontal gyrus [including FEF]	603	10.47	26	−8	52
R precentral gyrus		9.97	42	−6	50
L precentral gyrus [including FEF]	611	10.16	−34	−8	50
L superior parietal lobule	442	9.52	−26	−54	56
L inferior parietal lobule		9.26	−30	−48	58
R superior parietal lobule	306	9.48	24	−56	52
L posterior-medial frontal cortex [including SEF]	179	8.56	−6	−6	62
R posterior-medial frontal cortex [including SEF]		7.58	6	−4	66
High frequency vs. fixation					
R calcarine gyrus [including V1]	17,893	22.43	10	−78	6
L lingual gyrus [including V1]		20.26	−10	−82	−4
L calcarine gyrus		19.63	−6	−84	6
L cuneus		19.27	0	−84	18
R cuneus		14.70	14	−72	22
L middle occipital gyrus [including V5]		13.06	−40	−80	4
Cerebellar vermis (7)		12.79	−2	−72	−26
R superior occipital gyrus		12.59	18	−78	28
R middle temporal gyrus [including V5]		12.27	44	−64	8
L inferior occipital gyrus		10.03	−36	−80	−10
L fusiform gyrus		9.44	−36	−62	−18
R middle occipital gyrus		8.55	38	−80	4
R cerebellum (VI)		7.27	38	−62	−22
L MCC	125	13.10	−12	−22	44
L precentral gyrus [including FEF]	2,070	13.06	−48	−6	46
L posterior-medial frontal cortex [including SEF]		10.66	−2	−6	62
R posterior-medial frontal cortex [including SEF]		10.60	2	−4	64
L superior frontal gyrus		6.98	−12	−2	72
R thalamus [including LGN]	160	11.69	24	−26	−4
L thalamus [including LGN]	211	11.63	−22	−28	−4
R precentral gyrus [including FEF]	1,291	11.51	42	−6	50
R superior frontal gyrus		10.03	26	−8	52
L inferior parietal lobule	763	10.25	−24	−54	54
L superior parietal lobule		10.24	−24	−60	64
L postcentral gyrus		7.63	−26	−38	54
Location not in atlas*	409	9.32	22	−56	52
R superior parietal lobule		8.95	18	−64	58
R MCC	93	8.70	14	−22	44
R superior frontal gyrus	28	7.33	20	−4	72
High frequency vs. low frequency					
L cuneus	4,344	11.93	−2	−78	20
R cuneus		10.64	6	−88	16
R calcarine gyrus		10.27	8	−82	10
R lingual gyrus [including V1]		9.99	8	−72	−2
L calcarine gyrus		8.81	−14	−64	6
L lingual gyrus [including V1]		8.52	−10	−80	0

BOLD, blood oxygen level dependent; FEF, frontal eye fields; L, left; LGN, lateral geniculate nucleus; MCC, middle cingulate cortex; MNI, Montreal Neurological Institute; R, right; SEF, supplementary eye fields; V1, primary visual cortex. *Extending into R superior parietal lobule.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

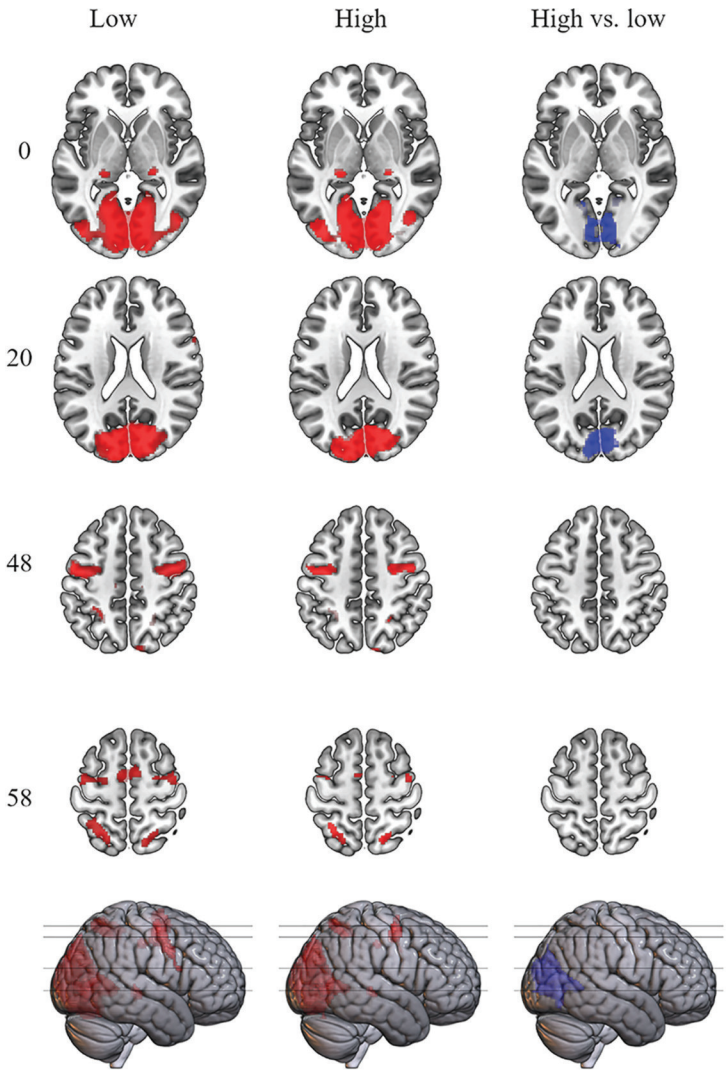

Fig. 1. Blood oxygen level-dependent (BOLD) response during smooth pursuit. Results of 1-sample *t* tests (random effects) of the low frequency vs. fixation, high frequency vs. fixation, and high vs. low frequency contrasts, respectively ($n = 54$; 46 male, 8 female). Results are reported whole-brain family-wise error rate (few) corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels. Labels on *left* refer to the *z* coordinate [Montreal Neurological Institute (MNI) space].

We first replicated findings concerning the neural systems underlying smooth pursuit in a large sample of healthy participants. At both target frequencies we observed significant activations in occipito-temporal areas, FEF, and SEF as well as middle cingulate gyrus, parietal cortex, and LGN.

We further observed that increasing target frequency led to behavioral performance decreases in all behavioral outcome variables (pursuit gain, saccade rate, and RMSE). At the neural level, higher compared with lower target frequency showed significantly stronger activations in occipital cortex but not in higher cortical areas.

Regarding connectivity, significant task-dependent changes in functional coupling were found for all 10 seed regions. Maps for right and left seed regions and for the low frequency versus fixation and high frequency versus fixation contrasts of the same seed region showed substantial overlap. All seed regions demonstrated significant self-connectivity as well as coupling to close and distant regions. LGN coupling encompassed mainly occipital, cingulate, and subcortical regions but also prefrontal cortex. V1 connectivity showed a strong regional focus in occipital cortex, which was also present in V5 connectivity maps. However, V5 maps incorporated additional clusters in frontal and parietal regions. Analyses starting in PPC and FEF showed widely distributed networks across the entire cortex.

Finally, concerning the question of brain-behavior relationships at the level of individual differences, surprisingly we could not delineate any significant correlations between behavioral outcome variables and task-related BOLD activity or functional connectivity.

Pursuit Network

In line with our hypothesis, both task effects (low frequency versus fixation and high frequency versus fixation) elicited BOLD activity in the known smooth pursuit network including

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

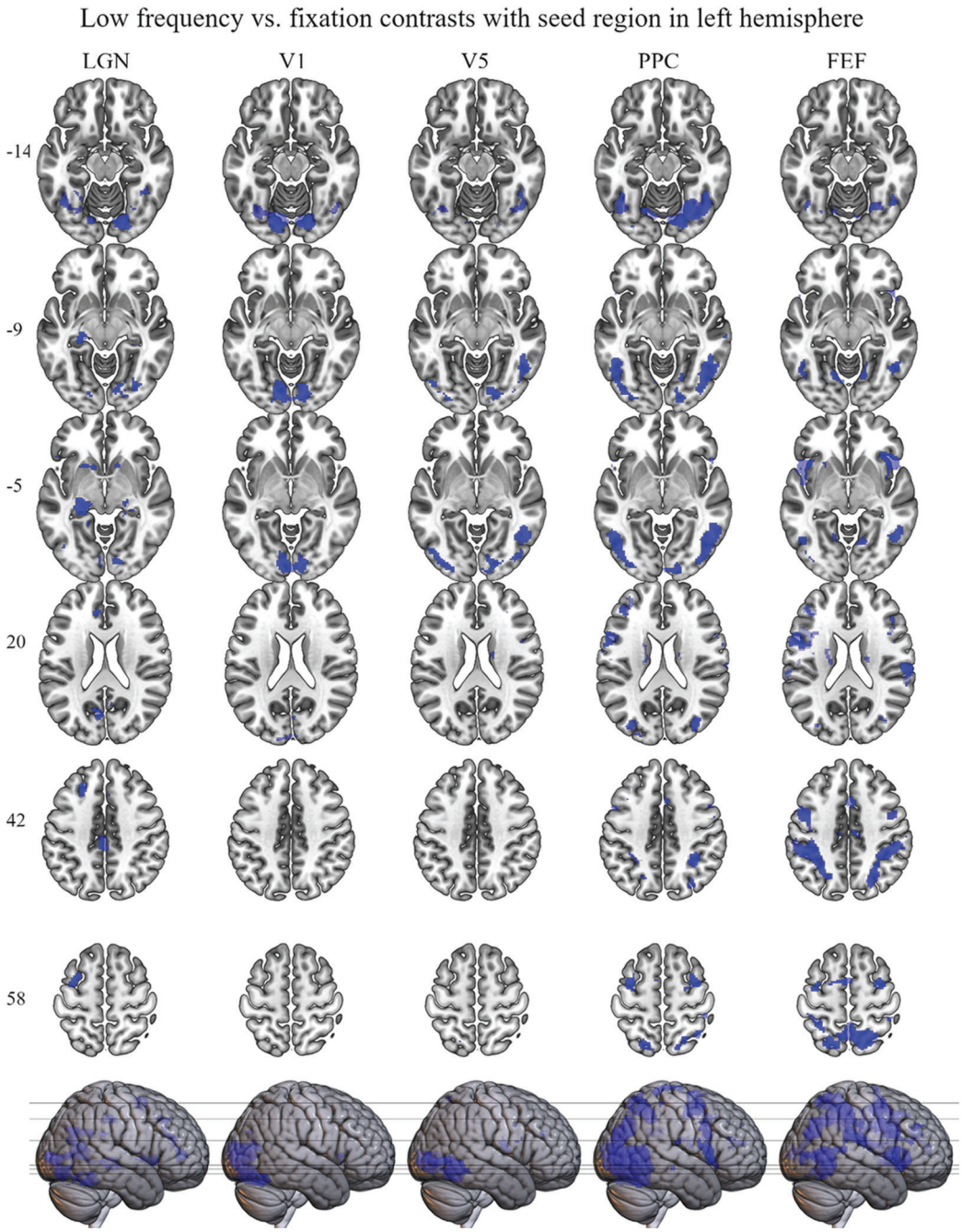

Fig. 2. Results of the 1-sample *t* tests (random effects) of the psychophysiological interaction (PPI) low frequency vs. fixation contrasts with seed region in left hemisphere. Each column represents 1 seed region: lateral geniculate nucleus (LGN): $n = 54$ (46 male, 8 female), V1: $n = 53$ (46 male, 7 female), V5: $n = 53$ (46 male, 7 female), posterior parietal cortex (PPC): $n = 52$ (45 male, 7 female), frontal eye fields (FEF): $n = 51$ (44 male, 7 female). Results are reported whole brain family-wise error rate (FWE) corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels. Labels on *left* refer to the *z* coordinate [Montreal Neurological Institute (MNI) space].

occipito-temporal cortex, bilateral LGN, FEF, SEF, and parietal cortex as well as left midcingulate cortex. Our results thus closely replicate earlier findings on smooth pursuit-related BOLD activity (Berman et al. 1999; Dieterich et al. 2009; Lencer et al. 2004; Nagel et al. 2008; Petit and Haxby 1999; Tanabe et al. 2002), highlighting the validity of our experimental paradigm and data analytic approach. Interestingly, despite the well-powered design, we could not find task-related activity

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

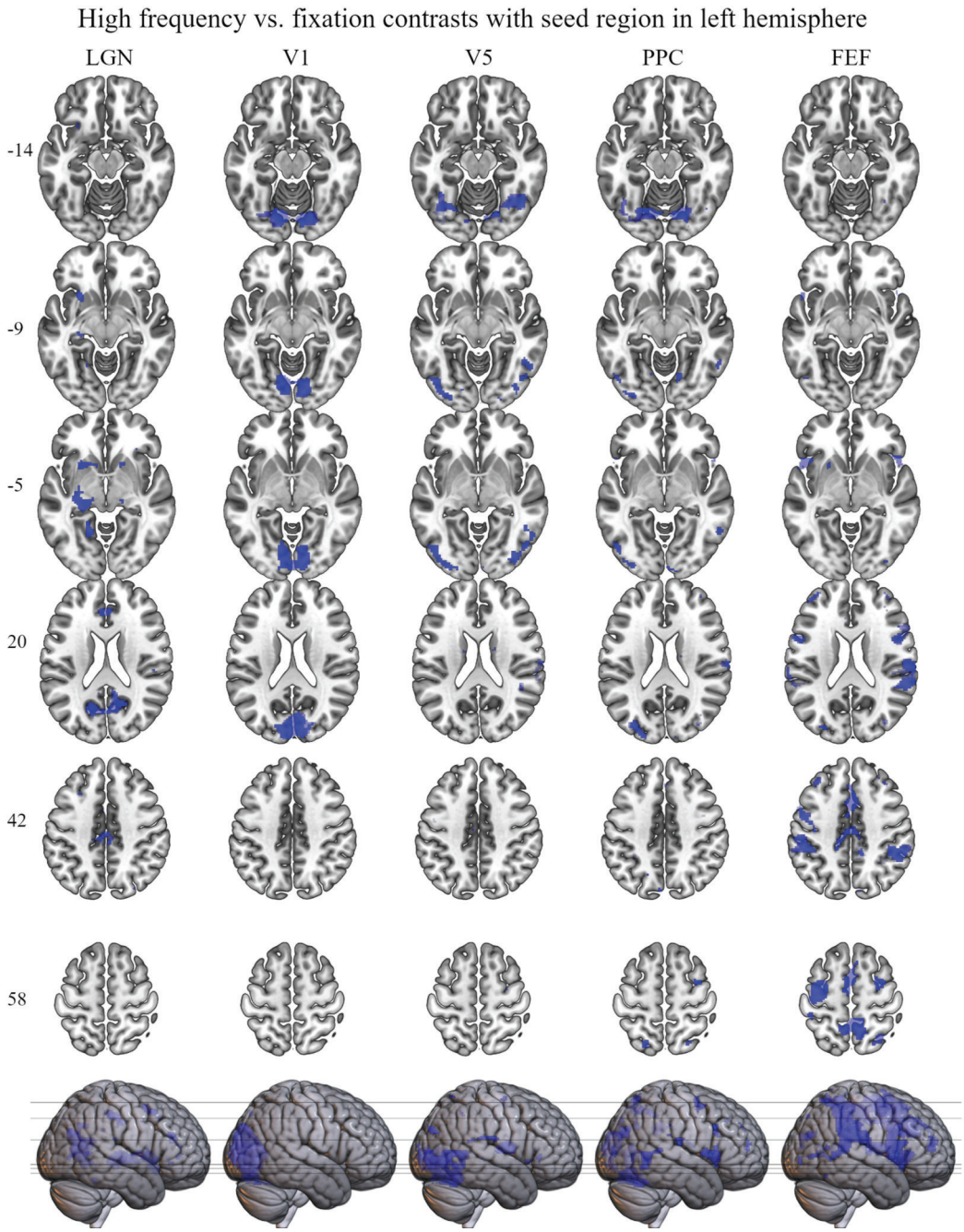

Fig. 3. Results of the 1-sample *t* tests (random effects) of the psychophysiological interaction (PPI) high frequency vs. fixation contrasts with seed region in left hemisphere. Each column represents 1 seed region: lateral geniculate nucleus (LGN): $n = 54$ (46 male, 8 female), V1: $n = 53$ (46 male, 7 female), V5: $n = 53$ (46 male, 7 female), posterior parietal cortex (PPC): $n = 52$ (45 male, 7 female), frontal eye fields (FEF): $n = 51$ (44 male, 7 female). Results are reported whole brain family-wise error rate (FWE) corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels. Labels on *left* refer to the *z* coordinate [Montreal Neurological Institute (MNI) space].

in higher cortical areas such as prefrontal cortex. Those areas have, however, been shown to be involved in more demanding smooth pursuit tasks, for example, when the target is briefly blanked and pursuit has to be generated on the basis of predictive processes (Lencer et al. 2004; Nagel et al. 2006).

Target Frequency Effects on Behavior and BOLD

As hypothesized, smooth pursuit performance decreased with higher target frequency (Collewijn and Tamminga 1984; Lisberger et al. 1981; Meyhöfer et al. 2019). This effect was

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

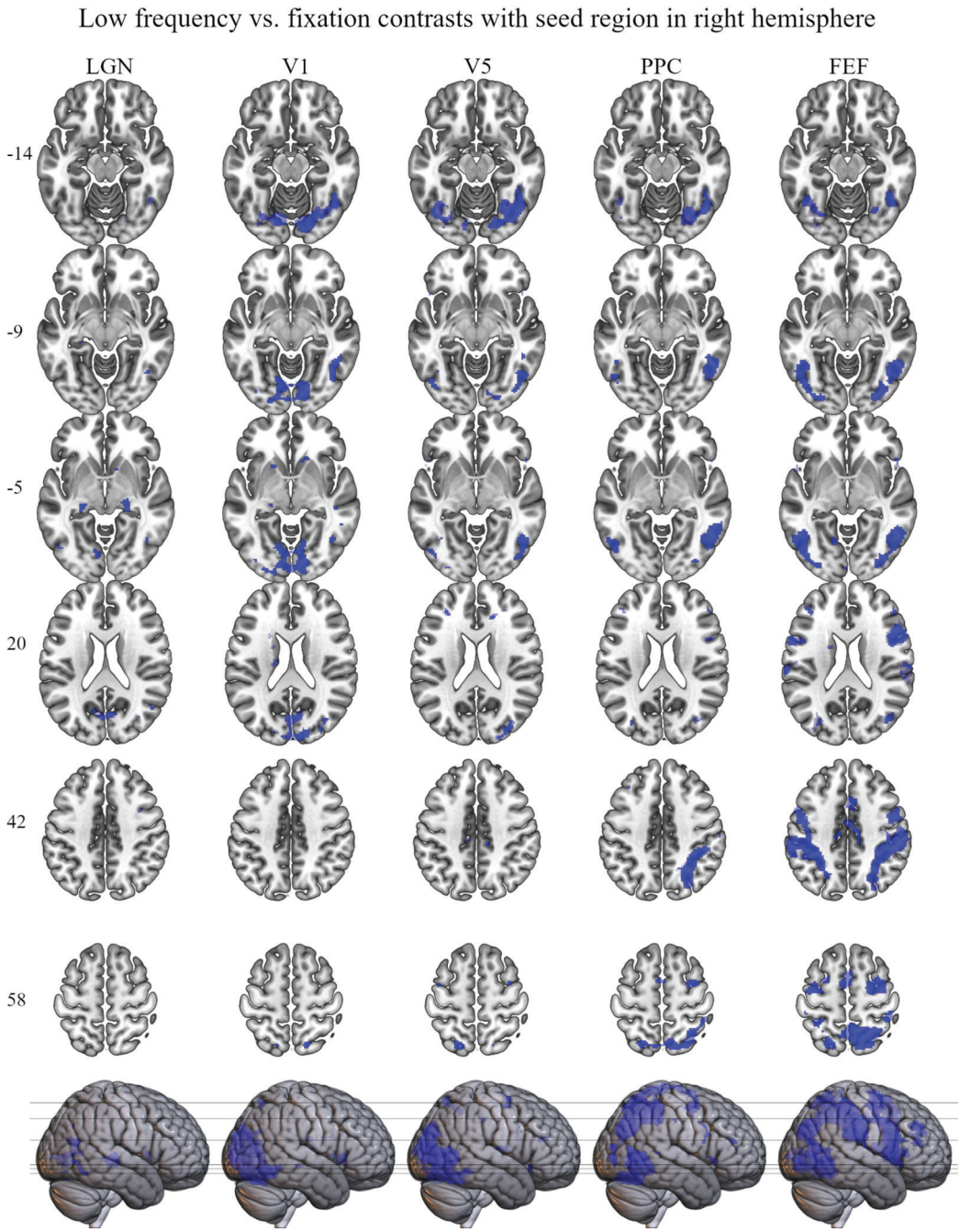

Fig. 4. Results of the 1-sample *t* tests (random effects) of the psychophysiological interaction (PPI) low frequency vs. fixation contrasts with seed region in right hemisphere. Each column represents 1 seed region: lateral geniculate nucleus (LGN): $n = 54$ (46 male, 8 female), V1: $n = 54$ (46 male, 8 female), V5: $n = 52$ (44 male, 8 female), posterior parietal cortex (PPC): $n = 52$ (44 male, 8 female), frontal eye fields (FEF): $n = 52$ (44 male, 8 female). Results are reported whole brain family-wise error rate (FWE) corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels. Labels on *left* refer to the *z* coordinate [Montreal Neurological Institute (MNI) space].

observed across all performance measures studied here, suggesting that the increase in (mostly compensatory) saccades was not sufficient to prevent the reduction in gain with increasing target frequency.

The behavioral data thus unambiguously demonstrate that the manipulation of target frequency increased the demands on the smooth pursuit system and that these demands were not fully met in terms of the desired motor response. Interestingly,

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

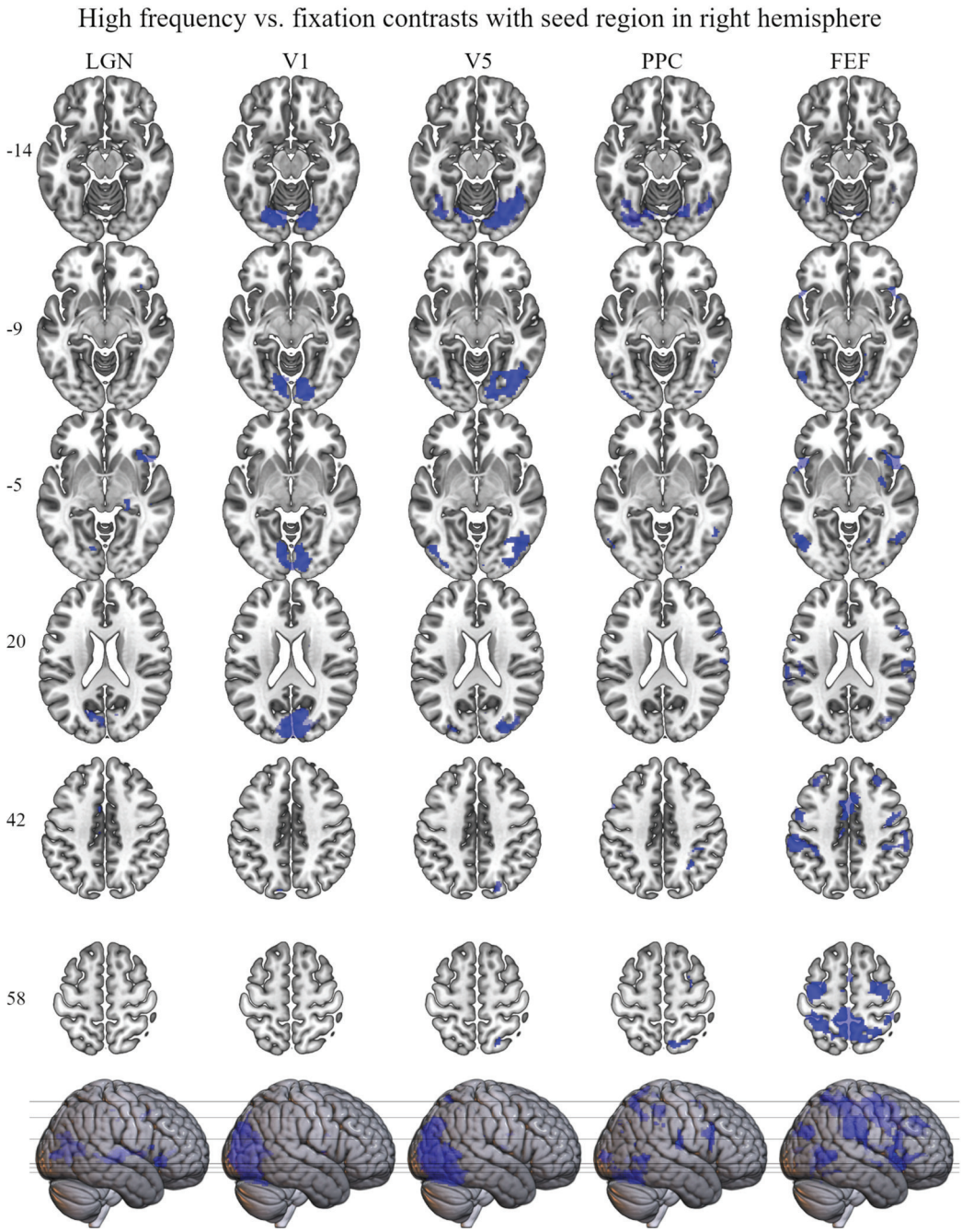

Fig. 5. Results of the 1-sample *t* tests (random effects) of the psychophysiological interaction (PPI) high frequency vs. fixation contrasts with seed region in right hemisphere. Each column represents 1 seed region: lateral geniculate nucleus (LGN): $n = 54$ (46 male, 8 female), V1: $n = 54$ (46 male, 8 female), V5: $n = 52$ (44 male, 8 female), posterior parietal cortex (PPC): $n = 52$ (44 male, 8 female), frontal eye fields (FEF): $n = 52$ (44 male, 8 female). Results are reported whole brain family-wise error rate (FWE) corrected ($P < 0.001$, peak level) for clusters of at least 25 voxels. Labels on *left* refer to the *z* coordinate [Montreal Neurological Institute (MNI) space].

however, this increased demand did not lead to a general increase in activity in the neural network underlying smooth pursuit. Instead, target frequency-induced changes in BOLD were relatively subtle and highly specific to occipital cortex including area V1 and surrounding visual areas. Most notably, there were no significant differences in V5, FEF, or SEF at the chosen level of statistical correction. Although these areas are clearly involved in the generation and maintenance of the

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

pursuit response, neither the overall velocity of pursuit nor its quality at a given target frequency appears to correlate with the overall BOLD signal in a block.

The lack of effects in V5 may be due to the fact that motion information in V5 is coded in terms of a place code, implying that different neurons are most sensitive to different target speeds (Lisberger 2010). Consequently, an increase in target frequency does not lead to an overall increase in firing rates but to activation of different groups of neurons, which cannot be dissociated in the BOLD response.

Unlike us, Nagel et al. (2008) detected additional velocity-dependent activations not only in visual cortex but also in subcortical and higher cortical areas. However, their results were obtained with a different experimental design, namely, with short target ramps as opposed to continuous target presentation and with a more liberal analysis approach. Thus, the contrasting results of Nagel et al. (2008) might be attributed to particularities of their study design in line with findings of varying smooth pursuit performance with different target motion patterns (Buizza and Schmid 1986). The presentation of ramp stimuli challenges the initiation of pursuit, whereas continuous target presentation is best used to study pursuit maintenance (Lencer and Trillenberg 2008). Gottlieb et al. (1994) showed that FEF neurons increase firing rates when target velocity is increased. However, like Nagel et al. (2008) they employed short target ramps (up to 2 s) so that it cannot be determined whether these effects would have remained stable with longer target presentation. Moreover, FEF neurons show robust sensitivity to eye acceleration (Mustari et al. 2009; Ono and Mustari 2009), corroborating their vital role in pursuit initiation (Drew and van Donkelaar 2007a).

In a motion tracking task, activation of FEF was independent of parametric attentional load manipulation similar to the results in our study (Culham et al. 2001). Although task demands were manipulated differently, the concordant results speak for the fundamental role of FEF in attentional motion tracking independent of task difficulty.

Summing up, these results suggest that frequency-related activity increases in higher cortical areas cannot be observed with highly predictable sinusoidal stimuli as used in this study. Scaling the pursuit response to target frequency might depend on adjusted levels of FEF activity during the early phases of pursuit (Drew and van Donkelaar 2007a), but no such relationship appears to occur during sustained pursuit maintenance.

Connectivity Results

LGN. Connectivity of LGN occurred mainly with occipital cortex as well as cingulate gyrus, striatum, and inferior frontal gyrus. Our finding of strong connections between LGN and visual cortex is consistent with evidence from resting-state and structural connectivity analyses (Genç et al. 2016; Nassi and Callaway 2009). Specifically, for some of the contrasts significant couplings to V5 were found, which is in line with previous literature (Gaglianese et al. 2015; Schmid et al. 2010; Sincich et al. 2004).

Connections between LGN and cingulate gyrus represent an interesting novel finding but should be interpreted with caution. Although the existence of a cingulate eye field has been proposed before (Amiez and Petrides 2009; Gaymard et al. 1998), findings in this field are heterogeneous and there are still many open questions (Coiner et al. 2019). Specifically, the possibly different location and function of the cingulate eye fields in human and nonhuman primates is an ongoing debate (Amiez and Petrides 2009; Gaymard et al. 1998; Paus et al. 1993; Schall and Boucher 2007; Wang et al. 2004). For example, in humans, posterior cingulate activity has been linked to attentional modulation during motion processing (Antal et al. 2008), whereas anterior cingulate activity occurs in tasks requiring inhibition (Jamadar et al. 2013). Proposed functions of cingulate oculomotor involvement lie in motor planning and monitoring (Berman et al. 1999). How this relates to LGN activity remains to be clarified.

Functional connectivity from LGN to inferior frontal gyrus might reflect orientation to salient stimulus features (Hampshire et al. 2010). Task-dependent connectivity changes in middle and superior frontal gyrus extending into FEF found in some of the contrasts underline the special importance of these regions in oculomotor function (Brandt et al. 2001). The fact that we found coupling between LGN with its assumed early role in perception and higher cortical areas like the FEF speaks for a strong interplay between perception and ocular motion during SPEM.

Additionally, we observed significant task-dependent connections from LGN to putamen and caudate. Because of the relatively low spatial resolution of fMRI data, these might not reflect specific LGN connectivity but general thalamo-striatal connections known to subserve oculomotor planning (Herrero et al. 2002; Leigh and Zee 2015).

In general, the functional LGN connections revealed in this study suggest that LGN may not only act as a simple relay between retina and primary visual cortex but may also be involved in more distributed processes such as dynamic signal integration and gain control (Ghodrati et al. 2017; Weyand 2016).

V1. The significant connectivity clusters from V1 seed regions entailed large parts of occipital cortex and striatum. V1 connectivity to other visual areas has previously been reported in resting state and structural connectivity analyses, corroborating our findings (Genç et al. 2016; Griffis et al. 2015, 2017; Nassi and Callaway 2009; Raemaekers et al. 2014; Rockland and Van Hoesen 1994). However, unlike Griffis et al. (2015), we could not find task-dependent coupling changes between V1 and higher cortical areas such as frontal lobe, perhaps because of higher attentional demands in the study by Griffis and colleagues.

Our results do not confirm findings of higher cortical task-dependent correlations with V1 (Griffis et al. 2015). Additionally, as PPI analyses are unable to provide information about the direction of effects (O'Reilly et al. 2012), it cannot be discerned whether the observed coupling changes in visual areas reflect nonretinal input to V1 (Muckli and Petro 2013) or signal propagation along the visual hierarchy.

Interestingly, we found functional connections between V1 and striatum, which to our knowledge have not previously been observed. Although an involvement of the basal ganglia in oculomotor control is well known (Jamadar et al. 2013; Neggers et al. 2012; O'Driscoll et al. 2000), previous literature has focused on fronto-striatal connections (Neggers et al. 2012). More specifically, a meta-analysis of functional connectivity between cortex and striatal nuclei could not identify any significant coactivations in primary visual cortex (Postuma and Dagher 2006). Thus, connectivity between primary visual cortex and striatum

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

is an intriguing new finding that is likely task dependent and needs further exploration.

All in all, our results of V1 connectivity substantiate the role of V1 during smooth pursuit as an area where retinal signals are recombined and sent to higher visual areas while incorporating complex feedback signals (Leigh and Zee 2015; Muckli and Petro 2013; Nassi and Callaway 2009).

V5. Clusters of significant connectivity with V5 seeds comprised visual areas in occipital and temporal lobe as well as superior parietal cortex, thalamus, cerebellum, and FEF.

In a motion-perception task by Taylor et al. (2018), V5 showed similar patterns of strong occipital connectivity maps extending into parietal and frontal lobe. In a very small sample, local connections from V5 to middle occipital gyrus during motion processing were found by Hampson et al. (2004), who also demonstrated more widespread connectivity from the same seed region in resting state. Moreover, our results are in line with structural investigations in nonhuman primates (Abe et al. 2018; Maunsell and van Essen 1983b) that provide evidence for reciprocal connections between V5 and visual areas V1 to V4 as well as to parietal and frontal cortex, striatum, and thalamus. A recent study suggests that V5 sends recurrent information back to V1 and provides evidence for driving inputs of parietal areas on V5 and other visual areas (Plomp et al. 2016), which was also reported elsewhere (Saalmann et al. 2007). However, parietal coordinates in that study were located more laterally than in our study (Plomp et al. 2016). As PPI cannot provide information about the directionality of effects, we cannot unequivocally conclude whether the observed correlations reflect backward or forward connections.

Clusters in precentral and middle frontal gyrus in this study were small and not significant in all contrasts but nevertheless support the hypothesis of coupling between V5 and FEF, in keeping with earlier findings (Leichnetz 1989; Ninomiya et al. 2012). V5 might provide the motion signal necessary for sensorimotor transformation in FEF.

Connectivity to thalamus might represent direct LGN inputs to V5 (Gaglianese et al. 2015), although the peak coordinates significant in the V5 PPIs models were more medial than LGN. However, involvement of thalamic nuclei in the processing of motion stimuli and the control of smooth pursuit has been proposed previously (Merabet et al. 1998; Tanaka 2005).

Our results offer compelling evidence in line with previous interpretation of V5 function as a key center of motion processing that is essential for successful smooth pursuit tracking (Leigh and Zee 2015; Zeki 2015). In contrast to V1, V5 showed connectivity to higher cortical areas such as FEF and parietal cortex, corroborating its major role in smooth pursuit eye movement control.

PPC. PPI analysis starting from PPC revealed significant clusters in large parts of parietal, occipital, temporal, and frontal cortex, including V5 and FEF, in line with the strong cortical interconnectivity of parietal lobe (Caspers and Zilles 2018). The connectivity maps obtained in this study showed remarkable similarities with an analysis of the same region at rest (Bueichekú et al. 2015). However, frontal connections were less strongly pronounced in our task-dependent data. This pattern of results corroborates earlier findings of similarities and dissimilarities between functional connectivity in resting state and during task performance (Rehme et al. 2013; Smith et al. 2009), suggesting that both approaches are valuable tools for different sets of research questions. Ramot et al. (2011) showed correlations between spontaneous eye movements and BOLD at rest, substantiating the neural significance of spontaneous BOLD activity in terms of coordinated motor programs. Similarities between task-dependent coupling changes and resting state data thus point to the validity of the observed connectivity patterns.

There are dense white matter connections between parietal and frontal cortex (Leichnetz 2001; Stanton et al. 2005; Thiebaut de Schotten et al. 2011a, 2011b), possibly mediating our result of functional connectivity between frontal and parietal pursuit areas. In fact, frontoparietal networks have been associated not only with oculomotor function but also with attention (Corbetta and Shulman 2002; Ohlendorf et al. 2007). Concerning the specific role of PPC in oculomotion and attention, Drew and van Donkelaar (2007b) suggested that it contributes to the attentional modulation of processes underlying smooth pursuit, whereas Raffi et al. (2007) proposed PPC involvement in spatial orientation.

In general, the observed connectivity patterns in this study are in agreement with the putative function of PPC as an interface between perceptive and motor systems (Grefkes and Fink 2005). PPC is involved in both pure visual and oculomotor signals, suggesting a role in sensorimotor transformation (Herweg et al. 2014; Kimmig et al. 2008), which is supported by our data showing connectivity to areas primarily involved in motion processing (V5) and motor transformation (FEF).

FEF. Of all seed regions investigated in this study, FEF showed the most widespread connectivity patterns based on the number of voxels in the PPI maps. Significant clusters entailed frontal, parietal, occipital, and temporal regions as well as subcortical structures.

There was substantial overlap between the connectivity maps of our study and the investigation of resting-state connectivity in human and nonhuman primates (Hutchison et al. 2012, 2013). Specifically, previous studies have provided evidence of resting-state FEF connectivity to superior and inferior parietal lobule, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and SEF (Hutchison et al. 2012, 2013). Compatible results were also obtained in diffusion-tensor imaging and tracing studies in humans and nonhuman primates, yielding evidence for strong structural connections between FEF and parietal cortex but also SEF, cingulate gyrus, and prefrontal and inferior frontal gyrus (Anderson et al. 2012; Schaeffer et al. 2018; Tomassini et al. 2007; Umarova et al. 2010). Whereas Anderson et al. (2012) found structural pathways to be more dominant in the right hemisphere, we could not observe strongly lateralized functional connectivity.

Interestingly, FEF also showed connectivity with regions that were not significant in the simple task versus fixation contrasts, such as DLPFC. According to O'Reilly et al. (2012) such a pattern can be attributed to unmodeled task-related variance. It is assumed that the PPI term models variance over and above what is explained by the blocked model of task-driven activity (O'Reilly et al. 2012). However, modeling task as a boxcar function is a simplification of the complex demands on the smooth pursuit system while tracking a constantly moving target (O'Reilly et al. 2012), as processes of pursuit initiation and maintenance as well as monitoring, anticipation, and prediction do not have exactly the same time course (Barnes 2008). Consequently, significant PPI results outside of the task effect masks might reflect task-related but unmodeled shared variance,

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

e.g., when seed region and the significant clusters are both involved in the same pursuit-related cognitive process.

One region showing task-dependent FEF coupling in the absence of a main task effect was DLPFC. Previously, DLPFC involvement in smooth pursuit has been linked to attentive monitoring and working memory-related processes as well as anticipation, especially during more challenging smooth pursuit tasks involving target blanking or unpredictable target motion (Lencer et al. 2004; Nagel et al. 2006; Pierrot-Deseilligny et al. 2003, 2005; Schmid et al. 2001). As we used predictable and continuously presented targets, we hypothesize that DLPFC involvement was not essential during the entire task block. Correlations with FEF, however, suggest that this region might have contributed to specific cognitive SPEM subprocesses with a more elaborate time course, in which both regions are engaged.

Similarly, there was functional connectivity between FEF and inferior frontal gyrus, although this region was not evident in the simple task versus fixation contrasts. Both regions have been associated with corrective saccades (Haller et al. 2008) as well as the inhibition of (oculo-)motor reactions (Chikazoe et al. 2007).

Similar to Neggers et al. (2012, 2015), we also found coupling between FEF and putamen, substantiating the role of fronto-striatal connections in cognition, motor, and eye movement control (Leigh and Zee 2015).

FEF was the only region investigated in this study consistently connected to SEF. Similar connections were found in resting-state and diffusion-tensor imaging data (Anderson et al. 2012; Hutchison et al. 2012), implying a strong interplay of these areas in the control of smooth pursuit (Drew and van Donkelaar 2007a; Gagnon et al. 2006) as well as other cognitive and oculomotor functions.

Although connectivity maps generally covered large parts of the cortex, functional connectivity to primary visual cortex was less pronounced than from the other seed regions, corroborating the role of FEF as an area of higher cortical processing not primarily involved in perception (Leigh and Zee 2015).

The extensive functional connectivity of FEF found in this study adds to the literature by substantiating the fundamental role of FEF in the control of smooth pursuit. FEF receive and send information to and from cortical and subcortical areas across almost the entire brain, confirming their involvement in pursuit initiation, maintenance, and prediction in terms of visuo-motor transformation (Leigh and Zee 2015; Lencer and Trillenberg 2008; Lisberger 2010).

Effects of target frequency on functional connectivity. The present study did not delineate any significant differences between the two frequency conditions concerning functional connectivity for any of the five seed regions. It is possible that in relation to the range of target frequencies to which humans can perform pursuit eye movements (>1 Hz; Barnes 2008), the difference between the two conditions examined here was relatively small, making it difficult to detect effects at the neural level. This may particularly apply to functional connectivity data, since PPI analyses are even more prone to power-related issues than standard GLM analyses (O'Reilly et al. 2012).

Brain-Behavior Relationships: Individual Differences

Unexpectedly, we did not find any significant correlations between the behavioral outcome variables we focused on in this study (pursuit gain, saccadic frequency, and RMSE) and BOLD activity at the level of individual differences. These findings contrast with previous results reported in the literature, in which individuals with poorer pursuit performance such as schizophrenia patients or schizotypal individuals showed reduced BOLD in task-related areas and negative correlations between BOLD in task-related areas and behavioral outcome variables (Lencer et al. 2005; Meyhöfer et al. 2015; Nagel et al. 2006). Given that those correlations have primarily, although not exclusively, been reported in groups with presumed impaired smooth pursuit performance (Lencer et al. 2005; Meyhöfer et al. 2015), it may be concluded that such associations only become apparent when the pursuit system does not work optimally. Instead, the sample in our study was relatively homogeneous, as participants were carefully screened and selected according to strict criteria, possibly making it more difficult to detect significant associations.

Another possibility for the failure to detect significant correlations could be that those may become apparent with other, more specific measures of pursuit performance or with pursuit tasks that tap specific underlying processes, such as extraretinal mechanisms in blanking tasks (Nagel et al. 2006).

Our study used a sample larger than all previous fMRI studies of smooth pursuit (see Supplemental Table S1). However, we did not achieve the minimum sample size recommended for individual difference research with fMRI data ($n > 100$; Dubois and Adolphs 2016). Thus, although the present study had sufficient power to detect task effects at the group level, more participants may have been needed to reveal correlations at the level of individual differences.

Moreover, it has been criticized that BOLD has relatively low within-subject reliability while producing robust effects at the group level (Plichta et al. 2012; Raemaekers et al. 2007). This factor may impede the discovery of significant correlations with individual differences measures (Hedge et al. 2018).

It has also been argued that between-subject variance might arise from different strategies employed to perform a certain task (Seghier and Price 2018). For example, participants might differ in how much they rely on retinal versus nonretinal information during pursuit and consequently show different activation patterns in the oculomotor network. Thus, no uniform change in network activations at higher performance levels could be observed across all subjects. It may therefore be of interest in future studies to identify subgroups with different strategies with complex classification approaches (Kherif et al. 2009).

Curiously, as described above, we found worse performance at higher target frequency, whereas accompanying BOLD changes occurred only in visual but not higher cortical regions and no differences in functional connectivity were observed. This raises the question of how these behavioral effects are generated at the neural level. It is possible that effects can only be revealed with more demanding tasks or with more elaborate study designs, for example, when behavioral outcome variables and BOLD are reported for single target ramps as different cognitive components become relevant at different time points. For example, it has been shown that FEF neurons control pursuit in different brief time epochs during the movement, suggesting that each neuron makes a unique contribution to smooth pursuit in a specific narrow time window (Lisberger 2010). Another explanation for the performance differences between the two frequency conditions without apparent BOLD correlates might be

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

that they originate from brain structures not easily accessible to fMRI, such as pontine nuclei and cerebellum (Beh et al. 2017; Mustari et al. 2009; Ono and Mustari 2007).

Limitations

A limitation of our study is that we employed only two target frequencies, with relatively low peak velocities (7.3°/s for 0.2 Hz and 14.8°/s for 0.4 Hz) compared with other studies (Lencer et al. 2008; Nagel et al. 2008). As humans are able to perform smooth pursuit to targets at velocities of up to 1 Hz (Barnes 2008), our study did not cover the full range of this oculomotor behavior. For future investigations of velocity effects on smooth pursuit performance and BOLD, a higher range of velocities would be desirable.

Another limitation concerns the identification of the individual seed regions. To do this, it might have been preferable to use a localizer task rather than extracting them from previous literature and the individual task contrasts.

A further limitation concerns the design of the task, in which fixation was used as a control condition for pursuit. Therefore, differences between these two conditions in BOLD are contaminated by retinal motion of the stimulus. As gain scores were generally high, the target stimulus on the retina was relatively stable. However, gain scores did not reach 1, suggesting that there was still some degree of retinal motion. Therefore, we cannot exclude that the differences revealed by contrasting the two frequencies might be a result of motion instead of pursuit. In future studies we recommend disentangling motion and pursuit by using more elegant designs (e.g., Kimmig et al. 2008).

A general limitation is that PPI analyses are restricted with regard to the research questions they can answer, as they can only determine task-dependent functional connectivity of a designated seed region with the rest of the brain. To better assess connectivity of the entire network, more advanced methods such as dynamic causal modeling approaches may be needed (Friston 2011). Still, PPI analysis is a valuable research tool for exploratory analysis of functional connectivity, which was the main objective of the present study.

Conclusions

Overall, our data provide evidence of a strongly interconnected network underlying the maintenance of smooth pursuit eye movements. PPI connectivity maps of different seed regions point to widespread, partially overlapping networks of different extent. Whereas FEF and PPC showed connectivity to large parts of the entire cortex, LGN, V1, and V5 had more regionally focused connections. Higher target frequency was associated with reduced performance and increased BOLD in occipital cortex but no change in functional connectivity. Interindividual associations between performance and BOLD could not be discerned. In summary, our study provides a comprehensive characterization of functional connectivity in SPEM and represents an important basis for further study of this fundamental sensorimotor system in healthy humans as well as patient populations known to have SPEM deficits.

ACKNOWLEDGMENTS

Present addresses A.-M. Kasparbauer, European Campus Rottal-Inn, Deggendorf Institute of Technology, Deggendorf, Germany; I. Meyhöfer, Dept. of Psychiatry and Psychotherapy, University of Muenster, Muenster, Germany, and Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Muenster, Muenster, Germany.

GRANTS

This work was supported in part by the Deutsche Forschungsgemeinschaft (Grant DFG Et 31/2-1).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.S., A.-M.K., I.M., M.S., P.T., and U.E. conceived and designed research; A.-M.K., I.M., and M.S. performed experiments; R.S. analyzed data; R.S., and U.E. interpreted results of experiments; R.S. prepared figures; R.S. drafted manuscript; R.S., A.-M.K., I.M., M.S., P.T., and U.E. edited and revised manuscript; R.S., A.-M.K., I.M., M.S., P.T., and U.E. approved final version of manuscript.

ENDNOTE

At the request of the author(s), readers are herein alerted to the fact that additional materials related to this manuscript may be found at https://osf.io/jc8su/. These materials are not a part of this manuscript and have not undergone peer review by the American Physiological Society (APS). APS and the journal editors take no responsibility for these materials, for the website address, or for any links to or from it.

REFERENCES

Abe H, **Tani T**, **Mashiko H**, **Kitamura N**, **Hayami T**, **Watanabe S**, **Sakai K**, **Suzuki W**, **Mizukami H**, **Watakabe A**, **Yamamori T**, **Ichinohe N.** Axonal projections from the middle temporal area in the common marmoset. *Front Neuroanat* 12: 89, 2018. doi:10.3389/fnana.2018.00089.

Ackenheil M, **Stotz-Ingenlath G**, **Dietz-Bauer R**, **Vossen A.** *MINI Mini International Neuropsychiatric Interview, German Version 5.0.0 DSM IV*. München, Germany: Psychiatrische Universitätsklinik München, 1999.

Acs F, **Greenlee MW.** Connectivity modulation of early visual processing areas during covert and overt tracking tasks. *Neuroimage* 41: 380–388, 2008. doi:10.1016/j.neuroimage.2008.02.007.

Adams RA, **Perrinet LU**, **Friston K.** Smooth pursuit and visual occlusion: active inference and oculomotor control in schizophrenia. *PLoS One* 7: e47502, 2012. doi:10.1371/journal.pone.0047502.

Amiez C, **Petrides M.** Anatomical organization of the eye fields in the human and non-human primate frontal cortex. *Prog Neurobiol* 89: 220–230, 2009. doi:10.1016/j.pneurobio.2009.07.010.

Amunts K, **Malikovic A**, **Mohlberg H**, **Schormann T**, **Zilles K.** Brodmann's areas 17 and 18 brought into stereotaxic space-where and how variable? *Neuroimage* 11: 66–84, 2000. doi:10.1006/nimg.1999.0516.

Anderson EJ, **Jones DK**, **O'Gorman RL**, **Leemans A**, **Catani M**, **Husain M.** Cortical network for gaze control in humans revealed using multimodal MRI. *Cereb Cortex* 22: 765–775, 2012. doi:10.1093/cercor/bhr110.

Andrews TJ, **Halpern SD**, **Purves D.** Correlated size variations in human visual cortex, lateral geniculate nucleus, and optic tract. *J Neurosci* 17: 2859–2868, 1997. doi:10.1523/JNEUROSCI.17-08-02859.1997.

Antal A, **Baudewig J**, **Paulus W**, **Dechent P.** The posterior cingulate cortex and planum temporale/parietal operculum are activated by coherent visual motion. *Vis Neurosci* 25: 17–26, 2008. doi:10.1017/S0952523808080024.

Barnes GR. Cognitive processes involved in smooth pursuit eye movements. *Brain Cogn* 68: 309–326, 2008. doi:10.1016/j.bandc.2008.08.020.

Beh SC, **Frohman TC**, **Frohman EM.** Cerebellar control of eye movements. *J Neuroophthalmol* 37: 87–98, 2017. doi:10.1097/WNO.0000000000000456.

Berman RA, **Colby CL**, **Genovese CR**, **Voyvodic JT**, **Luna B**, **Thulborn KR**, **Sweeney JA.** Cortical networks subserving pursuit and saccadic eye movements in humans: an FMRI study. *Hum Brain Mapp* 8: 209–225, 1999. doi:10.1002/(SICI)1097-0193(1999)8:4<209:AID-HBM5>3.0.CO;2-0.

Brandt SA, **Brocke J**, **Röricht S**, **Ploner CJ**, **Villringer A**, **Meyer BU.** In vivo assessment of human visual system connectivity with transcranial electrical stimulation during functional magnetic resonance imaging. *Neuroimage* 14: 366–375, 2001. doi:10.1006/nimg.2001.0847.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

Brett M, **Anton JL**, **Valabreque R**, **Poline JB.** Region of interest analysis using the MarsBar toolbox for SPM 99 (Abstract). *Neuroimage* 16: S497, 2002.

Bueichekú E, **Ventura-Campos N**, **Palomar-García MÁ**, **Miró-Padilla A**, **Parcet MA**, **Ávila C.** Functional connectivity between superior parietal lobule and primary visual cortex "at rest" predicts visual search efficiency. *Brain Connect* 5: 517–526, 2015. doi:10.1089/brain.2015.0352.

Buizza A, **Schmid R.** Velocity characteristics of smooth pursuit eye movements to different patterns of target motion. *Exp Brain Res* 63: 395–401, 1986. doi:10.1007/BF00236858.

Calkins ME, **Iacono WG**, **Ones DS.** Eye movement dysfunction in first-degree relatives of patients with schizophrenia: a meta-analytic evaluation of candidate endophenotypes. *Brain Cogn* 68: 436–461, 2008. doi:10.1016/j.bandc.2008.09.001.

Caspers S, **Zilles K.** Microarchitecture and connectivity of the parietal lobe. In: *Handbook of Clinical Neurology: The Parietal Lobe*, Vallar G, Coslett HB. Amsterdam: Elsevier, 2018, chapt 3, p. 53–72.

Chikazoe J, **Konishi S**, **Asari T**, **Jimura K**, **Miyashita Y.** Activation of right inferior frontal gyrus during response inhibition across response modalities. *J Cogn Neurosci* 19: 69–80, 2007. doi:10.1162/jocn.2007.19.1.69.

Cisler JM, **Bush K**, **Steele JS.** A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *Neuroimage* 84: 1042–1052, 2014. doi:10.1016/j.neuroimage.2013.09.018.

Coiner B, **Pan H**, **Bennett ML**, **Bodien YG**, **Iyer S**, **O'Neil-Pirozzi TM**, **Leung L**, **Giacino JT**, **Stern E.** Functional neuroanatomy of the human eye movement network: a review and atlas. *Brain Struct Funct* 224: 2603–2617, 2019. doi:10.1007/s00429-019-01932-7.

Collewijn H, **Tamminga EP.** Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *J Physiol* 351: 217–250, 1984. doi:10.1113/jphysiol.1984.sp015242.

Corbetta M, **Shulman GL.** Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3: 201–215, 2002. doi:10.1038/nrn755.

Culham JC, **Cavanagh P**, **Kanwisher NG.** Attention response functions: characterizing brain areas using fMRI activation during parametric variations of attentional load. *Neuron* 32: 737–745, 2001. doi:10.1016/S0896-6273(01)00499-8.

Dieterich M, **Müller-Schunk S**, **Stephan T**, **Bense S**, **Seelos K**, **Yousry TA.** Functional magnetic resonance imaging activations of cortical eye fields during saccades, smooth pursuit, and optokinetic nystagmus. *Ann NY Acad Sci* 1164: 282–292, 2009. doi:10.1111/j.1749-6632.2008.03718.x.

Drew AS, **van Donkelaar P.** The contribution of the human FEF and SEF to smooth pursuit initiation. *Cereb Cortex* 17: 2618–2624, 2007a. doi:10.1093/cercor/bhl169.

Drew AS, **van Donkelaar P.** The contribution of the human PPC to the orienting of visuospatial attention during smooth pursuit. *Exp Brain Res* 179: 65–73, 2007b. doi:10.1007/s00221-006-0769-z.

Dubois J, **Adolphs R.** Building a science of individual differences from fMRI. *Trends Cogn Sci* 20: 425–443, 2016. doi:10.1016/j.tics.2016.03.014.

Dukelow SP, **DeSouza JF**, **Culham JC**, **van den Berg AV**, **Menon RS**, **Vilis T.** Distinguishing subregions of the human MT+ complex using visual fields and pursuit eye movements. *J Neurophysiol* 86: 1991–2000, 2001. doi:10.1152/jn.2001.86.4.1991.

Eickhoff SB, **Stephan KE**, **Mohlberg H**, **Grefkes C**, **Fink GR**, **Amunts K**, **Zilles K.** A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 25: 1325–1335, 2005. doi:10.1016/j.neuroimage.2004.12.034.

Friston KJ. Functional and effective connectivity: a review. *Brain Connect* 1: 13–36, 2011. doi:10.1089/brain.2011.0008.

Friston KJ, **Buechel C**, **Fink GR**, **Morris J**, **Rolls E**, **Dolan RJ.** Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6: 218–229, 1997. doi:10.1006/nimg.1997.0291.

Gaglianese A, **Costagli M**, **Ueno K**, **Ricciardi E**, **Bernardi G**, **Pietrini P**, **Cheng K.** The direct, not V1-mediated, functional influence between the thalamus and middle temporal complex in the human brain is modulated by the speed of visual motion. *Neuroscience* 284: 833–844, 2015. doi:10.1016/j.neuroscience.2014.10.042.

Gagnon D, **Paus T**, **Grosbras M-H**, **Pike GB**, **O'Driscoll GA.** Transcranial magnetic stimulation of frontal oculomotor regions during smooth pursuit. *J Neurosci* 26: 458–466, 2006. doi:10.1523/JNEUROSCI.2789-05.2006.

Gaymard B, **Rivaud S**, **Cassarini JF**, **Dubard T**, **Rancurel G**, **Agid Y**, **Pierrot-Deseilligny C.** Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Exp Brain Res* 120: 173–183, 1998. doi:10.1007/s002210050391.

Genç E, **Schölvinck ML**, **Bergmann J**, **Singer W**, **Kohler A.** Functional connectivity patterns of visual cortex reflect its anatomical organization. *Cereb Cortex* 26: 3719–3731, 2016. doi:10.1093/cercor/bhv175.

Ghodrati M, **Khaligh-Razavi SM**, **Lehky SR.** Towards building a more complex view of the lateral geniculate nucleus: recent advances in understanding its role. *Prog Neurobiol* 156: 214–255, 2017. doi:10.1016/j.pneurobio.2017.06.002.

Gottlieb JP, **MacAvoy MG**, **Bruce CJ.** Neural responses related to smooth-pursuit eye movements and their correspondence with electrically elicited smooth eye movements in the primate frontal eye field. *J Neurophysiol* 72: 1634–1653, 1994. doi:10.1152/jn.1994.72.4.1634.

Grefkes C, **Fink GR.** The functional organization of the intraparietal sulcus in humans and monkeys. *J Anat* 207: 3–17, 2005. doi:10.1111/j.1469-7580.2005.00426.x.

Griffis JC, **Elkhetali AS**, **Burge WK**, **Chen RH**, **Bowman AD**, **Szaflarski JP**, **Visscher KM.** Retinotopic patterns of functional connectivity between V1 and large-scale brain networks during resting fixation. *Neuroimage* 146: 1071–1083, 2017. doi:10.1016/j.neuroimage.2016.08.035.

Griffis JC, **Elkhetali AS**, **Burge WK**, **Chen RH**, **Visscher KM.** Retinotopic patterns of background connectivity between V1 and fronto-parietal cortex are modulated by task demands. *Front Hum Neurosci* 9: 338, 2015. doi:10.3389/fnhum.2015.00338.

Haller S, **Fasler D**, **Ohlendorf S**, **Radue EW**, **Greenlee MW.** Neural activation associated with corrective saccades during tasks with fixation, pursuit and saccades. *Exp Brain Res* 184: 83–94, 2008. doi:10.1007/s00221-007-1077-y.

Hampshire A, **Chamberlain SR**, **Monti MM**, **Duncan J**, **Owen AM.** The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* 50: 1313–1319, 2010. doi:10.1016/j.neuroimage.2009.12.109.

Hampson M, **Olson IR**, **Leung HC**, **Skudlarski P**, **Gore JC.** Changes in functional connectivity of human MT/V5 with visual motion input. *Neuroreport* 15: 1315–1319, 2004. doi:https://cran.r-project.org/web/packages/Hmisc/index.html.

Harrell FE. *Hmisc: Harrell Miscellaneous*. 2020. https://CRAN.R-project.org/package=Hmisc.

Hedge C, **Powell G**, **Sumner P.** The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behav Res Methods* 50: 1166–1186, 2018. doi:10.3758/s13428-017-0935-1.

Heinzle J, **Kahnt T**, **Haynes JD.** Topographically specific functional connectivity between visual field maps in the human brain. *Neuroimage* 56: 1426–1436, 2011. doi:10.1016/j.neuroimage.2011.02.077.

Herrero MT, **Barcia C**, **Navarro JM.** Functional anatomy of thalamus and basal ganglia. *Childs Nerv Syst* 18: 386–404, 2002. doi:10.1007/s00381-002-0604-1.

Herweg NA, **Weber B**, **Kasparbauer A**, **Meyhöfer I**, **Steffens M**, **Smyrnis N**, **Ettinger U.** Functional magnetic resonance imaging of sensorimotor transformations in saccades and antisaccades. *Neuroimage* 102: 848–860, 2014. doi:10.1016/j.neuroimage.2014.08.033.

Hutchison RM, **Gallivan JP**, **Culham JC**, **Gati JS**, **Menon RS**, **Everling S.** Functional connectivity of the frontal eye fields in humans and macaque monkeys investigated with resting-state fMRI. *J Neurophysiol* 107: 2463–2474, 2012. doi:10.1152/jn.00891.2011.

Hutchison RM, **Womelsdorf T**, **Gati JS**, **Everling S**, **Menon RS.** Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. *Hum Brain Mapp* 34: 2154–2177, 2013. doi:10.1002/hbm.22058.

Ilg UJ, **Thier P.** The neural basis of smooth pursuit eye movements in the rhesus monkey brain. *Brain Cogn* 68: 229–240, 2008. doi:10.1016/j.bandc.2008.08.014.

Ivleva EI, **Moates AF**, **Hamm JP**, **Bernstein IH**, **O'Neill HB**, **Cole D**, **Clementz BA**, **Thaker GK**, **Tamminga CA.** Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. *Schizophr Bull* 40: 642–652, 2014. doi:10.1093/schbul/sbt047.

Jamadar SD, **Fielding J**, **Egan GF.** Quantitative meta-analysis of fMRI and PET studies reveals consistent activation in fronto-striatal-parietal regions and cerebellum during antisaccades and prosaccades. *Front Psychol* 4: 749, 2013. doi:10.3389/fpsyg.2013.00749.

Kasparbauer AM, **Meyhöfer I**, **Steffens M**, **Weber B**, **Aydin M**, **Kumari V**, **Hurlemann R**, **Ettinger U.** Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. *Neuroimage* 141: 52–59, 2016. doi:10.1016/j.neuroimage.2016.07.012.

Kherif F, **Josse G**, **Seghier ML**, **Price CJ.** The main sources of intersubject variability in neuronal activation for reading aloud. *J Cogn Neurosci* 21: 654–668, 2009. doi:10.1162/jocn.2009.21084.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

Kimmig H, Ohlendorf S, Speck O, Sprenger A, Rutschmann RM, Haller S, Greenlee MW. fMRI evidence for sensorimotor transformations in human cortex during smooth pursuit eye movements. *Neuropsychologia* 46: 2203–2213, 2008. doi:10.1016/j.neuropsychologia.2008.02.021.

Krauzlis RJ, Lisberger SG. A model of visually-guided smooth pursuit eye movements based on behavioral observations. *J Comput Neurosci* 1: 265–283, 1994. doi:10.1007/BF00961876.

Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol* 4: 863, 2013. doi:10.3389/fpsyg.2013.00863.

Lebranchu P, Bastin J, Pelegrini-Issac M, Lehericy S, Berthoz A, Orban GA. Retinotopic coding of extraretinal pursuit signals in early visual cortex. *Cereb Cortex* 20: 2172–2187, 2010. doi:10.1093/cercor/bhp286.

Leichnetz GR. Inferior frontal eye field projections to the pursuit-related dorsolateral pontine nucleus and middle temporal area (MT) in the monkey. *Vis Neurosci* 3: 171–180, 1989. doi:10.1017/S0952523800004478.

Leichnetz GR. Connections of the medial posterior parietal cortex (area 7m) in the monkey. *Anat Rec* 263: 215–236, 2001. doi:10.1002/ar.1082.

Leigh RJ, Zee DS. *The Neurology of Eye Movements*. New York: Oxford University Press, 2015.

Lencer R, Nagel M, Sprenger A, Heide W, Binkofski F. Reduced neuronal activity in the V5 complex underlies smooth-pursuit deficit in schizophrenia: evidence from an fMRI study. *Neuroimage* 24: 1256–1259, 2005. doi:10.1016/j.neuroimage.2004.11.013.

Lencer R, Nagel M, Sprenger A, Zapf S, Erdmann C, Heide W, Binkofski F. Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *Eur J Neurosci* 19: 1430–1436, 2004. doi:10.1111/j.1460-9568.2004.03229.x.

Lencer R, Sprenger A, Harris MS, Reilly JL, Keshavan MS, Sweeney JA. Effects of second-generation antipsychotic medication on smooth pursuit performance in antipsychotic-naive schizophrenia. *Arch Gen Psychiatry* 65: 1146–1154, 2008. doi:10.1001/archpsyc.65.10.1146.

Lencer R, Sprenger A, Reilly JL, McDowell JE, Rubin LH, Badner JA, Keshavan MS, Pearlson GD, Tamminga CA, Gershon ES, Clementz BA, Sweeney JA. Pursuit eye movements as an intermediate phenotype across psychotic disorders: evidence from the B-SNIP study. *Schizophr Res* 169: 326–333, 2015. doi:10.1016/j.schres.2015.09.032.

Lencer R, Trillenberg P. Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain Cogn* 68: 219–228, 2008. doi:10.1016/j.bandc.2008.08.013.

Lisberger SG. Visual guidance of smooth-pursuit eye movements: sensation, action, and what happens in between. *Neuron* 66: 477–491, 2010. doi:10.1016/j.neuron.2010.03.027.

Lisberger SG, Evinger C, Johanson GW, Fuchs AF. Relationship between eye acceleration and retinal image velocity during foveal smooth pursuit in man and monkey. *J Neurophysiol* 46: 229–249, 1981. doi:10.1152/jn.1981.46.2.229.

Lisberger SG, Morris EJ, Tychsen L. Visual motion processing and sensory-motor integration for smooth pursuit eye movements. *Annu Rev Neurosci* 10: 97–129, 1987. doi:10.1146/annurev.ne.10.030187.000525.

Maunsell JH, Van Essen DC. Functional properties of neurons in middle temporal visual area of the macaque monkey. I. Selectivity for stimulus direction, speed, and orientation. *J Neurophysiol* 49: 1127–1147, 1983a. doi:10.1152/jn.1983.49.5.1127.

Maunsell JH, van Essen DC. The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J Neurosci* 3: 2563–2586, 1983b. doi:10.1523/JNEUROSCI.03-12-02563.1983.

McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage* 61: 1277–1286, 2012. doi:10.1016/j.neuroimage.2012.03.068.

Merabet L, Desautels A, Minville K, Casanova C. Motion integration in a thalamic visual nucleus. *Nature* 396: 265–268, 1998. doi:10.1038/24382.

Meyhöfer I, Kasparbauer AM, Steffens M, Ettinger U. Effects of nicotine on smooth pursuit eye movements in healthy non-smokers. *Psychopharmacology (Berl)* 236: 2259–2271, 2019. doi:10.1007/s00213-019-05223-1.

Meyhöfer I, Steffens M, Kasparbauer A, Grant P, Weber B, Ettinger U. Neural mechanisms of smooth pursuit eye movements in schizotypy. *Hum Brain Mapp* 36: 340–353, 2015. doi:10.1002/hbm.22632.

Muckli L, Petro LS. Network interactions: non-geniculate input to V1. *Curr Opin Neurobiol* 23: 195–201, 2013. doi:10.1016/j.conb.2013.01.020.

Mustari MJ, Ono S, Das VE. Signal processing and distribution in cortical-brainstem pathways for smooth pursuit eye movements. *Ann NY Acad Sci* 1164: 147–154, 2009. doi:10.1111/j.1749-6632.2009.03859.x.

Nagel M, Sprenger A, Hohagen F, Binkofski F, Lencer R. Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *Neuroimage* 41: 483–492, 2008. doi:10.1016/j.neuroimage.2008.02.058.

Nagel M, Sprenger A, Steinlechner S, Binkofski F, Lencer R. Altered velocity processing in schizophrenia during pursuit eye tracking. *PLoS One* 7: e38494, 2012. doi:10.1371/journal.pone.0038494.

Nagel M, Sprenger A, Zapf S, Erdmann C, Kömpf D, Heide W, Binkofski F, Lencer R. Parametric modulation of cortical activation during smooth pursuit with and without target blanking. an fMRI study. *Neuroimage* 29: 1319–1325, 2006. doi:10.1016/j.neuroimage.2005.08.050.

Nassi JJ, Callaway EM. Parallel processing strategies of the primate visual system. *Nat Rev Neurosci* 10: 360–372, 2009. doi:10.1038/nrn2619.

Neggers SF, Diepen RM, Zandbelt BB, Vink M, Mandl RC, Gutteling TP. A functional and structural investigation of the human fronto-basal volitional saccade network. *PLoS One* 7: e29517, 2012. doi:10.1371/journal.pone.0029517.

Neggers SF, Zandbelt BB, Schall MS, Schall JD. Comparative diffusion tractography of corticostriatal motor pathways reveals differences between humans and macaques. *J Neurophysiol* 113: 2164–2172, 2015. doi:10.1152/jn.00569.2014.

Newsome WT, Wurtz RH, Komatsu H. Relation of cortical areas MT and MST to pursuit eye movements. II. Differentiation of retinal from extraretinal inputs. *J Neurophysiol* 60: 604–620, 1988. doi:10.1152/jn.1988.60.2.604.

Ninomiya T, Sawamura H, Inoue K, Takada M. Segregated pathways carrying frontally derived top-down signals to visual areas MT and V4 in macaques. *J Neurosci* 32: 6851–6858, 2012. doi:10.1523/JNEUROSCI.6295-11.2012.

O'Driscoll GA, Callahan BL. Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993. *Brain Cogn* 68: 359–370, 2008. doi:10.1016/j.bandc.2008.08.023.

O'Driscoll GA, Wolff AL, Benkelfat C, Florencio PS, Lal S, Evans AC. Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport* 11: 1335–1340, 2000. doi:10.1097/00001756-200004270-00037.

O'Reilly JX, Woolrich MW, Behrens TE, Smith SM, Johansen-Berg H. Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci* 7: 604–609, 2012. doi:10.1093/scan/nss055.

Ohlendorf S, Kimmig H, Glauche V, Haller S. Gaze pursuit, 'attention pursuit' and their effects on cortical activations. *Eur J Neurosci* 26: 2096–2108, 2007. doi:10.1111/j.1460-9568.2007.05824.x.

Ono S, Mustari MJ. Horizontal smooth pursuit adaptation in macaques after muscimol inactivation of the dorsolateral pontine nucleus (DLPN). *J Neurophysiol* 98: 2918–2932, 2007. doi:10.1152/jn.00115.2007.

Ono S, Mustari MJ. Smooth pursuit-related information processing in frontal eye field neurons that project to the NRTP. *Cereb Cortex* 19: 1186–1197, 2009. doi:10.1093/cercor/bhn166.

Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol* 70: 453–469, 1993. doi:10.1152/jn.1993.70.2.453.

Petit L, Haxby JV. Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *J Neurophysiol* 82: 463–471, 1999. doi:10.1152/jn.1999.82.1.463.

Pierrot-Deseilligny C, Müri RM, Nyffeler T, Milea D. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. *Ann NY Acad Sci* 1039: 239–251, 2005. doi:10.1196/annals.1325.023.

Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain* 126: 1460–1473, 2003. doi:10.1093/brain/awg148.

Plichta MM, Schwarz AJ, Grimm O, Morgen K, Mier D, Haddad L, Gerdes AB, Sauer C, Tost H, Esslinger C, Colman P, Wilson F, Kirsch P, Meyer-Lindenberg A. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *Neuroimage* 60: 1746–1758, 2012. doi:10.1016/j.neuroimage.2012.01.129.

Plomp G, Hervais-Adelman A, Astolfi L, Michel CM. Early recurrence and ongoing parietal driving during elementary visual processing. *Sci Rep* 5: 18733, 2016. doi:10.1038/srep18733.

Postuma RB, Dagher A. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

resonance imaging publications. *Cereb Cortex* 16: 1508–1521, 2006. doi:10.1093/cercor/bhj088.

R Core Team. *R: A Language and Environment for Statistical Computing.* Vienna, Austria, 2020. https://www.R-project.org/.

Raemaekers M, **Schellekens W**, **van Wezel RJ**, **Petridou N**, **Kristo G**, **Ramsey NF.** Patterns of resting state connectivity in human primary visual cortical areas: a 7T fMRI study. *Neuroimage* 84: 911–921, 2014. doi:10.1016/j.neuroimage.2013.09.060.

Raemaekers M, **Vink M**, **Zandbelt B**, **van Wezel RJ**, **Kahn RS**, **Ramsey NF.** Test-retest reliability of fMRI activation during prosaccades and antisaccades. *Neuroimage* 36: 532–542, 2007. doi:10.1016/j.neuroimage.2007.03.061.

Raffi M, **Squatrito S**, **Maioli MG.** Gaze and smooth pursuit signals interact in parietal area 7m of the behaving monkey. *Exp Brain Res* 182: 35–46, 2007. doi:10.1007/s00221-007-0967-3.

Ramot M, **Wilf M**, **Goldberg H**, **Weiss T**, **Deouell LY**, **Malach R.** Coupling between spontaneous (resting state) fMRI fluctuations and human oculomotor activity. *Neuroimage* 58: 213–225, 2011. doi:10.1016/j.neuroimage.2011.06.015.

Rehme AK, **Eickhoff SB**, **Grefkes C.** State-dependent differences between functional and effective connectivity of the human cortical motor system. *Neuroimage* 67: 237–246, 2013. doi:10.1016/j.neuroimage.2012.11.027.

Robinson DA, **Gordon JL**, **Gordon SE.** A model of the smooth pursuit eye movement system. *Biol Cybern* 55: 43–57, 1986. doi:10.1007/BF00363977.

Rockland KS, **Van Hoesen GW.** Direct temporal-occipital feedback connections to striate cortex (V1) in the macaque monkey. *Cereb Cortex* 4: 300–313, 1994. doi:10.1093/cercor/4.3.300.

Saalmann YB, **Pigarev IN**, **Vidyasagar TR.** Neural mechanisms of visual attention: how top-down feedback highlights relevant locations. *Science* 316: 1612–1615, 2007. doi:10.1126/science.1139140.

Schaeffer DJ, **Johnston KD**, **Gilbert KM**, **Gati JS**, **Menon RS**, **Everling S.** In vivo manganese tract tracing of frontal eye fields in rhesus macaques with ultra-high field MRI: comparison with DWI tractography. *Neuroimage* 181: 211–218, 2018. doi:10.1016/j.neuroimage.2018.06.072.

Schall JD, **Boucher L.** Executive control of gaze by the frontal lobes. *Cogn Affect Behav Neurosci* 7: 396–412, 2007. doi:10.3758/CABN.7.4.396.

Schmid A, **Rees G**, **Frith C**, **Barnes G.** An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport* 12: 1409–1414, 2001. doi:10.1097/00001756-200105250-00023.

Schmid MC, **Mrowka SW**, **Turchi J**, **Saunders RC**, **Wilke M**, **Peters AJ**, **Ye FQ**, **Leopold DA.** Blindsight depends on the lateral geniculate nucleus. *Nature* 466: 373–377, 2010. doi:10.1038/nature09179.

Seghier ML, **Price CJ.** Interpreting and utilising intersubject variability in brain function. *Trends Cogn Sci* 22: 517–530, 2018. doi:10.1016/j.tics.2018.03.003.

Shakespeare TJ, **Kaski D**, **Yong KX**, **Paterson RW**, **Slattery CF**, **Ryan NS**, **Schott JM**, **Crutch SJ.** Abnormalities of fixation, saccade and pursuit in posterior cortical atrophy. *Brain* 138: 1976–1991, 2015. doi:10.1093/brain/awv103.

Sharpe JA. Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. *Brain Cogn* 68: 241–254, 2008. doi:10.1016/j.bandc.2008.08.015.

Sincich LC, **Park KF**, **Wohlgemuth MJ**, **Horton JC.** Bypassing V1: a direct geniculate input to area MT. *Nat Neurosci* 7: 1123–1128, 2004. doi:10.1038/nn1318.

Smith SM, **Fox PT**, **Miller KL**, **Glahn DC**, **Fox PM**, **Mackay CE**, **Filippini N**, **Watkins KE**, **Toro R**, **Laird AR**, **Beckmann CF.** Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci USA* 106: 13040–13045, 2009. doi:10.1073/pnas.0905267106.

Smyrnis N. Metric issues in the study of eye movements in psychiatry. *Brain Cogn* 68: 341–358, 2008. doi:10.1016/j.bandc.2008.08.022.

Spunt B. *spunt/bspmview: BSPMVIEW v*.20161108 (version 20161108). Zenodo. 2016. doi:10.5281/zenodo.168074.

Stanton GB, **Friedman HR**, **Dias EC**, **Bruce CJ.** Cortical afferents to the smooth-pursuit region of the macaque monkey's frontal eye field. *Exp Brain Res* 165: 179–192, 2005. doi:10.1007/s00221-005-2292-z.

Steffens M, **Becker B**, **Neumann C**, **Kasparbauer AM**, **Meyhöfer I**, **Weber B**, **Mehta MA**, **Hurlemann R**, **Ettinger U.** Effects of ketamine on brain function during smooth pursuit eye movements. *Hum Brain Mapp* 37: 4047–4060, 2016. doi:10.1002/hbm.23294.

Tanabe J, **Tregellas J**, **Miller D**, **Ross RG**, **Freedman R.** Brain activation during smooth-pursuit eye movements. *Neuroimage* 17: 1315–1324, 2002. doi:10.1006/nimg.2002.1263.

Tanaka M. Involvement of the central thalamus in the control of smooth pursuit eye movements. *J Neurosci* 25: 5866–5876, 2005. doi:10.1523/JNEUROSCI.0676-05.2005.

Tanaka M, **Lisberger SG.** Regulation of the gain of visually guided smooth-pursuit eye movements by frontal cortex. *Nature* 409: 191–194, 2001. doi:10.1038/35051582.

Taylor CM, **Olulade OA**, **Luetje MM**, **Eden GF.** An fMRI study of coherent visual motion processing in children and adults. *Neuroimage* 173: 223–239, 2018. doi:10.1016/j.neuroimage.2018.02.001.

Thiebaut de Schotten M, **Dell'Acqua F**, **Forkel S**, **Simmons A**, **Vergani F**, **Murphy DG**, **Catani M.** A lateralized brain network for visuospatial attention. *Nat Neurosci* 14: 1245–1246, 2011a. doi:10.1038/nn.2905.

Thiebaut de Schotten M, **Ffytche DH**, **Bizzi A**, **Dell'Acqua F**, **Allin M**, **Walshe M**, **Murray R**, **Williams SC**, **Murphy DG**, **Catani M.** Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage* 54: 49–59, 2011b. doi:10.1016/j.neuroimage.2010.07.055.

Tomassini V, **Jbabdi S**, **Klein JC**, **Behrens TE**, **Pozzilli C**, **Matthews PM**, **Rushworth MF**, **Johansen-Berg H.** Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. *J Neurosci* 27: 10259–10269, 2007. doi:10.1523/JNEUROSCI.2144-07.2007.

Umarova RM, **Saur D**, **Schnell S**, **Kaller CP**, **Vry MS**, **Glauche V**, **Rijntjes M**, **Hennig J**, **Kiselev V**, **Weiller C.** Structural connectivity for visuospatial attention: significance of ventral pathways. *Cereb Cortex* 20: 121–129, 2010. doi:10.1093/cercor/bhp086.

Underwood BJ. Individual differences as a crucible in theory construction. *Am Psychol* 30: 128–134, 1975. doi:10.1037/h0076759.

Vincent JL, **Patel GH**, **Fox MD**, **Snyder AZ**, **Baker JT**, **Van Essen DC**, **Zempel JM**, **Snyder LH**, **Corbetta M**, **Raichle ME.** Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* 447: 83–86, 2007. doi:10.1038/nature05758.

Vogel EK, **Awh E.** How to exploit diversity for scientific gain. *Curr Dir Psychol Sci* 17: 171–176, 2008. doi:10.1111/j.1467-8721.2008.00569.x.

Wang Y, **Matsuzaka Y**, **Shima K**, **Tanji J.** Cingulate cortical cells projecting to monkey frontal eye field and primary motor cortex. *Neuroreport* 15: 1559–1563, 2004. doi:10.1097/01.wnr.0000133300.62031.9b.

Weyand TG. The multifunctional lateral geniculate nucleus. *Rev Neurosci* 27: 135–157, 2016. doi:10.1515/revneuro-2015-0018.

Wilms M, **Eickhoff SB**, **Specht K**, **Amunts K**, **Shah NJ**, **Malikovic A**, **Fink GR.** Human V5/MT+: comparison of functional and cytoarchitectonic data. *Anat Embryol (Berl)* 210: 485–495, 2005. doi:10.1007/s00429-005-0064-y.

Zeki S. Area V5—a microcosm of the visual brain. *Front Integr Neurosci* 9: 21, 2015. doi:10.3389/fnint.2015.00021.

Downloaded from journals.physiology.org/journal/jn at ULB Bonn (131.220.201.088) on February 8, 2021.

Appendix D | Study IV

Schröder R., Keidel, K., Trautner, P., Radbruch, A., & Ettinger, U. (2022). Neural mechanisms of background and velocity effects in smooth pursuit eye movements. *Human Brain Mapping, 44*(3), 1002–1018. https://doi.org/10.1002/hbm.26127

Licensed under CC BY-NC 4.0.

Received: 17 June 2022 | Revised: 30 August 2022 | Accepted: 30 September 2022
DOI: 10.1002/hbm.26127

RESEARCH ARTICLE

WILEY

Neural mechanisms of background and velocity effects in smooth pursuit eye movements

Rebekka Schröder[1] | Kristof Keidel[1,2] | Peter Trautner[3] | Alexander Radbruch[4,5] | Ulrich Ettinger[1]

[1]Department of Psychology, University of Bonn, Bonn, Germany
[2]Department of Finance, The University of Melbourne, Australia
[3]Institute for Experimental Epileptology and Cognition Research, University of Bonn, Bonn, Germany
[4]Clinic of Neuroradiology, University Hospital, Bonn, Germany
[5]Clinical Neuroimaging, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Correspondence
Ulrich Ettinger, Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, D-53111 Bonn, Germany.
Email: ulrich.ettinger@uni-bonn.de

Funding information
Rebekka Schröder was funded by Studienstiftung des Deutschen Volkes

Abstract

Smooth pursuit eye movements (SPEM) are essential to guide behaviour in complex visual environments. SPEM accuracy is known to be degraded by the presence of a structured visual background and at higher target velocities. The aim of this preregistered study was to investigate the neural mechanisms of these robust behavioural effects. $N = 33$ participants performed a SPEM task with two background conditions (present and absent) at two target velocities (0.4 and 0.6 Hz). Eye movement and BOLD data were collected simultaneously. Both the presence of a structured background and faster target velocity decreased pursuit gain and increased catch-up saccade rate. Faster targets additionally increased position error. Higher BOLD response with background was found in extensive clusters in visual, parietal, and frontal areas (including the medial frontal eye fields; FEF) partially overlapping with the known SPEM network. Faster targets were associated with higher BOLD response in visual cortex and left lateral FEF. Task-based functional connectivity analyses (psychophysiological interactions; PPI) largely replicated previous results in the basic SPEM network but did not yield additional information regarding the neural underpinnings of the background and velocity effects. The results show that the presentation of visual background stimuli during SPEM induces activity in a widespread visuo-parieto-frontal network including areas contributing to cognitive aspects of oculomotor control such as medial FEF, whereas the response to higher target velocity involves visual and motor areas such as lateral FEF. Therefore, we were able to propose for the first time different functions of the medial and lateral FEF during SPEM.

KEYWORDS
background, distractor, fMRI, frontal eye fields, functional connectivity, smooth pursuit

1 | INTRODUCTION

Smooth pursuit eye movements (SPEM) enable the tracking of a small slowly moving object with our eyes. As such they are an essential element of our oculomotor system (Leigh & Zee, 2015). Functional magnetic resonance imaging (fMRI) studies have shown that smooth pursuit performance is accompanied by activation in visual areas such as V5, lateral geniculate nucleus (LGN), posterior parietal cortex (PPC), supplementary eye fields (SEF), and medial as well as lateral frontal eye fields (FEF; Lencer & Trillenberg, 2008). Two common findings in

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2022 The Authors. *Human Brain Mapping* published by Wiley Periodicals LLC.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the literature are that pursuit performance deteriorates (1) in the presence of visual background stimuli and (2) with higher target velocity (Barnes & Crombie, 1985; Buizza & Schmid, 1986; Collewijn & Tamminga, 1984; Hutton et al., 2000; Kaufman & Abel, 1986; Kreyenmeier et al., 2017; Lisberger et al., 1981; Masson et al., 1995; Meyhöfer et al., 2019). Both effects are very robust and show high reliability over time but also substantial interindividual differences (Schröder et al., 2021). The background effect is thought to be due to mechanisms counteracting the optokinetic drive induced by the background (Barnes, 2008). The velocity effect is related to eye velocity and/or acceleration saturation (Buizza & Schmid, 1986). Critically, little research has been done concerning the neural underpinnings of these effects.

Evidence concerning the neural mechanisms of the background effect comes from fMRI and transcranial magnetic stimulation (TMS) literature. An fMRI study by Ohlendorf et al. (2010) identified the middle temporal area (MT+) and the visual area V7 as important visuomotor transformation sites as they were active during visual, oculomotor, and visuo-oculomotor task conditions and thus receive all necessary information to successfully transform visual information into a motor command. In addition, PPC was found to specifically respond to differential motion between the structured background and the target highlighting the pivotal role of the PPC in integrating the movement of a frame of reference relative to the target. Another line of evidence concerning the neural mechanisms underlying smooth pursuit over a structured background comes from a TMS study (Haarmeier & Kammer, 2010) pointing to the crucial role of the temporoparietal junction (TPJ) in the suppression of the optokinetic nystagmus during SPEM over a structured background. This finding is also supported by Lawden et al. (1995) who demonstrated that lesions in the inferior parietal cortex (BA 40) are associated with greater background-induced impairments in SPEM performance and additionally stressed the importance of intact cortical white matter connections.

For the velocity effect, contributions of visual cortex, angular gyrus, cerebellum, and basal ganglia could be established, as indicated by increased activation at higher velocities (Nagel et al., 2008; Nagel et al., 2012; Schröder et al., 2020). These increases in BOLD response are likely due to greater retinal slip when tracking faster stimuli (Lencer & Trillenberg, 2008).

Hence, while there is already some evidence for the neural mechanisms underlying background and velocity effects, they have not yet been systematically studied jointly. It is, therefore, important to close this significant gap in the literature as smooth pursuit in natural environments occurs almost exclusively under more complex conditions than with uniform backgrounds used in most studies (Agtzidis et al., 2020; Goettker et al., 2020). This is particularly important since known pursuit-related deficits in patient populations (e.g., schizophrenia; Levy et al., 2010) have recently been shown to be present when viewing more complex, natural stimuli (Silberg et al., 2019).

Therefore, the aim of the present study was to investigate the neural mechanisms underlying the velocity and background effects in SPEM with traditional and functional connectivity approaches in a sample of healthy participants. Specifically, we preregistered the following hypotheses: at the behavioural level, we expected lower pursuit velocity gain, higher root mean square error (RMSE), and higher catch-up saccade rate at higher compared to lower target velocity (Meyhöfer et al., 2019; Schröder et al., 2021) as well as lower gain and higher RMSE with a structured compared to a uniform background (Meyhöfer et al., 2019; Schröder et al., 2021). In addition, we expected an interaction effect of the velocity and background conditions with a larger background effect at higher compared to lower velocity for all three dependent variables (Meyhöfer et al., 2019; Schröder et al., 2021). At the neural level, we expected higher activations in the pursuit network (FEF, SEF, PPC, visual areas V1 and V5, and LGN) during pursuit versus fixation as well as higher activations in visual areas (Schröder et al., 2020) with higher compared to lower target velocity. In the background condition (vs. no background), we hypothesised higher activations in a fronto-parietal network. In addition, preregistered exploratory analyses were carried out to investigate functional connectivity differences between task conditions using psychophysiological interaction analyses (PPI; Friston et al., 1997; O'Reilly et al., 2012) and to examine associations between behavioural and BOLD effects.

2 | MATERIALS AND METHODS

This study was preregistered at https://osf.io/j8w26 and approved by the ethics committee of the Department of Psychology at the University of Bonn (#21–06-30).

2.1 | Participants

We aimed for 32 participants to take part in the study. This sample size is large enough to detect the behavioural effects observed previously, for example, $\eta_p^2 = .62$ (Meyhöfer et al., 2019; Schröder et al., 2021) for the background effects on gain. With this effect size, a minimum sample size of 11 participants is required with 95% power and a 5% α-threshold (calculated in G*Power, 3.1.9.7; Faul et al., 2007). Our target sample size of 32 is also substantially larger than sample sizes in studies analysing BOLD effects similar to those we investigated here (e.g., Nagel et al., 2008; Ohlendorf et al., 2010).

Inclusion criteria were current enrolment at a university as a student, age between 18 and 35 years, male or female gender (not diverse), right-handedness, physically, neurologically and psychiatrically healthy, normal or corrected-to-normal eye-sight (contact lenses), and good command of German language.

In this study, only healthy subjects were to be examined. Therefore, exclusion criteria were current psychiatric disorder, current or history of neurological disorders, current or history of psychotic disorders, learning disabilities, loss of consciousness for more than five minutes, and serious physical illness. To ensure safe performance of the MRI measurements, additional exclusion criteria were claustrophobia, metalliferous implants, large tattoos on the upper half of the

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

body, history of welding work, injury or disease of the inner ear with loss of hearing, visual impairments other than corrective contact lenses, pregnancy, currently breastfeeding a baby, and history of any heart or head surgery. To minimize effects of drugs or substances that might affect the central nervous system, we excluded subjects with a history of alcohol or drug abuse within the last twelve months and consumption of any prescription or over-the-counter medication three days previous to the examination (apart from contraceptives, thyroid medications, or vitamin supplements).

Participants were compensated with money or course credits according to their time spent in the study (€30 for full participation).

2.2 | Study procedure

Participants were recruited via advertisements on the campus of the University of Bonn, emails, and social media. The procedure was as follows.

First, participants who responded to study advertisements were invited to fill in a short online questionnaire in order to obtain basic inclusion and exclusion criteria. Suitable participants were invited to an in-person screening at the University of Bonn. In the screening, participants provided written and informed consent. Inclusion and exclusion criteria were assessed with a semi-structured interview including detailed screening for psychiatric disorders (Ackenheil et al., 1999). Then, participants filled in a short questionnaire to obtain demographic information. Finally, they practiced the tasks they later performed in the scanner (see Section 2.3). Specifically, participants were asked to follow a moving grey pursuit target with their eyes and fixate a stationary target displayed on a computer monitor at a distance of approximately 60 cm. A total of eight blocks were presented (one 10 s-block of each pursuit condition, see Section 2.3., and four 5 s-fixation blocks). During these practice trials, eye movements were not recorded, as the main purpose was to familiarize participants with the task. The in-person screening visit took about 45 min.

Participants who met all inclusion criteria and no exclusion criteria were invited to the University Core Facility Human 3 T MRI at the University Hospital Bonn for the experimental assessment.

At the beginning of each fMRI assessment, inclusion criteria were re-confirmed verbally, and female participants were asked to provide a urine sample to test for pregnancy (OneStep®, 10 miu/ml). Then, two tasks (first a decision task not relevant to the present article and then the smooth pursuit task) were performed in the scanner and a structural scan was obtained. The experimental session took about 1 h 30 min in total.

2.3 | Task

The smooth pursuit task was designed in Experiment Builder (SR Research Ltd., Ontario, Canada, version 2.3.38) and presented on a 32-inch LCD monitor (NordicNeuroLab, 1920 × 1080 px, refresh rate: 120 Hz). The monitor was positioned at the head end of the scanner. Subjects lay on their backs—head first—in the scanner and viewed the monitor image via a first-surface reflection mirror. Distance from eye to monitor via the mirror was approximately 190 cm.

The smooth pursuit target was a grey (RGB: 192, 192, 192) circle (0.33° diameter) moving horizontally with a sinusoidal velocity pattern at two different target velocities (0.4 and 0.6 Hz) between ±6.99°. The target reached peak velocities of 17.56°/s and 26.35°/s and the duration of a full sinus cycle was 2.5 s and 1.67 s, respectively. For half of the pursuit blocks, the target was presented on a structured background (symmetrical 6-by-6-grid of white circles [0.33° diameter] on black background). For the other half of the blocks, it was presented on a blank, black background. A total of 28 pursuit blocks were presented in randomized order (sampling without replacement; 7 blocks of each task condition: 0.4 Hz no background, 0.4 Hz background, 0.6 Hz no background, 0.6 Hz background). Each pursuit block (20 s) was followed by a fixation block (10 s) where a stationary target (RGB: 192, 192, 192; 0.33° diameter) was presented at the centre of the screen. Participants were instructed to follow the target as accurately as possible with their eyes while keeping their head still in the pursuit blocks and to fixate the target in the fixation blocks. A schematic depiction of the task procedure is in Figure 1.

2.4 | Eye-movement assessment and preprocessing

Eye movements were assessed with an MR-compatible video-based combined pupil and corneal reflection long-range eye-tracker (EyeLink 1000, SR Research Ltd., Ottawa, ON, Canada). Pupil and corneal reflection of the right eye were detected with a centroid pupil-tracking algorithm at a sampling rate of 1000 Hz. Prior to the task, a five-point horizontal-vertical calibration was performed (calibration coordinates: [960,540], [960,92], [960,988], [115,540], [1805,540]).

Smooth pursuit gain was calculated as the average of the ratio of eye velocity to target velocity for the middle 50% of each half-cycle (i.e., an excursion of the target from right to left or vice versa) after blinks and saccades were excluded. Only pursuit segments longer than 50 ms were included and gain scores were time-weighted according to the duration of the segments. RMSE was obtained as a global measure of eye position error. To do so, blinks were first excluded. Then, the mean of the squared angular distance between eye and target location across time points was determined. The final RMSE measure was the square root of this mean. Saccades were detected using velocity (≥ 22°/s), amplitude (>1°), and acceleration (≥ 3800°/s^2) criteria. Saccades were defined as catch-up saccades if they improved eye position error, started behind the target, and landed behind the target or if they reduced position error by at least 50% and started behind the target and landed ahead of the target. Saccadic frequency (N/s) was obtained for catch-up saccades.

2.5 | BOLD image acquisition

Imaging was conducted using a 3 T MRI scanner (Magnetom Tim Trio, Siemens, Erlangen, Germany) in the Core Facility Human 3 T MRI of

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

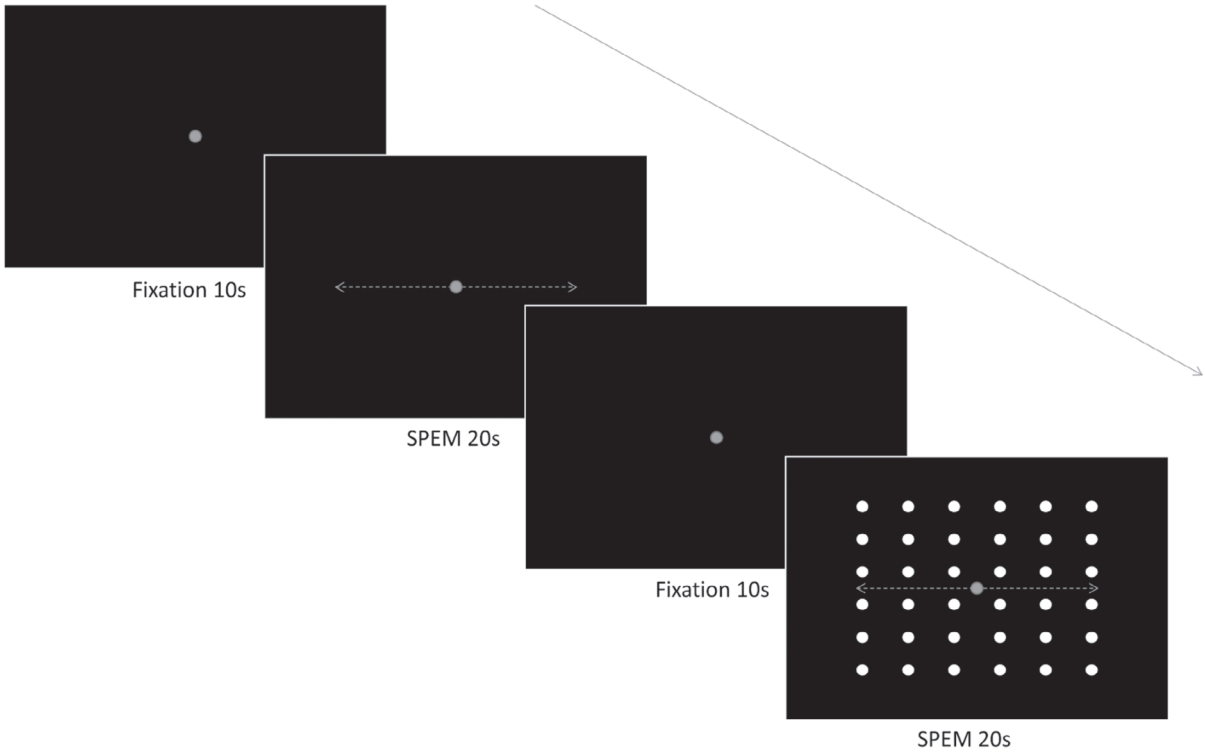

FIGURE 1 Schematic depiction of the task. Smooth pursuit eye movement (SPEM) blocks (20 s) alternated with fixation blocks (10 s). The target moved at one of two different velocities in a sinusoidal velocity pattern (0.4 vs. 0.6 Hz) and was presented on a blank screen or with background stimuli. Order of the conditions in the SPEM blocks was randomized

the University of Bonn at the University Hospital of Bonn. During the pursuit task, BOLD fMRI data were acquired with a T2*-weighted echo-planar imaging sequence (TR = 2500 ms; TE = 30 ms, matrix size = 96 × 96, number of slices = 37, slice thickness = 3 mm, interslice gap = 0.3 mm, FoV = 192 mm, flip angle = 90°, voxel size = 2 × 2 × 3.3 mm). The standard 32-channel head coil from Siemens was used for radio frequency reception. Additionally, for each participant, a three-dimensional T1-weighted high-resolution structural scan was acquired using Magnetization Prepared Rapid Acquisition with Gradient Echoes (MPRAGE) with the following parameters: TR = 1660 ms, TE = 2.54 ms, matrix size = 320 × 320, number of slices = 208, slice thickness = 0.8 mm, no interslice gap, FoV = 256 mm, flip angle = 9°, and voxel size = 0.8 × 0.8 × 0.8 mm.

2.6 | BOLD preprocessing and preregistered analyses

BOLD data were preprocessed and analysed in SPM12 running in Matlab 2018A. All fMRI results are reported whole-brain family-wise error rate (FWE) corrected ($p < .05$, peak level) voxelwise with an additional minimum cluster size threshold of 10 voxels. However, following a reviewer comment, we also report uncorrected results in the supplementary materials. Anatomical labels were obtained with the SPM Anatomy Toolbox (Eickhoff et al., 2005).

Preprocessing included realignment to the first image of the time series using a least squares approach and a six parameter (rigid body) spatial transformation, coregistration of the anatomical and functional images using the individual T1-scans, and normalization into standard space (MNI template). As a final step, the normalized images were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel.

At the first level, data were analysed with a general linear model (GLM) approach. The time course of each task condition (i.e., 0.4 Hz no background, 0.6 Hz no background, 0.4 Hz background, 0.6 Hz background) was modelled as a separate regressor with 20 s boxcar functions. A 128-s high-pass filter was applied to remove slow signal drifts. The six individual realignment parameters were added as additional regressors of no interest. The fixation blocks were not modelled and served as implicit baseline. First-level contrasts were calculated for the following three main effects using *t*-tests: pursuit (all conditions) versus fixation, the background effect (0.4 Hz background, 0.6 Hz background > 0.4 Hz no background, 0.6 Hz no background), and the velocity effect (0.6 Hz no background, 0.6 Hz background > 0.4 Hz no background 0.4 Hz background). In addition, the interaction contrast of the background and velocity factors was modelled ((0.6 Hz background > 0.6 Hz no background) > (0.4 Hz background > 0.4 Hz no background)). These first-level contrasts were then taken to the second level to calculate one-sample *t*-tests (random effects) for each type of first-level contrast.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2.7 | Preregistered exploratory analyses of BOLD data

2.7.1 | Functional connectivity

In addition, task-dependent functional connectivity analyses were performed with generalized psychophysiological interaction analyses (gPPI; Friston et al., 1997; McLaren et al., 2012). Ten seed regions (left and right LGN, V1, V5, PPC, FEF) were selected because of their known roles in SPEM. Seed coordinates were taken from previous literature (Schröder et al., 2020: LGN [−24, −26, −4; 22, −26, 0], V1 [−11, −80, −1; 20, −75, −3], V5 [−44, −76, 2; 43, −73, 5], FEF [−30, −6, 55; 30, −9, 50], PPC [−25, −60, 56; 24, −56, 47]). For V1, V5, PPC, and FEF, individual seed regions were identified by first positioning a 12 mm-sphere around these coordinates and then identifying the largest individual SPEM-related peak in those larger spheres (omnibus-F-map, corrected at $p < .001$) to account for inter-individual anatomical variability. In a second step, a 4 mm-sphere was placed around these individual coordinates; these smaller spheres were then used for BOLD activity extraction (see below). If no individual peak could be determined in the larger sphere, the smaller sphere was positioned around the literature coordinates. This procedure resulted in a 4 mm-sphere for every participant and seed region which was either at the coordinates of the individual BOLD peak or at the abovementioned coordinates if no significant peak was detected nearby. However, this procedure was not suitable for identifying the LGN seed regions as the 12-mm sphere is too large for LGN which is a small structure (Li et al., 2012) risking that the identified peak is not in the targeted brain area. Therefore, for LGN analyses, the same coordinates identified from the literature were used for all participants (i.e., [−24, −26, −4; 22, −26, 0]).

The first eigenvariate of the timeseries of all voxels within these 4 mm-spheres was extracted. After deconvolution, it was multiplied with the task regressors and the resulting products (i.e., the psychophysiological interaction terms) were then reconvolved with the HRF. Next, for each seed region, a GLM was modelled with all task vectors (the four SPEM conditions) and the corresponding gPPI terms as well as the seed region time course. The six motion parameters (from realignment) were entered as regressors of no interest. Then, first-level contrasts were set up: a SPEM (all four gPPI terms) versus fixation contrast, a background versus no background contrast, and a high versus low target velocity contrast. For group-level analyses, these three contrasts were taken to the second level to calculate one-sample *t*-tests.

2.7.2 | Multiple regressions

To explore brain-behaviour relationships, separate regression analyses were calculated at the second level using two different approaches. First, to identify correlations between BOLD response and behavioural outcomes, the first-level task contrasts for each task condition (e.g., 0.4 Hz no background, 0.6 Hz no background, 0.4 Hz background, 0.6 Hz background) were entered into separate multiple-regression models along with the three behavioural outcome measures (gain, RMSE and catch-up saccade frequency) of the corresponding condition (12 models). Second, to identify correlations between task effects (difference measures), the first-level contrasts of these task effects (e.g., background effect, velocity effect) were entered into separate multiple-regression models along with the behavioural task effect (6 models).

2.7.3 | Correlations

In order to further explore correlations between behavioural outcomes and BOLD response, regions of interest (ROIs) were defined as significant clusters in each of the contrasts of the task effects (background vs. no background and high vs. low target velocity contrasts) and each task condition versus fixation (0.4 Hz no background versus fixation, 0.4 Hz background vs. fixation, 0.6 Hz no background vs. fixation and 0.6 Hz background vs. fixation). Mean beta weights from these ROIs were then extracted for each participant with the MarsBaR toolbox (Brett et al., 2002) yielding summary time courses for each cluster and participant. These values were then correlated with the behavioural outcome measures of the corresponding task effect (difference measure) or condition (direct performance outcome) using *R* and the *Hmisc* package (V.4.4.0; Harrell, 2020). Statistical outliers (see Section 2.8) were excluded. Results were corrected for multiple correlations using Bonferroni correction.

2.8 | Preregistered statistical analyses of the eye-tracking data

Behavioural data were analysed in *R* using the *ez* package (V.4.4.0; Lawrence, 2016) with two-factorial repeated measures ANOVA with the factors background (present and absent) and target velocity (0.4 Hz or 0.6 Hz) for each of the dependent variables smooth pursuit gain, RMSE, and catch-up saccade frequency. The alpha-level to determine significance was set to .05. Outliers were identified with boxplot criteria, that is, participants with values 1.5 times the interquartile range above the upper quartile and below the lower quartile were excluded. Analyses without the removal of outliers are reported in the supplementary material (Table S1).

3 | RESULTS

The eye-tracking data that support the findings of this study are openly available at the Open Science Framework (OSF) at https://osf.io/uez5f/. The MRI data that support the findings of this study are available on request from the corresponding author. The MRI data are not publicly available due to privacy and ethical restrictions.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3.1 | Participants

A total of 33 (16 female, 17 male) participants took part in the study. On average, participants were 23.30 years old ($SD = 3.14$). For one participant (male), BOLD data were not saved due to technical failure. This participant is only included in the analyses of eye movement data. Data screening for movement showed that, overall, participants moved very little. However, BOLD data from one participant had to be excluded due to excessive movement ($z > 4$ and $y > 4$ mm). After exclusion of this participant, mean displacement for the six realignment parameters across participants was x: $M = -0.35$ mm, SD = 0.34 mm, y: $M = -0.22$ mm, SD = 0.25 mm, z: $M = 0.51$ mm, SD = 0.42 mm, pitch: $M = 0.35°$, SD = 0.37°, roll: $M = 0.09°$, SD = 0.36°, yaw: $M = 0.04°$, SD = 0.26°.

3.2 | Eye movements

Due to poor eye-tracking quality, data from three participants could be analysed for only a subset of the blocks (35, 22 and 30 blocks respectively, out of the total of 56 blocks) and data from one participant had to be excluded altogether. Descriptive statistics are in Table 1 and Figure 2 (visualised using raincloud plots; Allen et al., 2018, 2019).

There were three statistical outliers for pursuit gain, four for RMSE and three for catch-up saccade rate. These participants were excluded from all analyses of the respective outcome measure. Importantly, results did not change when these outliers were included (see Table S1).

Analyses of pursuit gain revealed main effects of the background ($F_{[1,\ 28]} = 70.55$, $p < .001$, $\eta_p^2 = .716$) and velocity factors ($F_{[1,\ 28]} = 542.04$, $p < .001$, $\eta_p^2 = .951$), indicating lower gain in the background condition and at higher target velocity, respectively. There was no interaction of the two factors ($p > .05$). Both effects were numerically evident in every single participant but also showed substantial variability between participants (Figure 2, panel a).

For RMSE, there was a significant main effect of velocity ($F_{[1,\ 27]} = 210.11$, $p < .001$, $\eta_p^2 = .886$), but no main effect of background and no interaction of the two factors (all $p > .05$; Figure 2, panel b).

Analyses of catch-up saccade rate revealed main effects of the background ($F_{[1,\ 28]} = 12.57$, $p < .001$, $\eta_p^2 = .311$) and velocity factors ($F_{[1,\ 28]} = 134.72$, $p < .001$, $\eta_p^2 = .828$). Catch-up saccade rate was higher in the background condition and at higher target velocity. There was no interaction of the two factors ($p > .05$, Figure 2, panel c).

3.3 | BOLD

3.3.1 | SPEM versus fixation

The SPEM task elicited higher BOLD response than fixation in a widespread network (Figure 3, Table 2). Higher activation during SPEM versus fixation was found in visual and motion processing areas (left and right calcarine, right lingual gyrus, left cuneus, and middle occipital gyrus) extending into cerebellum. SPEM also led to increased activity in left LGN, bilateral precentral gyrus (including left medial and lateral FEF and right lateral FEF), right superior parietal cortex, left midcingulate cortex (MCC) as well as posterior-medial frontal cortex (including SEF).

For the reverse contrast (Fixation > SPEM, Figure S1), significant BOLD response differences were observed in bilateral middle occipital gyrus (extending into right angular gyrus), left and right fusiform gyrus (extending into cerebellum), bilateral insulae (extending into right Heschl's Gyrus) as well as left Rolandic Operculum.

3.3.2 | Background versus no background

The background condition elicited greater BOLD response than the no background condition in nine clusters (Figure 3, Table 3). The largest cluster encompassed visual cortex (lingual, calcarine and middle occipital gyri) and extended into left superior parietal cortex and precuneus. There were separate clusters containing right superior parietal cortex and middle occipital gyrus and left middle temporal gyrus. In addition, increased BOLD response was found in left LGN, bilateral superior frontal gyrus (containing medial FEF and extending into precentral gyrus), left lateral FEF and right posterior-medial frontal cortex (including SEF). The opposite contrast (no background > background, Figure S1) yielded greater BOLD response in one cluster in right cuneus. Results without correction for multiple comparisons yielded even more widespread activity (Figure S2 and Table S2).

3.3.3 | High versus low target velocity

Faster targets yielded greater BOLD response than slower targets in two clusters (Figure 3, Table 4). The first large cluster was located in the visual cortex (bilateral calcarine gyri and left cuneus) and encompassed V1 and surrounding areas. The second (smaller) cluster

TABLE 1 Descriptive statistics of smooth pursuit performance outcomes

		Gain		RMSE		Catch-up saccade rate	
Velocity	Background	*M*	*SD*	*M*	*SD*	*M*	*SD*
0.4 Hz	absent	77.44	7.51	2.50	0.38	1.01	0.35
	present	67.40	14.86	2.45	0.38	1.22	0.36
0.6 Hz	absent	56.95	10.39	3.46	0.58	1.60	0.38
	present	46.82	13.26	3.43	0.53	1.74	0.41

Note: Means (M) and standard deviations (SD) of the behavioural outcome measures gain (in %), root mean square error (RMSE; in °), and catch-up saccade rate (N/s) in the four task conditions.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

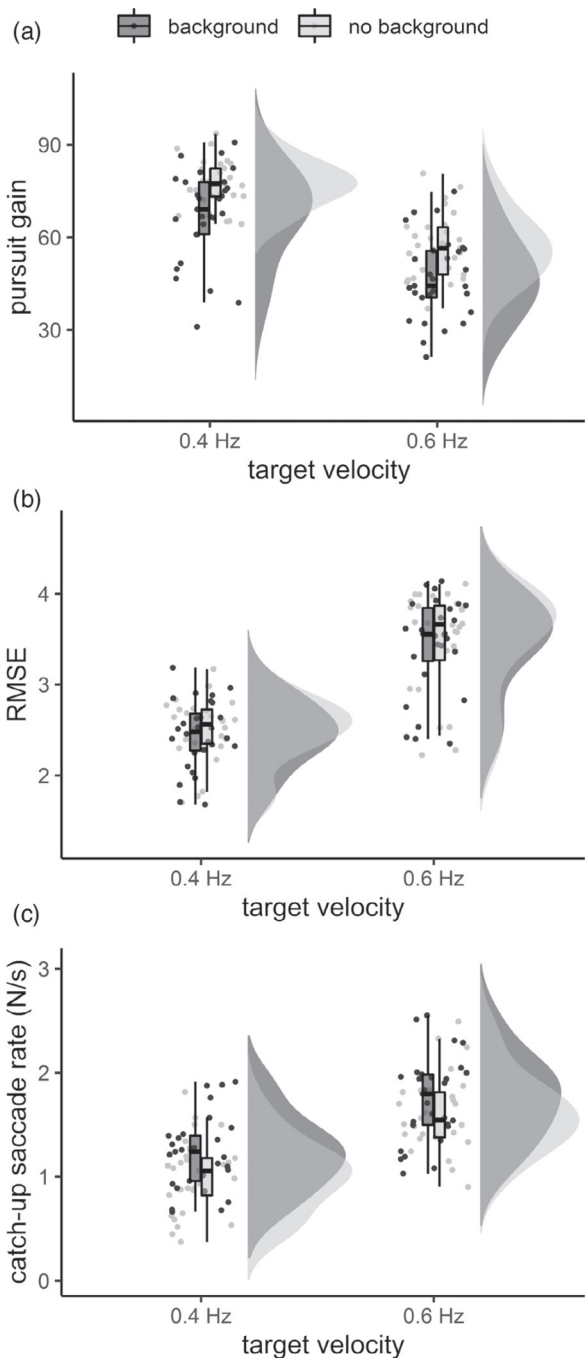

FIGURE 2 Effects of background and target velocity on smooth pursuit gain (in %; panel a), root mean square error (RMSE; in °; panel b), and catch-up saccade rate (N/s; panel c)

comprised left precentral gyrus (including lateral FEF). For the reverse contrast (Figure S1), higher BOLD response with slower versus faster targets was observed in left temporal pole. Positive results without correction for multiple comparisons were also found outside primary visual cortex (e.g., in FEF, SEF and V5; Figure S3 and Table S3).

3.3.4 | Background velocity interaction

There were no activation differences for the background effect at higher versus lower target velocity and the reverse contrast. Results without correction for multiple comparisons yielded two small clusters for the positive and three small clusters for the negative contrast (Figure S4 and Table S4).

3.4 | Functional connectivity

PPI analyses did not yield any significant differences in functional connectivity between the background and no background conditions, between the high and low target velocity conditions or in the reverse contrasts for any of the seed regions. A detailed description of the connectivity maps underlying the SPEM versus fixation contrasts is in the supplementary material (Figures S5 and S6 and Tables S5–S14). These are broadly similar to those reported in our previous study using the same seed voxels (Schröder et al., 2020).

3.5 | Brain-behaviour relationships

3.5.1 | Multiple regressions

The multiple regression analyses did not yield any significant associations between BOLD and the behavioural outcome variables.

3.5.2 | Correlations

There were no significant correlations between BOLD response and the behavioural variables for the task effects. For the direct performance outcomes, we found three significant correlations before correction for multiple analyses. Note, that these correlations did not survive Bonferroni correction. There was a negative correlation between the BOLD response in left V5 and pursuit gain in the 0.6 Hz no background condition ($R = -.47$, $p_{uncorr} = .01$) indicating that higher BOLD response in this area was associated with poorer pursuit performance. Catch-up saccade rate was positively correlated with activity in right FEF (lateral extending into medial) in the 0.6 Hz no background condition ($R = .50$, $p_{uncorr} = .009$). In the 0.4 Hz background condition, pursuit gain positively correlated with activity in left medial FEF ($R = .38$, $p_{uncorr} = .048$). There were no further significant correlations for any of the clusters and direct performance measures. Detailed correlation results are in Tables S15–S20.

4 | DISCUSSION

In this preregistered study, eye movement and BOLD data from 33 healthy participants were collected as they performed SPEM in the presence and absence of a structured background at two different target velocities.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

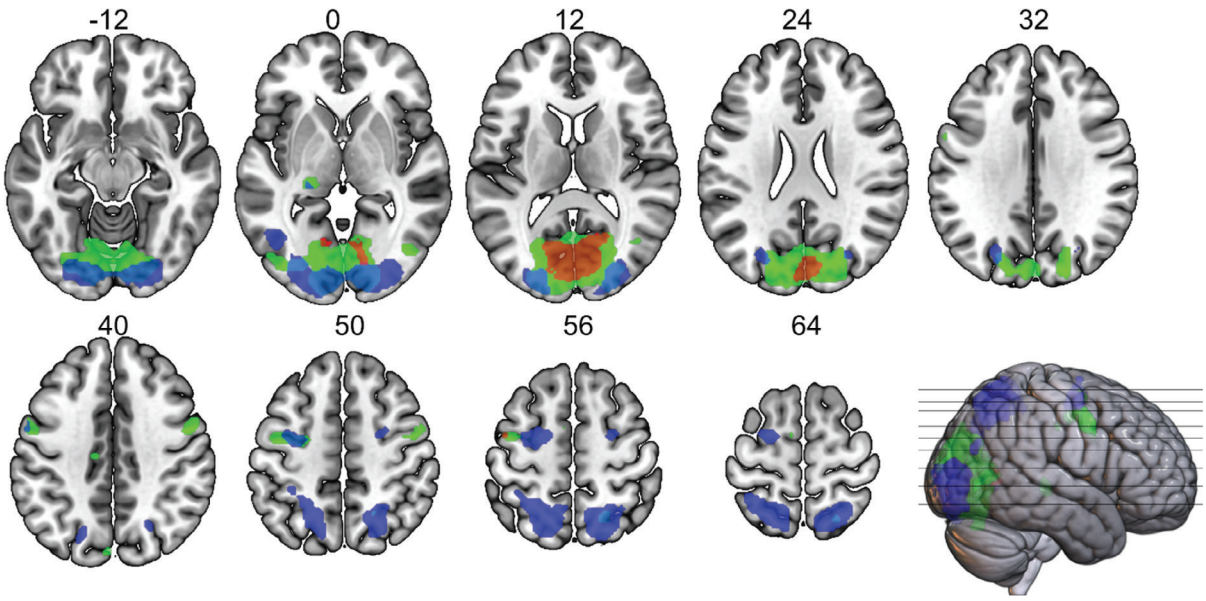

FIGURE 3 Blood oxygen level-dependent (BOLD) response during smooth pursuit. Results of one-sample t-tests (random effects) of the SPEM versus fixation (green), background versus no background (blue) and high versus low target velocity (red) conditions, respectively. Results are reported whole-brain family-wise error rate (FWE) corrected voxelwise ($p < .05$, peak level) with an additional minimum cluster size threshold of 10 voxels. The left hemisphere is depicted on the left. Upper labels refer to the *z* coordinate of the slices (Montreal Neurological Institute [MNI] space). Significant clusters are binarized.

At the behavioural level, the presence of a structured background decreased pursuit gain and increased the number of catch-up saccades but had no effect on RMSE. Faster targets led to decreased pursuit gain, increased RMSE, and increased rates of catch-up saccades. No interaction of the velocity and background factors could be observed for any of the dependent variables.

In terms of BOLD activity, the smooth pursuit task activated areas in the known oculomotor network including LGN, visual cortex, PPC, medial and lateral FEF, SEF, and cingulate gyrus. Differences in BOLD response between the background conditions were found in extensive clusters in visual, parietal, and frontal areas. In contrast, the velocity effects yielded BOLD response only in visual areas and a small left-hemispheric lateral FEF cluster. Functional connectivity analyses revealed widespread connectivity maps for the SPEM contrasts but did not provide any additional information concerning the neural underpinnings of the background and velocity effects. Correlations of behaviour and BOLD response could only be identified for pursuit gain and saccade frequency at 0.6 Hz in the no background condition, where higher BOLD response was associated with poorer performance, and for the 0.4 Hz background condition, where higher gain was associated with higher BOLD response in left medial FEF. However, none of these survived correction.

4.1 | Behavioural effects

In line with our hypotheses and previous studies, pursuit gain was reduced and saccade rate increased in the presence of a structured background and with faster targets (Meyhöfer et al., 2019; Schröder et al., 2021). Strikingly, effects on gain were highly robust as they were identified in every single participant. Likely, pursuit performance was affected because the structured background induced optokinetic drive (Barnes, 2008) which had to be cancelled. This cancellation might be based on the processing of extraretinal signals and accomplished by reducing sensitivity to global motion in the direction opposite of the pursuit eye movement (Lindner et al., 2001; Lindner & Ilg, 2006).

Contrary to our hypotheses, we did not observe interactions of background and target velocity for any of the dependent variables although we had purposely selected stimuli conditions that had yielded a strong interactive effect in a prior behavioural study (Schröder et al., 2021). A reason for this discrepancy could be that pursuit performance was generally worse compared to previous laboratory investigations using similar tasks (Meyhöfer et al., 2019; Schröder et al., 2021; Schröder et al., 2022) presumably because of the unusual and uncomfortable environment in the scanner and distracting external stimuli such as scanner noise in this study (see also Koch et al., 2003). Therefore, it can be assumed that participants did not reach optimal performance levels and thus more subtle effects such as the interaction reported previously could not emerge. Importantly, there was also no evidence for interactive effects at the level of neural activity. However, it should be noted that even small changes in task design could have prevented the emergence of such effects as has been shown for other cognitive tasks (Ruge et al., 2013). For example, SPEM blocks in this study were shorter in the fMRI design compared to our earlier study (Schröder et al., 2021),

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 BOLD response during SPEM versus fixation and fixation versus SPEM

Anatomical label *(functional label)*	Cluster size	*t*-value	MNI coordinates *x*	*y*	*z*
SPEM > Fixation					
L Cerebellum	9744	13.16	−10	−78	−14
R Calcarine Gyrus *(V1)*		12.88	12	−80	10
R Lingual Gyrus		12.68	14	−90	−6
R Calcarine Gyrus		12.24	6	−88	6
L Calcarine Gyrus		11.89	−6	−82	12
L Calcarine Gyrus		11.17	−6	−88	4
R Lingual Gyrus		10.73	10	−78	−2
L Cuneus		10.66	−6	−86	26
L Middle Occipital Gyrus		10.32	−18	−94	6
L Calcarine Gyrus		10.22	−14	−78	16
L Thalamus (including LGN)	98	8.88	−20	−28	2
R Precentral Gyrus *(lateral FEF)*	178	8.09	50	−2	40
R Precentral Gyrus		6.12	42	−8	48
L Precentral Gyrus *(lateral FEF)*	285	7.77	−26	−8	48
L Precentral Gyrus *(extending into medial FEF)*		7.45	−36	−8	52
R Middle Temporal Gyrus	237	7.74	44	−64	6
N/A[a]		6.87	34	−64	8
L Precentral Gyrus *(lateral FEF)*	76	7.27	−56	2	38
L Precentral Gyrus		6.34	−60	6	30
R Superior Parietal Lobule	86	7.07	20	−58	54
R Superior Parietal Lobule		7.05	22	−60	62
L Posterior-Medial Frontal Cortex *(SEF)*	25	6.89	−8	−2	60
N/A[b]	13	6.65	−12	−18	38
Fixation > SPEM					
L Middle Occipital Gyrus	39	7.69	−42	−80	30
L Rolandic Operculum	72	7.25	−42	−18	12
R Insula Lobe	152	6.96	42	−10	4
R Insula Lobe		6.13	38	−18	14
R Middle Occipital Gyrus	19	6.90	44	−78	28
R Angular Gyrus		6.27	48	−70	38
R ACC	15	6.58	10	34	6
L Fusiform Gyrus	84	6.51	−26	−42	−20
R Fusiform Gyrus	14	6.28	26	−48	−16
L Insula Lobe	13	6.23	−40	4	−12

[a]Nearest grey matter: R Calcarine Gyrus.
[b]Nearest grey matter. L MCC.

and SPEM blocks were interleaved with fixation blocks. Therefore, the sensitivity of the background × target velocity interaction effect to changes in task configurations should be systematically investigated in the future.

While the velocity effect was also found for RMSE, there was no background effect on this variable which is not consistent with our hypotheses and our own previous result (Schröder et al., 2021). This failure to obtain the RMSE background effect was surprising especially given the large effect on pursuit gain. A first explanation may be that RMSE is primarily a measure of eye position while gain reflects velocity. RMSE is thus a much more global measure of pursuit quality that is dependent on multiple influences (Smyrnis, 2008). Second, RMSE is calculated for the entire duration of the pursuit segments (excluding blinks) while gain is calculated only for the middle 50% of each half-cycle after exclusion of blinks and saccades. Crucially, however, limiting the calculation of RMSE to the same time window as pursuit did not change the pattern of results (data not shown). Third, it is conceivable that the highly structured background distractor

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 BOLD response in the background versus no background and no background versus background contrasts

Anatomical label *(functional label)*	Cluster size	*t*-value	MNI coordinates x	y	z
Background present > absent					
R Calcarine Gyrus *(V1)*	5419	15.03	16	−92	−4
L Calcarine Gyrus *(V1)*		13.43	−10	−98	−4
L Middle Occipital Gyrus		13.40	−18	−100	2
L Superior Parietal Lobule		13.38	−22	−56	60
R Middle Occipital Gyrus		12.96	26	−94	8
L Lingual Gyrus		11.18	−14	−92	−12
L Superior Parietal Lobule		10.63	−30	−54	66
L Middle Occipital Gyrus		10.41	−26	−90	0
L Lingual Gyrus		9.84	−26	−88	−16
L Precuneus		8.99	−12	−64	58
L Middle Occipital Gyrus		7.92	−24	−72	30
L Superior Frontal Gyrus *(medial FEF)*	453	9.78	−26	−6	58
L Precentral Gyrus *(medial FEF)*		7.84	−36	−6	50
L Superior Frontal Gyrus		6.22	−14	−6	72
R Superior Parietal Lobule	1205	9.21	24	−64	62
R Superior Parietal Lobule		7.90	22	−68	48
R Superior Frontal Gyrus *(medial FEF)*	86	7.87	24	−4	52
R Precentral Gyrus *(medial FEF)*		5.93	32	−2	48
L Middle Temporal Gyrus	187	7.86	−44	−64	2
N/A[a]	20	6.86	−22	−30	2
R Middle Occipital Gyrus	38	6.68	30	−74	24
R Posterior-Medial Frontal Cortex *(SEF)*	14	6.57	12	−4	70
L Precentral Gyrus	25	6.54	−56	0	38
Background absent > present					
R Cuneus	19	6.58	14	−84	26

[a]Nearest grey matter: L Thalamus (including LGN).

TABLE 4 BOLD response in the 0.6 versus 0.4 Hz and 0.4 versus 0.6 Hz contrasts

Anatomical label *(functional label)*	Cluster size	*t*-value	MNI coordinates x	y	z
0.6 Hz > 0.4 Hz					
L Cuneus *(V1)*	2214	10.13	2	−86	20
L Calcarine Gyrus *(V1)*		9.51	−8	−76	10
L Calcarine Gyrus		8.73	−16	−66	8
L Precentral Gyrus *(lateral FEF)*	14	7.02	−46	−6	54
0.4 Hz > 0.6 Hz					
L Temporal Pole	32	7.91	−40	14	−26

stimuli are not only disruptive but also help to guide eye movements, for example, by limiting the vertical displacement of the target to a confined space (Eggert et al., 2009; Goettker et al., 2020; Ladda et al., 2007). This is especially important since RMSE (in contrast to gain) comprises horizontal and vertical deviations. At a descriptive level, vertical deviation of the eye from the target was indeed lower in the background condition in our data (data not shown). Thus, the background distractors may have simultaneously reduced vertical eye displacements and increased horizontal displacements (as evidenced by reduced gain) but these two processes may have cancelled each other out when measured in terms of RMSE. However, these speculations cannot fully explain the divergence from previous studies and should, therefore, be addressed systematically in future investigations.

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4.2 | Pursuit network

The task-related activations in visual cortex, medial and lateral FEF, SEF, PPC, cingulate gyrus, and LGN for the SPEM versus fixation contrasts were in line with our hypotheses and corresponded well with the results from previous investigations (Berman et al., 1999; Dieterich et al., 2009; Haller et al., 2008; Kimmig et al., 2008; Konen et al., 2005; Konen & Kastner, 2008; Lencer et al., 2004; Nagel et al., 2006; Nagel et al., 2008; Petit & Haxby, 1999; Schröder et al., 2020; Tanabe et al., 2002). This underlines the validity of our task design, the accurate recording and analysis of the BOLD signal and the overall robustness of SPEM BOLD correlates for sinusoidal target stimuli in the medium velocity range.

Higher BOLD response during fixation (vs. SPEM) might reflect deactivations during SPEM or increased BOLD during fixation. The results found in bilateral insulae have also been observed in past oculomotor studies, albeit with less consistency compared to the results for the reverse contrast (Dieterich et al., 2003; Dieterich et al., 2009; Konen et al., 2005). Clusters in angular gyrus might reflect default mode network activity (Seghier, 2013) during fixation or deactivation during SPEM, respectively.

4.3 | Background effect

The BOLD response in the background versus no background contrasts spread across almost the entire SPEM network and also included regions that were not significant in the simple SPEM contrast. Specifically, we observed increased BOLD in visual cortex, superior and inferior parietal cortex, FEF and LGN. Decreased BOLD in the background condition was found in one cluster in right cuneus.

4.3.1 | LGN and visual cortex

The widespread cluster located in LGN and visual cortex during pursuit with (vs. without) a structured background is not surprising, given the higher visual complexity of the structured background pattern compared to the simple black background (Kastner et al., 2006; Ohlendorf et al., 2010). In addition, there was evidence of increased BOLD response in the laterally located left visual area V5, an area which is essential for motion processing, but not in its right counterpart (Zeki, 2015). Similarly, no target-velocity-related BOLD modulation was found for V5 in the current and a previous investigation (Schröder et al., 2020). It has been shown that V5 is more strongly activated by pursuit of a single dot compared to motion tracking of a large pattern of stimuli (Schraa-Tam et al., 2009). This pattern of results along with evidence that TMS induced perturbations on area V5 affect pursuit performance independent of background (Haarmeier & Kammer, 2010) suggests that area V5—albeit essential for successful pursuit performance—does not contribute significantly to the inhibition of interfering, stationary background stimuli. Instead, it might preferably process the local movement of the pursuit target.

The only region deactivated during background processing was cuneus which could be associated with the execution of eye movements without sustained attention (Corbetta et al., 1998).

4.3.2 | Parietal cortex

In line with our hypotheses, we observed increased BOLD response in areas of the parietal cortex, especially superior and PPC. While peaks were in a similar location to the SPEM versus fixation contrast peaks, the background-related clusters had a much wider extent. Consistent with previous investigations, results were stronger in the right hemisphere (Corbetta et al., 1993; Nobre et al., 1997; Thiebaut de Schotten et al., 2011).

The PPC has been associated with a number of different functions during pursuit. First of all, it is worth stating its pivotal role in guiding attention (Corbetta et al., 1995; Culham et al., 1998; Thiebaut de Schotten et al., 2011). Crucially, pursuit of a visual stimulus with an auditory stimulus moving in antiphase (vs. phase) led to increased posterior parietal BOLD response while not impacting performance (Baumann & Greenlee, 2009). Similarly, Ohlendorf et al. (2007) identified PPC as the only region differentially activated in conditions with divided versus focused attention during pursuit. This pattern of results was further elaborated by Ohlendorf et al. (2010) who found PPC to react to differential motion of target and background. In addition, BOLD response in PPC increased with higher numbers of background stimuli. This suggests that PPC might integrate movement of the target relative to a frame of reference. This line of argument is also supported by Trenner et al. (2008) who found increased BOLD response in PPC in response to a critical SPEM stimulus that was preceded by a faster versus slower background stimulus suggesting that PPC contributes to perceptual stability during SPEM by comparing internal reference signals with retinal signals. In summary, PPC appears to serve smooth pursuit by guiding attention and processing movements relative to an internal and/or external frame of reference (Ohlendorf et al., 2010; Tikhonov et al., 2004; Trenner et al., 2008).

While effects in PPC were very strong, we could not find evidence for differential BOLD response in TPJ and/or inferior parietal cortex during background versus no background processing as we had hypothesised based on previous literature (Haarmeier & Kammer, 2010; Lawden et al., 1995). TPJ might become relevant only when the pursuit system has to operate against even more salient background patterns (Lawden et al., 1995) or with brief (vs. continuous) background perturbations (Haarmeier & Kammer, 2010).

4.3.3 | Frontal eye fields

In agreement with our findings, smooth pursuit and saccade task performance typically involves both medial and lateral subregions of FEF (both located in Brodmann area 6 and also referred to as superior and inferior FEF; Cieslik et al., 2016; Dieterich et al., 2009; Ettinger

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

et al., 2008; Lencer et al., 2004; McDowell et al., 2008; Vernet et al., 2014). Interestingly, the peak coordinates of FEF activations in the background conditions were located more medially than in the conditions without background and in the overall SPEM contrast, although there was also substantial overlap of the clusters. While the literature is scarce concerning the roles of FEF subregions in pursuit (Coiner et al., 2019), more evidence regarding their function in saccades has been accumulated (McDowell et al., 2008). Specifically, McDowell et al. (2008) proposed that medial FEF is more involved in volitional saccades whereas lateral FEF is more closely associated with reflex-like, automatic saccadic eye movements. More recent meta-analytical evidence showed that FEF activation peaks during prosaccades lie more laterally than FEF activation peaks in antisaccades (Cieslik et al., 2016). Strikingly, the activation peaks in that study correspond remarkably well with the lateral and medial peaks in our data. The authors proposed that lateral FEF is involved in the motor output, whereas medial FEF plays a more important role in higher cognitive processes (Cieslik et al., 2016). A similar pattern of results was also observed by Ettinger et al. (2008) who temporally differentiated the saccadic inhibition and response generation phases of antisaccades to provide evidence suggesting that medial FEF is more strongly related to saccadic inhibition whereas lateral FEF is more closely linked to generation of the motor command. Lee et al. (2006) demonstrated that the number of alternatives in a cued saccade task correlates positively with activation in medial but not in lateral FEF suggesting that the former can be regarded as an interface between stimulus inputs and responses whereas the latter is associated with processes such as response execution. Similarly, there is evidence for stronger involvement of medial FEF in the execution of new sequences of saccades compared to familiar sequences, possibly due to higher demands on sensorimotor transformation processes (Grosbras et al., 2001; Simó et al., 2005).

In addition to these findings from saccade research, the literature on decision-making presents evidence that more lateral regions in PFC and PPC are involved with action planning based on rules and external cues while more medial regions in these areas are involved in voluntary, self-determined action plans (Bode et al., 2014).

But how do these results from research on saccades and action planning relate to smooth pursuit? To our knowledge, the question of functional specialization of FEF subregions during pursuit has not yet been systematically investigated. Here, we argue that a similar pattern of functional specialization of FEF subregions can be found in pursuit as in saccades: lateral FEF take on a more motor-related role involved in the execution of the movement—which is supported by findings of stronger connectivity of lateral FEF and motor areas (Cieslik et al., 2016)—while medial FEF come into play mainly when more complex demands are placed on the system and higher cognitive processes are of greater importance (Jin et al., 2021), for example, by inhibiting the processing of distracting background stimuli. How medial and lateral FEF subregions correspond to the dynamic gain control of retinal and extraretinal signals during ongoing pursuit has to be investigated in the future (Drew & van Donkelaar, 2007; Gagnon et al., 2006; Nuding et al., 2009). Nevertheless, it is important to emphasise that both regions are necessary for successful pursuit. For example, Lencer et al. (2004) showed that both lateral and medial FEF are active in a standard pursuit task. However, increased BOLD response related to predictive pursuit during target blanking was robustly observed in bilateral medial FEF and left lateral but not in right lateral FEF, confirming that medial FEF are particularly important under circumstances of higher cognitive demands (Jin et al., 2021).

4.3.4 | Other areas

Lindner et al. (2006) identified the Crus I in the lateral cerebellum as the functional correlate of an internal reference signal that is engaged in predicting sensory experiences during smooth pursuit over structured backgrounds. While some of the clusters related to increased BOLD response in the background (vs. no background) conditions extended into the cerebellum in our study, we are unable to directly compare our results as the cerebellum was not entirely inside the mask of our second level analysis. We, therefore, strongly recommend that future analyses include cerebellar regions to further investigate their role in smooth pursuit with structured background stimuli.

In contrast to our hypotheses, we did not obtain increased activation in prefrontal cortex in the background versus no background conditions as could have been expected based on previous literature (Bucher et al., 1997; Schmid et al., 2001; Wager et al., 2005). Thus, while pursuit over structured backgrounds draws on networks generally associated with oculomotor function and the control of attention, it does not appear to particularly rely on areas of higher cognitive control. However, it is possible that these higher cognitive areas are not consistently involved throughout the entire pursuit block, but only at certain points in time, for example, at pursuit initiation or when predictive or memory-related processes are more important (Ding et al., 2009; Kawawaki et al., 2006; Nagel et al., 2006; Schmid et al., 2001).

4.4 | Velocity effect

Interestingly, while the velocity effect was large at the behavioural level and could be observed in every single participant, neural effects were limited to the visual cortex and a small cluster in the left lateral FEF. The increased BOLD response in visual cortex is not only consistent with our hypothesis but also a very close replication of our own previous study with slower targets (0.2 and 0.4 Hz) in an even larger sample, in which, however, we did not observe increased FEF activity with faster targets (Schröder et al., 2020). In contrast to Nagel et al. (2008, 2012), we could not identify increased BOLD response with higher target velocities in other areas. However, there were significant differences in task design that might have led to the observed differences. Crucially, Nagel et al. (2008, 2012) presented short target ramps and a higher number of velocity conditions better fit to study the initiation of pursuit whereas our design was optimized to capture the neural mechanisms of continuous pursuit suggesting that the

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

contribution of different brain areas to pursuit of different velocities is time-dependent.

Higher BOLD response in visual areas might reflect differences in retinal input between the two conditions as higher target frequency was associated with lower gain and thus higher retinal image slip. The BOLD response in the lateral FEF cluster (also observed by Nagel et al., 2008; Nagel et al., 2012) could reflect higher demands on the motor output system in the higher velocity condition (Cieslik et al., 2016).

The only area with higher BOLD response during lower (vs. higher) target velocity was left temporal pole, an area that has been associated with mind wandering (Christoff et al., 2009).

4.5 | Task-based functional connectivity

Connectivity maps from the five seed regions (bilateral) showed widespread connectivity patterns, similar to those observed in a previous investigation from our group (Schröder et al., 2020). Strikingly, however, we could not delineate any differences in connectivity between the task conditions, that is, in the background versus no background or high versus low target velocity contrasts. While the latter matches our previous observation at target velocities of 0.2 and 0.4 Hz (Schröder et al., 2020), the former was surprising at first sight, given the large background effect in the traditional BOLD analyses and our a priori expectation that the increased demands in the background condition may be accompanied by enhanced connectivity. However, it should be noted that PPI analyses tend to have higher numbers of false negative results due to the high correlation of the PPI and task vectors (O'Reilly et al., 2012) which could have hindered the detection of significant differences.

4.6 | Brain-behaviour relationships

Correlations between BOLD response and the behavioural performance outcomes became nonsignificant after appropriately correcting for multiple testing. Due to their exploratory nature, the three correlations that were significant without correction are briefly discussed here. In the ROI-based analysis, there was a negative correlation between activity in left V5 and pursuit gain in the no background condition at 0.6 Hz indicating that poorer performance was associated with higher response in that area. This pattern of results is surprising and not in line with a prior study that found positive correlations between V5 activity and pursuit velocity (Nagel et al., 2006). A possible explanation of this finding is that participants with poorer performance rely more heavily on visual (vs. extraretinal) information. There was a positive correlation between BOLD response in left medial FEF and pursuit gain, which is also not in line with Nagel et al. (2006) who reported negative correlations between pursuit velocity and BOLD response in FEF. Our results highlight the importance of medial FEF for SPEM performance in the presence of structured backgrounds.

Furthermore, a positive correlation between catch-up saccade rate and BOLD response in right FEF (lateral FEF extending into medial FEF) was obtained at 0.6 Hz in the no background condition which means that higher BOLD response in that area was associated with more frequent catch-up saccades consistent with the involvement of lateral and medial FEF in the generation of both pursuit and saccades (Haller et al., 2008; Petit et al., 1997). Interestingly, however, Haller et al. (2008) did not obtain event-related BOLD response during SPEM related to corrective saccades. The discrepancy between our and their result may lie in the different target velocities applied and the different statistical design as we did not use an event-related design but focused on correlations between BOLD and overall rate of catch-up saccades. In addition, the positive association was only found in one of four conditions in our study in only one of multiple clusters, strongly calling for replication. In general, these results should be interpreted with caution, as they did not survive correction for multiple analyses. This is further supported by the fact that in another study with an even larger sample we did not find such correlations (Schröder et al., 2020). However, we strongly recommend to investigate how activity in the components of the oculomotor network relates to individual differences in SPEM performance in future studies appropriately powered for interindividual differences research.

4.7 | Limitations

The results presented in this study have to be interpreted in the light of some limitations. First, while we had sufficient statistical power to detect the expected background and velocity effects at the behavioural and neural levels, statistical power might have been too low to observe significant correlations between these two levels of measurement and to determine BOLD differences in terms of task-dependent functional connectivity (Dubois & Adolphs, 2016; O'Reilly et al., 2012). This criticism is supported by the fact that coactivations in the regression analyses were indeed evident at a more liberal threshold but did not survive FWE-correction. Second, while our study—along with others (Agtzidis et al., 2020)—can be seen as a first step towards studying smooth pursuit BOLD correlates of more complex visual scenes, the background stimuli we employed here were still artificial. Therefore, future studies should focus on more natural and dynamic scenes in order to broaden our understanding of how the smooth pursuit system works in more complex contexts with higher ecological validity (Goettker et al., 2020).

Third, we did not include a fixation control condition with structured background but without pursuit eye movements. Therefore, part of the activation differences between the background conditions can simply be attributed to different visual content. However, it should be noted that this cannot be the only source of differences in BOLD response, as other studies have shown activations unique to pursuit (Dieterich et al., 2009; Kimmig et al., 2008; Ohlendorf et al., 2010; Schraa-Tam et al., 2009). Fourth, we employed two relatively high target velocities, for example, as compared to Kimmig et al. (2008). Adding further and slower velocities might have been useful to explore the

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

BOLD correlates of SPEM velocity effects in even more detail. However, we carefully selected the 0.4 Hz and 0.6 Hz velocities employed here based on the magnitudes of effects and good to excellent reliabilities in our own previous investigation (Schröder et al., 2021).

Fifth, we did not account for individual differences in anatomical location of the LGN in every participant. Therefore, analyses with seed regions in this area should be interpreted with caution as we cannot ultimately dismiss the possibility that we did not hit the targeted brain area. Future studies could use a localizer task to inform decisions on seed region centre coordinates.

Lastly, we cannot ultimately rule out that part of the BOLD response during the pursuit task was accounted for by saccades. Crucially, however, saccadic frequency only correlated with BOLD response in one ROI (right lateral FEF extending into medial FEF) in one of four conditions. In addition, saccadic frequency did not predict BOLD response in our regression analyses, and in an elaborate study that independently modelled pursuit blocks and corrective saccades, no saccade-specific activation could be obtained (Haller et al., 2008).

5 | CONCLUSION

In this preregistered study, we identified distinct BOLD correlates of behaviourally robust background and velocity effects in SPEMs. Despite greater performance deterioration with increased target velocity, BOLD response for this contrast was limited to visual cortex and lateral FEF. Conversely, pursuit over a structured background was associated with a distributed visuo-fronto-parietal network of perceptual, oculomotor, and attentional brain regions. To our knowledge, this is the first study to propose distinct functions of medial and lateral FEF in smooth pursuit and we strongly recommend further investigation of functional specialisation of these regions in the future.

ACKNOWLEDGMENTS

We would like to thank Luise Thönes and Paulina Quint for their invaluable help in organizing the study and data collection. In addition, we would like to thank the Core Facility Human 3 T MRI of the Medical Faculty at the University of Bonn for providing support and instrumentation funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The eye-tracking data that support the findings of this study are openly available at the Open Science Framework (OSF) at https://osf.io/uez5f. The MRI data that support the findings of this study are available on request from the corresponding author. The MRI data are not publicly available due to privacy and ethical restrictions.

ORCID

Rebekka Schröder https://orcid.org/0000-0002-0206-4484

REFERENCES

Ackenheil, M., Stotz-Ingenlath, G., Dietz-Bauer, R., & Vossen, A. (1999). *MINI Mini international neuropsychiatric interview, German version 5.0.0 DSM IV*. Psychiatrische Universitätsklinik München.

Agtzidis, I., Meyhöfer, I., Dorr, M., & Lencer, R. (2020). Following Forrest Gump: Smooth pursuit related brain activation during free movie viewing. *NeuroImage*, *216*, 116491. https://doi.org/10.1016/j.neuroimage.2019.116491

Allen M., Poggiali D., Whitaker K., Marshall T. R., Kievit R. (2018). Raincloud plots: A multi-platform tool for robust data visualization.

Allen, M., Poggiali, D., Whitaker, K., Marshall, T. R., van Langen, J., & Kievit, R. A. (2019). Raincloud plots: A multi-platform tool for robust data visualization. *Wellcome Open Research*, *4*, 63. https://doi.org/10.12688/wellcomeopenres.15191.2

Barnes, G. R. (2008). Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition*, *68*, 309–326. https://doi.org/10.1016/j.bandc.2008.08.020

Barnes, G. R., & Crombie, J. W. (1985). The interaction of conflicting retinal motion stimuli in oculomotor control. *Experimental Brain Research*, *59*, 548–558. https://doi.org/10.1007/BF00261346

Baumann, O., & Greenlee, M. W. (2009). Effects of attention to auditory motion on cortical activations during smooth pursuit eye tracking. *PLoS One*, *4*, e7110. https://doi.org/10.1371/journal.pone.0007110

Berman, R. A., Colby, C. L., Genovese, C. R., Voyvodic, J. T., Luna, B., Thulborn, K. R., & Sweeney, J. A. (1999). Cortical networks subserving pursuit and saccadic eye movements in humans: An FMRI study. *Human Brain Mapping*, *8*, 209–225. https://doi.org/10.1002/(sici)1097-0193(1999)8:4<209:aid-hbm5>3.0.co;2-0

Bode, S., Murawski, C., Soon, C. S., Bode, P., Stahl, J., & Smith, P. L. (2014). Demystifying "free will": The role of contextual information and evidence accumulation for predictive brain activity. *Neuroscience and Biobehavioral Reviews*, *47*, 636–645. https://doi.org/10.1016/j.neubiorev.2014.10.017

Brett, M., Anton, J.-L., Valabreque, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox. Presented at the eighth International Conference on Functional Mapping of the Human Brain, June 2-6, Sendai, Japan. Available on CD-ROM in NeuroImage, 16, 2.

Bucher, S. F., Dieterich, M., Seelos, K. C., & Brandt, T. (1997). Sensorimotor cerebral activation during optokinetic nystagmus. *Neurology*, *49*, 1370–1377. https://doi.org/10.1212/WNL.49.5.1370

Buizza, A., & Schmid, R. (1986). Velocity characteristics of smooth pursuit eye movements to different patterns of target motion. *Experimental Brain Research*, *63*, 395–401. https://doi.org/10.1007/BF00236858

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 8719–8724. https://doi.org/10.1073/pnas.0900234106

Cieslik, E. C., Seidler, I., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2016). Different involvement of subregions within dorsal premotor and medial frontal cortex for pro- and antisaccades. *Neuroscience and Biobehavioral Reviews*, *68*, 256–269. https://doi.org/10.1016/j.neubiorev.2016.05.012

Coiner, B., Pan, H., Bennett, M. L., Bodien, Y. G., Iyer, S., O'Neil-Pirozzi, T. M., Leung, L., Giacino, J. T., & Stern, E. (2019). Functional neuroanatomy of the human eye movement network: A review and atlas. *Brain Structure & Function*, *224*, 2603–2617. https://doi.org/10.1007/s00429-019-01932-7

Collewijn, H., & Tamminga, E. P. (1984). Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *Journal of Physiology (London)*, *351*, 217–250. https://doi.org/10.1113/jphysiol.1984.sp015242

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., Linenweber, M. R., Petersen, S. E., Raichle, M. E., van Essen, D. C., & Shulman, G. L. (1998). A common network of functional

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

areas for attention and eye movements. *Neuron*, *21*, 761–773. https://doi.org/10.1016/S0896-6273(00)80593-0

Corbetta, M., Miezin, F. M., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *The Journal of Neuroscience*, *13*, 1202–1226. https://doi.org/10.1523/JNEUROSCI.13-03-01202.1993

Corbetta, M., Shulman, G. L., Miezin, F. M., & Petersen, S. E. (1995). Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science*, *270*, 802–805. https://doi.org/10.1126/science.270.5237.802

Culham, J. C., Brandt, S. A., Cavanagh, P., Kanwisher, N. G., Dale, A. M., & Tootell, R. B. (1998). Cortical fMRI activation produced by attentive tracking of moving targets. *Journal of Neurophysiology*, *80*, 2657–2670. https://doi.org/10.1152/jn.1998.80.5.2657

Dieterich, M., Bense, S., Stephan, T., Yousry, T. A., & Brandt, T. (2003). fMRI signal increases and decreases in cortical areas during small-field optokinetic stimulation and central fixation. *Experimental Brain Research*, *148*, 117–127. https://doi.org/10.1007/s00221-002-1267-6

Dieterich, M., Muller-Schunk, S., Stephan, T., Bense, S., Seelos, K., & Yousry, T. A. (2009). Functional magnetic resonance imaging activations of cortical eye fields during saccades, smooth pursuit, and optokinetic nystagmus. *Annals of the New York Academy of Sciences*, *1164*, 282–292. https://doi.org/10.1111/j.1749-6632.2008.03718.x

Ding, J., Powell, D., & Jiang, Y. (2009). Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. *Human Brain Mapping*, *30*, 3541–3552. https://doi.org/10.1002/hbm.20777

Drew, A. S., & van Donkelaar, P. (2007). The contribution of the human FEF and SEF to smooth pursuit initiation. *Cerebral Cortex*, *17*, 2618–2624. https://doi.org/10.1093/cercor/bhl169

Dubois, J., & Adolphs, R. (2016). Building a science of individual differences from fMRI. *Trends in Cognitive Sciences*, *20*, 425–443. https://doi.org/10.1016/j.tics.2016.03.014

Eggert, T., Ladda, J., & Straube, A. (2009). Inferring the future target trajectory from visual context: Is visual background structure used for anticipatory smooth pursuit? *Experimental Brain Research*, *196*, 205–215. https://doi.org/10.1007/s00221-009-1840-3

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, *25*, 1325–1335. https://doi.org/10.1016/j.neuroimage.2004.12.034

Ettinger, U., Ffytche, D. H., Kumari, V., Kathmann, N., Reuter, B., Zelaya, F., & Williams, S. C. R. (2008). Decomposing the neural correlates of Antisaccade eye movements using event-related fMRI. *Cerebral Cortex*, *18*, 1148–1159. https://doi.org/10.1093/cercor/bhm147

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175–191. https://doi.org/10.3758/bf03193146

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, *6*, 218–229. https://doi.org/10.1006/nimg.1997.0291

Gagnon, D., Paus, T., Grosbras, M.-H., Pike, G. B., & O'Driscoll, G. A. (2006). Transcranial magnetic stimulation of frontal oculomotor regions during smooth pursuit. *The Journal of Neuroscience*, *26*, 458–466. https://doi.org/10.1523/JNEUROSCI.2789-05.2006

Goettker, A., Agtzidis, I., Braun, D. I., Dorr, M., & Gegenfurtner, K. R. (2020). From Gaussian blobs to naturalistic videos: Comparison of oculomotor behavior across different stimulus complexities. *Journal of Vision*, *20*, 1–16. https://doi.org/10.1167/jov.20.8.26

Grosbras, M. H., Leonards, U., Lobel, E., Poline, J. B., LeBihan, D., & Berthoz, A. (2001). Human cortical networks for new and familiar sequences of saccades. *Cerebral Cortex*, *11*, 936–945. https://doi.org/10.1093/cercor/11.10.936

Haarmeier, T., & Kammer, T. (2010). Effect of TMS on oculomotor behavior but not perceptual stability during smooth pursuit eye movements. *Cerebral Cortex*, *20*, 2234–2243. https://doi.org/10.1093/cercor/bhp285

Haller, S., Fasler, D., Ohlendorf, S., Radue, E. W., & Greenlee, M. W. (2008). Neural activation associated with corrective saccades during tasks with fixation, pursuit and saccades. *Experimental Brain Research*, *184*, 83–94. https://doi.org/10.1007/s00221-007-1077-y

Harrell F. E. (2020). Hmisc: Harrell Miscellaneous. https://CRAN.R-project.org/package=Hmisc

Hutton, S. B., Crawford, T. J., Kennard, C., Barnes, T. R., & Joyce, E. M. (2000). Smooth pursuit eye tracking over a structured background in first-episode schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience*, *250*, 221–225. https://doi.org/10.1007/s004060070011

Jin, Z., Gou, R., Zhang, J., & Li, L. (2021). The role of frontal pursuit area in interaction between smooth pursuit eye movements and attention: A TMS study. *Journal of Vision*, *21*, 11. https://doi.org/10.1167/jov.21.3.11

Kastner, S., Schneider, K. A., & Wunderlich, K. (2006). Chapter 8 beyond a relay nucleus: Neuroimaging views on the human LGN. In S. Martinez-Conde, S. Macknik, & M. M. Martinez (Eds.), *Visual perception part 2: Fundamentals of awareness, multi-sensory integration and high-order perception* (Vol. 155, 1st ed., pp. 125–143). Elsevier textbooks, s.l..

Kaufman, S. R., & Abel, L. A. (1986). The effects of distraction on smooth pursuit in normal subjects. *Acta Oto-Laryngologica*, *102*, 57–64. https://doi.org/10.3109/00016488609108647

Kawawaki, D., Shibata, T., Goda, N., Doya, K., & Kawato, M. (2006). Anterior and superior lateral occipito-temporal cortex responsible for target motion prediction during overt and covert visual pursuit. *Neuroscience Research*, *54*, 112–123. https://doi.org/10.1016/j.neures.2005.10.015

Kimmig, H., Ohlendorf, S., Speck, O., Sprenger, A., Rutschmann, R. M., Haller, S., & Greenlee, M. W. (2008). fMRI evidence for sensorimotor transformations in human cortex during smooth pursuit eye movements. *Neuropsychologia*, *46*, 2203–2213. https://doi.org/10.1016/j.neuropsychologia.2008.02.021

Koch, I., Ruge, H., Brass, M., Rubin, O., Meiran, N., & Prinz, W. (2003). Equivalence of cognitive processes in brain imaging and behavioral studies: Evidence from task switching. *NeuroImage*, *20*, 572–577. https://doi.org/10.1016/S1053-8119(03)00206-4

Konen, C. S., & Kastner, S. (2008). Representation of eye movements and stimulus motion in topographically organized areas of human posterior parietal cortex. *The Journal of Neuroscience*, *28*, 8361–8375. https://doi.org/10.1523/JNEUROSCI.1930-08.2008

Konen, C. S., Kleiser, R., Seitz, R. J., & Bremmer, F. (2005). An fMRI study of optokinetic nystagmus and smooth-pursuit eye movements in humans. *Experimental Brain Research*, *165*, 203–216. https://doi.org/10.1007/s00221-005-2289-7

Kreyenmeier, P., Fooken, J., & Spering, M. (2017). Context effects on smooth pursuit and manual interception of a disappearing target. *Journal of Neurophysiology*, *118*, 404–415. https://doi.org/10.1152/jn.00217.2017

Ladda, J., Eggert, T., Glasauer, S., & Straube, A. (2007). Velocity scaling of cue-induced smooth pursuit acceleration obeys constraints of natural motion. *Experimental Brain Research*, *182*, 343–356. https://doi.org/10.1007/s00221-007-0988-y

Lawden, M. C., Bagelmann, H., Crawford, T. J., Matthews, T. D., & Kennard, C. (1995). An effect of structured backgrounds on smooth pursuit eye movements in patients with cerebral lesions. *Brain*, *118*, 37–48. https://doi.org/10.1093/brain/118.1.37

Lawrence M. A. (2016). Ez: Easy analysis and visualization of factorial experiments. https://CRAN.R-project.org/package=ez

Lee, K.-M., Wade, A. R., & Lee, B.-T. (2006). Differential correlation of frontal and parietal activity with the number of alternatives for cued choice saccades. *NeuroImage*, *33*, 307–315. https://doi.org/10.1016/j.neuroimage.2006.06.039

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Leigh, R. J., & Zee, D. S. (2015). *The neurology of eye movements* (5th ed.). Oxford University Press.

Lencer, R., Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Heide, W., & Binkofski, F. (2004). Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *European Journal of Neuroscience*, *19*, 1430–1436. https://doi.org/10.1111/j.1460-9568.2004.03229.x

Lencer, R., & Trillenberg, P. (2008). Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition*, *68*, 219–228. https://doi.org/10.1016/j.bandc.2008.08.013

Levy, D. L., Sereno, A. B., Gooding, D. C., & O'Driscoll, G. A. (2010). Eye tracking dysfunction in schizophrenia: Characterization and pathophysiology. *Current Topics in Behavioral Neurosciences*, *4*, 311–347.

Li, M., He, H. G., Shi, W., Li, J., Lv, B., Wang, C. H., Miao, Q. W., Wang, Z. C., Wang, N. L., Walter, M., & Sabel, B. A. (2012). Quantification of the human lateral geniculate nucleus in vivo using MR imaging based on morphometry: Volume loss with age. *AJNR. American Journal of Neuroradiology*, *33*, 915–921. https://doi.org/10.3174/ajnr.A2884

Lindner, A., Haarmeier, T., Erb, M., Grodd, W., & Thier, P. (2006). Cerebrocerebellar circuits for the perceptual cancellation of eye-movement-induced retinal image motion. *Journal of Cognitive Neuroscience*, *18*, 1899–1912. https://doi.org/10.1162/jocn.2006.18.11.1899

Lindner, A., & Ilg, U. J. (2006). Suppression of optokinesis during smooth pursuit eye movements revisited: The role of extra-retinal information. *Vision Research*, *46*, 761–767. https://doi.org/10.1016/j.visres.2005.09.033

Lindner, A., Schwarz, U., & Ilg, U. J. (2001). Cancellation of self-induced retinal image motion during smooth pursuit eye movements. *Vision Research*, *41*, 1685–1694. https://doi.org/10.1016/S0042-6989(01)00050-5

Lisberger, S. G., Evinger, C., Johanson, G. W., & Fuchs, A. F. (1981). Relationship between eye acceleration and retinal image velocity during foveal smooth pursuit in man and monkey. *Journal of Neurophysiology*, *46*, 229–249. https://doi.org/10.1152/jn.1981.46.2.229

Masson, G., Proteau, L., & Mestre, D. R. (1995). Effects of stationary and moving textured backgrounds on the visuo-oculo-manual tracking in humans. *Vision Research*, *35*, 837–852. https://doi.org/10.1016/0042-6989(94)00185-O

McDowell, J. E., Dyckman, K. A., Austin, B. P., & Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. *Brain and Cognition*, *68*, 255–270. https://doi.org/10.1016/j.bandc.2008.08.016

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *NeuroImage*, *61*, 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Meyhöfer, I., Kasparbauer, A.-M., Steffens, M., & Ettinger, U. (2019). Effects of nicotine on smooth pursuit eye movements in healthy nonsmokers. *Psychopharmacology*, *236*, 2259–2271. https://doi.org/10.1007/s00213-019-05223-1

Nagel, M., Sprenger, A., Hohagen, F., Binkofski, F., & Lencer, R. (2008). Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *NeuroImage*, *41*, 483–492. https://doi.org/10.1016/j.neuroimage.2008.02.058

Nagel, M., Sprenger, A., Steinlechner, S., Binkofski, F., & Lencer, R. (2012). Altered velocity processing in schizophrenia during pursuit eye tracking. *PLoS One*, *7*, e38494. https://doi.org/10.1371/journal.pone.0038494

Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Kompf, D., Heide, W., Binkofski, F., & Lencer, R. (2006). Parametric modulation of cortical activation during smooth pursuit with and without target blanking. An fMRI study. *NeuroImage*, *29*, 1319–1325. https://doi.org/10.1016/j.neuroimage.2005.08.050

Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain*, *120*(Pt 3), 515–533. https://doi.org/10.1093/brain/120.3.515

Nuding, U., Kalla, R., Muggleton, N. G., Büttner, U., Walsh, V., & Glasauer, S. (2009). TMS evidence for smooth pursuit gain control by the frontal eye fields. *Cerebral Cortex*, *19*, 1144–1150. https://doi.org/10.1093/cercor/bhn162

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E. J., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: Psychophysiological interactions and functional connectivity. *Social Cognitive and Affective Neuroscience*, *7*, 604–609. https://doi.org/10.1093/scan/nss055

Ohlendorf, S., Kimmig, H., Glauche, V., & Haller, S. (2007). Gaze pursuit, 'attention pursuit' and their effects on cortical activations. *The European Journal of Neuroscience*, *26*, 2096–2108. https://doi.org/10.1111/j.1460-9568.2007.05824.x

Ohlendorf, S., Sprenger, A., Speck, O., Glauche, V., Haller, S., & Kimmig, H. (2010). Visual motion, eye motion, and relative motion: A parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. *Journal of Vision*, *10*, 21. https://doi.org/10.1167/10.14.21

Petit, L., Clark, V. P., Ingeholm, J., & Haxby, J. V. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *Journal of Neurophysiology*, *77*, 3386–3390. https://doi.org/10.1152/jn.1997.77.6.3386

Petit, L., & Haxby, J. V. (1999). Functional anatomy of pursuit eye movements in humans as revealed by fMRI. *Journal of Neurophysiology*, *82*, 463–471. https://doi.org/10.1152/jn.1999.82.1.463

Ruge, H., Jamadar, S., Zimmermann, U., & Karayanidis, F. (2013). The many faces of preparatory control in task switching: Reviewing a decade of fMRI research. *Human Brain Mapping*, *34*, 12–35. https://doi.org/10.1002/hbm.21420

Schmid, A., Rees, G., Frith, C., & Barnes, G. R. (2001). An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport*, *12*, 1409–1414. https://doi.org/10.1097/00001756-200105250-00023

Schraa-Tam, C. K. L., van der Lugt, A., Smits, M., Frens, M. A., van Broekhoven, P. C. A., & van der Geest, J. N. (2009). Differences between smooth pursuit and optokinetic eye movements using limited lifetime dot stimulation: A functional magnetic resonance imaging study. *Clinical Physiology and Functional Imaging*, *29*, 245–254. https://doi.org/10.1111/j.1475-097X.2009.00858.x

Schröder, R., Baumert, P. M., & Ettinger, U. (2021). Replicability and reliability of the background and target velocity effects in smooth pursuit eye movements. *Acta Psychologica*, *219*, 103364. https://doi.org/10.1016/j.actpsy.2021.103364

Schröder, R., Kasparbauer, A.-M., Meyhöfer, I., Steffens, M., Trautner, P., & Ettinger, U. (2020). Functional connectivity during smooth pursuit eye movements. *Journal of Neurophysiology*, *124*, 1839–1856. https://doi.org/10.1152/jn.00317.2020

Schröder, R., Reuter, M., Faßbender, K., Plieger, T., Poulsen, J., Lui, S. S. Y., Chan, R. C. K., & Ettinger, U. (2022). The role of the SLC6A3 3' UTR VNTR in nicotine effects on cognitive, affective, and motor function. *Psychopharmacology*, *239*, 489–507. https://doi.org/10.1007/s00213-021-06028-x

Seghier, M. L. (2013). The angular gyrus: Multiple functions and multiple subdivisions. *The Neuroscientist*, *19*, 43–61. https://doi.org/10.1177/1073858412440596

Silberg, J. E., Agtzidis, I., Startsev, M., Fasshauer, T., Silling, K., Sprenger, A., Dorr, M., & Lencer, R. (2019). Free visual exploration of natural movies in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *269*, 407–418. https://doi.org/10.1007/s00406-017-0863-1

Simó, L. S., Krisky, C. M., & Sweeney, J. A. (2005). Functional neuroanatomy of anticipatory behavior: Dissociation between sensory-driven and memory-driven systems. *Cerebral Cortex*, *15*, 1982–1991. https://doi.org/10.1093/cercor/bhi073

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Smyrnis, N. (2008). Metric issues in the study of eye movements in psychiatry. *Brain and Cognition*, *68*, 341–358. https://doi.org/10.1016/j.bandc.2008.08.022

Tanabe, J. L., Tregellas, J., Miller, D., Ross, R. G., & Freedman, R. (2002). Brain activation during smooth-pursuit eye movements. *NeuroImage*, *17*, 1315–1324. https://doi.org/10.1006/nimg.2002.1263

Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuo-spatial attention. *Nature Neuroscience*, *14*, 1245–1246. https://doi.org/10.1038/nn.2905

Tikhonov, A., Haarmeier, T., Thier, P., Braun, C., & Lutzenberger, W. (2004). Neuromagnetic activity in medial parietooccipital cortex reflects the perception of visual motion during eye movements. *NeuroImage*, *21*, 593–600. https://doi.org/10.1016/j.neuroimage.2003.09.045

Trenner, M. U., Fahle, M., Fasold, O., Heekeren, H. R., Villringer, A., & Wenzel, R. (2008). Human cortical areas involved in sustaining perceptual stability during smooth pursuit eye movements. *Human Brain Mapping*, *29*, 300–311. https://doi.org/10.1002/hbm.20387

Vernet, M., Quentin, R., Chanes, L., Mitsumasu, A., & Valero-Cabré, A. (2014). Frontal eye field, where art thou? Anatomy, function, and non-invasive manipulation of frontal regions involved in eye movements and associated cognitive operations. *Frontiers in Integrative Neuroscience*, *8*, 66. https://doi.org/10.3389/fnint.2014.00066

Wager, T. D., Sylvester, C.-Y. C., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *NeuroImage*, *27*, 323–340. https://doi.org/10.1016/j.neuroimage.2005.01.054

Zeki, S. (2015). Area V5-a microcosm of the visual brain. *Frontiers in Integrative Neuroscience*, *9*, 21. https://doi.org/10.3389/fnint.2015.00021

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schröder, R., Keidel, K., Trautner, P., Radbruch, A., & Ettinger, U. (2022). Neural mechanisms of background and velocity effects in smooth pursuit eye movements. *Human Brain Mapping*, 1–17. https://doi.org/10.1002/hbm.26127

10970193, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/hbm.26127 by Cochrane Germany, Wiley Online Library on [04/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Appendix E | Study V

Schröder, R., Faiola, E., Urquijo, M. F., Bey, K., Meyhöfer, I., Steffens, M., Kasparbauer, A. M., Ruef, A., Högenauer, H., Hurlemann, R., Kambeitz, J., Philipsen, A., Wagner, M., Koutsouleris, N., & Ettinger, U. (2022). Neural correlates of smooth pursuit eye movements in schizotypy and recent onset psychosis: A multivariate pattern classification approach. *Schizophrenia Bulletin Open*, *3*(1), 1–13. https://doi.org/10.1093/schizbullopen/sgac034

Licensed under CC BY-NC 4.0.

Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgac034

Neural Correlates of Smooth Pursuit Eye Movements in Schizotypy and Recent Onset Psychosis: A Multivariate Pattern Classification Approach

Rebekka Schröder[1], Eliana Faiola[1], Maria Fernanda Urquijo[2], Katharina Bey[3], Inga Meyhöfer[1], Maria Steffens[1], Anna-Maria Kasparbauer[1], Anne Ruef[2], Hanna Högenauer[3], René Hurlemann[4,5], Joseph Kambeitz[6], Alexandra Philipsen[3], Michael Wagner[3], Nikolaos Koutsouleris[2], and Ulrich Ettinger[1,*]

[1]Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, 53111, Bonn, Germany; [2]Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University of Munich, Nußbaumstr. 7, 80336, Munich, Germany; [3]Department of Psychiatry and Psychotherapy, University of Bonn, Sigmund-Freud-Str. 25, 53127, Bonn, Germany; [4]Department of Psychiatry, University of Oldenburg Medical Campus, Hermann-Ehlers-Str. 7, 26160, Bad Zwischenahn, Germany; [5]Department of Psychiatry and Division of Medical Psychology, University Hospital Bonn, Venusberg-Campus 1, 53127, Bonn, Germany; [6]Department of Psychiatry and Psychotherapy, University of Cologne, Faculty of Medicine and University Hospital Cologne, Kerpener Str. 62, 50931, Cologne, Germany

*To whom correspondence should be addressed: Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, 53111 Bonn, Germany, tel: +49 228 734208, fax: +49 228 7362323, e-mail: ulrich.ettinger@uni-bonn.de

Schizotypy refers to a set of personality traits that bear resemblance, at subclinical level, to psychosis. Despite evidence of similarity at multiple levels of analysis, direct comparisons of schizotypy and clinical psychotic disorders are rare. Therefore, we used functional magnetic resonance imaging (fMRI) to examine the neural correlates and task-based functional connectivity (psychophysiological interactions; PPI) of smooth pursuit eye movements (SPEM) in patients with recent onset psychosis (ROP; *n* = 34), participants with high levels of negative (HNS; *n* = 46) or positive (HPS; *n* = 41) schizotypal traits, and low-schizotypy control participants (LS; *n* = 61) using machine-learning. Despite strong previous evidence that SPEM is a highly reliable marker of psychosis, patients and controls could not be significantly distinguished based on SPEM performance or blood oxygen level dependent (BOLD) signal during SPEM. Classification was, however, significant for the right frontal eye field (FEF) seed region in the PPI analyses but not for seed regions in other key areas of the SPEM network. Applying the right FEF classifier to the schizotypal samples yielded decision scores between the LS and ROP groups, suggesting similarities and dissimilarities of the HNS and HPS samples with the LS and ROP groups. The very small difference between groups is inconsistent with previous studies that showed significant differences between patients with ROP and controls in both SPEM performance and underlying neural mechanisms with large effect sizes. As the current study had sufficient power to detect such differences, other reasons are discussed.

Key words: machine-learning, schizophrenia spectrum, eye movements, functional magnetic resonance imaging

Introduction

Schizotypy refers to a set of personality traits that resemble the symptoms of psychosis in an attenuated, subclinical form.[1] Similarities of schizotypy with psychosis include cognitive deficits, morphological and functional neural correlates and environmental risk factors.[1–5] Despite these similarities, [1–14] transition rates from schizotypy to psychosis are low.[15,16] This may suggest that although persons with high schizotypy carry risk for psychosis, protective mechanisms operate which lower the risk of transition.[17–19] Alternatively, high schizotypy may result from insufficiency of risk factors for psychosis (despite higher risk than in low-schizotypy).[16,20] These theoretical issues aside, there should not only be similarities, but also dissimilarities between schizotypy and psychotic disorders. Several such differences have been reported. Contradictory to findings of volume reductions in schizophrenia,[10,21–25] schizotypy is associated with increased cortical thickness in frontal lobe[12] and volume in cingulate cortex.[26,27] Additionally, positive schizotypy is also associated with beneficial characteristics, such as enhanced creativity.[28,29]

However, studies directly comparing people with high levels of schizotypy and patients with psychotic disorders are scant,[30] although this is essential to detect

© The Author(s) 2022. Published by Oxford University Press on behalf of the University of Maryland's school of medicine, Maryland Psychiatric Research Center.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

both similarities and differences.[3,19] The present study, therefore, compared positive and negative schizotypal individuals to patients with recent onset psychosis and low-schizotypy controls in one of the most robust biomarkers of psychosis, smooth pursuit eye movements (SPEM).[31–33] Whilst persons with high schizotypy have been reported to show impaired SPEM,[34–40] differences to psychotic patients have also been detected in indirect comparisons. For example, the neural correlates of SPEM in schizotypy and schizophrenia show only partial overlap. Whilst both persons with high schizotypy and patients exhibit reduced activity in visual areas (e.g., occipital cortex),[36,41–44] reductions in frontal areas (e.g., frontal eye fields) found in schizophrenia[41,42,44] have not been observed in schizotypy.[36] However, no direct comparison between schizotypal individuals and schizophrenia patients is available.

Importantly, previous studies have found not only altered brain structure and function in schizophrenia,[10,21–25,41–44] but also aberrant brain connectivity,[45–48] a finding that has also been demonstrated in persons with high schizotypy.[49–55] However, it has not previously been investigated whether functional connectivity during SPEM is altered in schizophrenia or schizotypy.

A final issue addressed here is that previous fMRI studies of SPEM have relied on univariate analyses.[36,41–44] However, classical fMRI analyses involve between-group overlap (i.e., despite brain activation differences between two groups, they show substantial overlap at certain voxels, reducing the likelihood of detecting the differences [56,57]), a problem addressed by multivariate machine-learning analyses [57,58]: instead of focusing on between-group differences regarding certain voxels, machine-learning allows to predict whether a participant belongs to group A (e.g., controls) or group B (e.g., patients) based on activity or connectivity patterns.[57,59] Moreover, the likelihood of a third group (e.g., persons with high schizotypy) being identified as controls or patients can be examined. Machine-learning has been shown to separate patients with a psychotic disorder and controls with high accuracy[58,60–63] and is sensitive to effects of schizotypy.[64,65]

We hypothesized that patients and controls would be differentiated with significant accuracy.[31,58,60–62] The strongest contribution to this differentiation was expected from brain regions known to underlie SPEM[66] or its dysfunction in schizophrenia.[43,44,67] Additionally, we explored whether persons with high schizotypy would be classified more as controls or as patients. We distinguished between persons with high schizotypy with primarily positive or negative schizotypal traits to explore potential differences regarding the classification. As SPEM deficits in schizotypy are less pronounced than in schizophrenia,[35,39,40] and activity reductions during SPEM in schizotypy show only partial overlap with those in schizophrenia,[36] persons with high schizotypy might be classified between patients and controls. Certain brain regions (e.g., occipital cortex[36]) might contribute to proximity of persons with high schizotypy and patients with ROP, while other areas (e.g., frontal eye fields[36]) might lead to higher classification of persons scoring high on schizotypy to the control group.

Methods

Recruitment and Selection of Participants

Participants for both schizotypy groups and the low-schizotypy control group were recruited from the general population through an online version of the Oxford-Liverpool Inventory of Feelings and Experiences short (O-LIFE, German version[68]), advertised via flyers and social media. Cut-offs for group assignment were based on an O-LIFE database of $n = 5006$[1]. Assignment to the positive schizotypy group (HPS) required a score ≥ 1.25 SD above the same sex mean on the unusual experiences (UE) and ≤ 0.5 SD below the same sex mean on the Introvertive Anhedonia (IA) scale, and vice versa for the negative schizotypy group (HNS), as described previously.[40] Participants were assigned to the low-schizotypy control group (LS) if they scored ≤ 0.5 SD below the same sex mean on both UE and IA scales. Participants who met these criteria were invited to a telephone screening in order to discuss exclusion criteria (see below for details).

Patients with recent onset psychosis (ROP) were recruited from in-patient and out-patient services. They were included in the study if they had i) a diagnosis of a psychotic disorder according to DSM-IV or ICD-10 criteria (F20, F22, F23, F25, F29) for a maximum of three years, with no more than one psychotic episode in the past, as determined by a medical doctor, and ii) a score of 6 on at least one of the P1–P5 items of the Structural Interview of Prodromal Symptoms (SIPS[69]). Moreover, patients were screened for exclusion criteria listed below.

The study was approved by the ethics committees of the Faculty of Medicine, University of Bonn, and the Faculty of Medicine, University of Munich. Participants provided written informed consent and were financially rewarded.

Exclusion criteria for all participants were age < 18 and > 40, insufficient knowledge of German, any neurological disorder, visual impairments (except for glasses/lenses) or eye surgery, MRI exclusion criteria such as pregnancy, claustrophobia and the presence of metal in the body, traumatic brain injury with loss of consciousness for more than five minutes, systemic disease involving the central nervous system, and a positive result in an alcohol (ACE AL5500) or drug screening (DrugScreen Multi 5T, nal von minden GmbH) during the time of the assessment.

Additional exclusion criteria for the schizotypy and control groups were having a first-degree relative with a psychotic disorder, regular medication intake except for contraceptives or thyroid medication, and any

[1]https://osf.io/bfxmt/

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

present Axis I disorder or past or present psychotic disorder (MINI International Neuropsychiatric Interview German Version 5.0.0[70]). In addition, participants with clinical high-risk for psychosis criteria according to the SIPS[69] were excluded. Additional exclusion criteria for patients were acute or chronic organic brain syndromes such as dementia or delirium, bipolar disorder, and unipolar depression with psychotic symptoms.

Study Procedure

Schizotypal and control participants first completed the O-LIFE and were then contacted via telephone for an informal briefing on the study, and then screened via telephone or in a personal meeting. For all groups, this initial screening was followed by two study sessions at intervals of no more than 1 month.

Participants were instructed not to drink alcohol starting one day before the study session, not to consume any caffeine 2 h before the session, and to get normal sleep the night before the session. The first study session included i) a screening for current alcohol and drug consumption, ii) SIPS and the Schizophrenia Proneness Instrument, Adult Version (SPI-A[71]), iii) a neuropsychological test battery, and iv) the *vocabulary* and *matrices* subtests of the WAIS-III as a measure of intelligence.[72] The second study session included i) a screening for current alcohol and drug consumption, and ii) an MRI measurement including a structural scan and two fMRI scans with concurrent oculographic measurement of SPEM and antisaccades. In addition, participants filled out several questionnaires as an online version from home.

SPEM Task. The SPEM task was programmed in ExperimentBuilder (SR Research Ltd., Ontario, Canada). Participants viewed a 32-inch MRI-compatible TFT LCD monitor (NordicNeuroLab, Bergen, Norway; resolution: 1024 × 768 pixels, refresh rate: 120 Hz) via a first-surface reflection mirror mounted on the head coil. They were instructed to follow a target with their eyes (SPEM blocks) and to fixate the target (fixation blocks) as accurately as possible whilst keeping the head still. The distance from participants' eyes to screen was 1600 mm. The target was a gray (RGB = 128,128,128) circle (diameter = 0.36°, stroke width = 0.11°) moving horizontally across the screen in front of a black (RGB = 0,0,0) background (figure 1). It moved horizontally in a sinusoidal pattern at low (0.2 Hz) and high velocity (0.4 Hz), and an excursion of ± 5.7° from the center. SPEM blocks (duration: 30 s each) alternated with fixation blocks (duration: 20 s each). During fixation blocks, the target was stationary in the center of the screen. In total, ten SPEM blocks (five each with low and high target frequencies) and ten fixation blocks were presented. A horizontal three-point calibration was carried out before the task. Movements of the right eye were recorded with an MRI-compatible video-based eye-tracker (EyeLink 1000, SR Research Ltd., Ontario, Canada; sampling rate 1000 Hz).

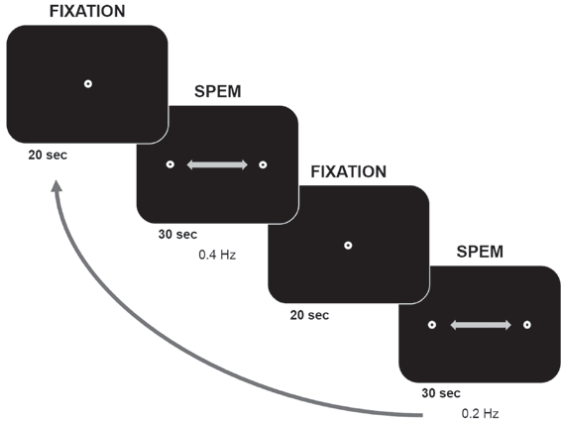

Fig. 1. Graphic representation of the fMRI SPEM task. 10 blocks of fixation (duration: 20 s each) alternate with 10 blocks of sinusoidal SPEM (5 blocks with a target velocity of 0.4 Hz, 5 blocks with a target velocity of 0.2 Hz; duration: 30 s each). During SPEM blocks, the target moves with an excursion of ± 5.7° from the center.

fMRI Data Acquisition. A Siemens 3 T Trio Scanner (Bonn) and a Philips Ingenia 3 T Scanner (Munich) were used. To reduce noise from the scanner, participants wore earplugs, and foam pads helped to minimize head movements. For radio frequency transmission and reception, both sites used a 32-channel head coil. First, a localizer scan was acquired to place the volume of interest. Then, a high-resolution structural scan for image co-registration and normalization was acquired, using the following parameters in Bonn (and in Munich): TR = 1600 ms, TE = 2.54 ms (5.53 ms), inversion time = 850 ms, flip angle = 9° (8°), FoV = 256 mm, matrix size = 320 × 320 (256 × 256), 160 slices (190 slices), slice thickness = 0.8 mm (1.0 mm), sequential slice-order with no inter-slice gap, and voxel size = 0.8 × 0.8 × 0.8 (0.9 × 0.9 × 0.9). During the SPEM task, at both sites, T2*-weighted MRI scans were collected with gradient-echo planar imaging sequences (TR = 2500 ms, TE = 30 ms, flip angle = 90°) that displayed the blood oxygenation level dependent (BOLD) response. Additional scan parameters were as follows: FoV = 192 mm; matrix size = 96 × 96; 37 slices; slice thickness = 3 mm; sequential slice-order with inter-slice gap of 0.3 mm; voxel size = 3 × 3 × 3. Slices were oriented parallel to the intercommissural plane (AC-PC line). 208 whole brain images were collected for each participant.

Data Processing

Behavioral Data. Data quality was first examined with DataViewer (SR Research Ltd., Ontario, Canada), before

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

being processed using scripts (See footnote 1) in Matlab (The Mathworks, Natick, MA), calculating SPEM parameters from eye position coordinates and time stamps in the raw data. Dependent variables were velocity gain (mean eye velocity relative to mean target velocity in %), root mean square error (RMSE, in degrees) and saccade frequency (N/s). SPEM variables were calculated for each of the frequencies (0.2 and 0.4 Hz) separately, excluding the first half-cycle of each block. Velocity gain was calculated for segments of pursuit in the middle 50% of each half-cycle, excluding blinks and saccades.[38] Saccadic frequency was calculated using amplitude (≥ 1°), acceleration (≥ 3800°/s^2) and velocity (≥ 30°/s) criteria. RMSE scores were calculated excluding blinks. A blink was identified automatically when the eye-tracker did not detect any eye position. Saccades occurring immediately before or after a blink were excluded for all SPEM parameter calculations.

fMRI Data. Data preprocessing and first-level analysis were performed using Statistical Parametric Mapping 12 (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/) running in MATLAB R2017a (The MathWorks, Natick, MA).

Data preprocessing included realignment of the images of each participant along the mean image in the time series to correct for head motion, using a least squares approach and a six-parameter rigid-body transformation. Additionally, images were unwarped to correct for image distortions due to magnetic field in homogeneities. Second, functional scans were co-registered to the T1-weighted anatomical image. Then, structural images were segmented in order to separate grey matter, white matter and cerebro-spinal fluid. The segmented images were used for normalization, in order to transform all images into standard space (Montreal Neurological Institute, MNI template) using 12-parameter affine linear transformation. Smoothing was applied using a Gaussian full-width-at-half-maximum filter of 8 mm.

First-level analyses were conducted to create, for each participant, a contrast for i) SPEM vs. Fixation blocks and ii) High Velocity vs. Low Velocity blocks (not thresholded). These contrasts were then used for pattern classification (see below). For first-level analysis, a general linear model was used, including a SPEM vector (all SPEM blocks) and a Velocity vector (0.2 Hz, 0.4 Hz). These vectors were contrasted against fixation. Six motion parameters entered the analysis as additional regressors. BOLD response was modelled as a canonical hemodynamic response-function. At the second level, each contrast was compared between-groups using one-way ANCOVA with site (Bonn, Munich) and sex (male, female) as covariates.

In addition, generalized psychophysiological interaction analyses[73,74] (gPPI) were performed to explore group differences in task-based functional connectivity of the pursuit network. Key areas of the pursuit network (LGN, V1, V5, posterior parietal cortex [PPC], frontal eye fields [FEF]) were selected as seed regions and seed coordinates were taken from a previous publication[75] (Supplementary table 1). To accommodate individual differences in the location of task activations and thus define individual seed spheres, first, for each region a 12 mm sphere was positioned around the coordinates derived from previous literature. Second, the largest individual task activation peak (omnibus-F-map, corrected at $P < .001$) within this sphere was identified and a smaller (4 mm sphere) was centered around these peak coordinates. For those participants, for whom no peak could be identified in the larger sphere, the 4 mm-sphere was centered around the literature-derived coordinates.

To determine the gPPI regressors, the first eigenvariate of the timeseries of all voxels within each individual sphere was extracted, deconvolved, multiplied with the task regressors and reconvolved with the HRF. Then, for each seed region, a GLM model was set up which included the psychophysiological interaction terms and the task and seed region timeseries vectors as regressors as well as the six motion vectors from the realignment preprocessing step as covariates of no interest. Two first-level contrasts were determined (PPI SPEM vs. fixation, PPI high velocity vs. low velocity SPEM) for each participant and each seed region, resulting in a total of 20 models per participant. These contrasts were taken to the second level for one-way ANCOVAs to analyze between-group differences with site and sex defined as covariates.

All fMRI results were family-wise error corrected (FWE, $P < .05$). Anatomical labels were obtained using the Anatomy Toolbox.[76]

Pattern Classification

Behavioral Data. To generate a classification model distinguishing between LS and ROP based on behavioral SPEM data, we established a machine-learning pipeline using NeuroMiner (http://www.proniapredictors.eu/neurominer/index.html). As behavioral data we used gain, saccade frequency and RMSE at each target velocity.

To first train the classification models and then evaluate their accuracy, we conducted a repeated nested cross-validation (CV[77,78]), with an inner CV cycle (CV1) to train and select optimally discriminative models, and an outer CV cycle (CV2) to validate the best models from CV1. Preprocessing of CV1 data included correction for effects of site and sex. To ensure that we corrected only for effects that were not attributable to disease-related factors, we added the variables as covariates and calculated beta coefficients only for the LS group, using partial correlation analysis. Then, we residualized the patient and healthy control data using the calculated coefficients.[78,79] Finally, data were scaled to [0, 1].

For both inner (CV1) and outer (CV2) cycles, we chose a 10 (folds/partitions) × 10 (permutations) CV, with each

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

permutation performing a reshuffling of participants within their groups. While in CV2, one partition at a time was held back as validation data, the nine remaining partitions entered CV1 as training data. In CV1, to create the classification models, 10 partitions with 10 repetitions were used. This means that for each validation fold at CV2, 100 different training data partitions were generated at CV1. In each training partition, linear support vector machines (LIBSVM 3.12; http://www.csie.ntu.edu.tw/~cjlin/libsvm) were used to find the hyperplane that separates best between the groups. This is done by maximizing the margin between the nearest data points of opposite classes.[58] Penalty strength was optimized as a hyperparameter with a range from 0.015624 to 16 in 11 steps. In addition, we weighted the hyperplane due to unequal sample sizes in the LS and ROP groups. This procedure yielded decision scores measuring the likeliness of a given participant being in the control or the patient group. The most discriminative sets of features were determined in each of these 100 training partitions. Each of the trained classification models was used to predict the group membership of the validation fold in CV2. Support vector machine-learning has been intensively applied in the study of psychosis during the last years and has, therefore, become one of the most established methods in this field. [58,60,63,78,80,81] Therefore, and to facilitate comparability with previous studies, we applied this method in the present study.

To measure the classifier's performance, we used sensitivity, specificity, and balanced accuracy [(sensitivity + specificity)/2]. To calculate the significance of the classification, we conducted a permutation analysis with 1000 random class label permutations. The null hypothesis, stating that the classifier cannot predict group memberships correctly, was rejected at $\alpha = .05$.

fMRI Data. To distinguish LS from ROP based on neural correlates of SPEM, we used first-level contrast images (SPEM vs. Fixation; high vs. low target velocity; 10 gPPI SPEM vs. Fixation contrasts and 10 gPPI high vs. low target velocity for each seed region in the left and right hemisphere) for the machine-learning pipeline.

The preprocessing of the BOLD data was identical to the behavioral data analysis, except for three additional steps: First, we pruned the data, in order to prevent overfitting of the algorithm. More precisely, we removed features with no variance within a fold as well as features with infinity values. Second, to correct for effects of site, we applied ComBat batch effect correction. Next, we applied principal component analysis (PCA) by mapping correlated voxels to a number of uncorrelated principal components. PCA was used as a statistical smoothing technique to reduce the dimensionality of discriminative patterns and eliminate noise. [58,78] The number of PCA components was optimized within the nested cross-validation approach described above. Specifically, the number of components was determined by the optimal PCA energy for class separation ranging from 0.5 to 0.9. Finally, data were scaled voxel-wise to [0, 1] following again a strict separation of CV1 training, CV1 test and CV2 validation data, where the scaling parameters were derived from the CV1 training sample and then applied to other data partitions.

The training pipeline for the BOLD data was identical to the pipeline for the behavioral data.

For reasons of computational efficiency, the permutation analyses for calculating the significance of the classification algorithms for the connectivity maps were first applied only to the first CV2 fold. If a classification algorithm was significant at trend-level ($P < .10$) in this fold, the permutation analyses were repeated for all 10 CV2 folds to ensure robustness of the results. Resulting P-values were corrected for multiple testing separately for each contrast (SPEM and Velocity) using the false discovery rate procedure.[82]

Sign-based consistency mapping was applied to determine brain areas contributing to classification of LS and ROP.[83] Images were thresholded at -log10(0.05), FDR-corrected.

In addition, stacking analyses were performed separately for the SPEM and Velocity contrasts in order to combine the predictions of the lower order classification algorithms. To do so, the decision scores from all modalities of each contrast (i.e., the standard fMRI contrast and all 10 gPPI contrasts) were entered into a single analysis, yielding two stacked analyses (SPEM contrast, Velocity contrast). The training pipeline of these stacked data sets was identical to the pipeline of the lower order fMRI trainings. The stacking pipeline was wrapped into the same repeated nested cross-validation setup as described above to exclude the possibility of information leakage, i.e., the first-level decision scores of a given CV1 partition were forwarded to the second-level SVM, which was then applied to the second-level CV2 data alongside the other trained SVM models of the given CV2 partition.

Model Application to Schizotypal Samples. In case of a significant classification, the trained models used to predict group membership for LS and ROP were applied to persons with high schizotypy. This allows to examine whether a schizotypal participant is more likely to be classified as LS or ROP, and thus, whether BOLD data during SPEM in schizotypy are more similar to those of LS or ROP. It produces decision scores indicating whether a participant is more likely to belong to the LS (positive decision scores) or the ROP group (negative scores). One-way ANOVA was employed to indicate whether the decision scores differed between groups.

In addition, a regression analysis was conducted where the HPS and HNS decision scores were used as a regressor to predict BOLD activity in the HPS and HNS groups.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

Univariate Group Comparisons for Behavioral SPEM Data

In addition to the classification analysis, we conducted mixed ANCOVA based on the behavioral SPEM data, with *Group* as a between- and *Velocity* as a within-subjects factor. Three separate analyses were conducted, with gain, saccade frequency or RMSE as dependent variables, and site (Bonn, Munich) and sex (male, female) as covariates.

Results

Descriptive Statistics, Sociodemographic and Clinical Variables

No significant group differences were found with respect to age and years of formal education. However, there were differences in distributions of participants across sites, as well as in sex distributions and intelligence (table 1). For additional characteristics of the ROP sample see table 2. Descriptive statistics of SPEM parameters are in table 3.

Behavioral Results

A total of 174 participants were included for the behavioral analyses (see table 3 for the number of participants in each group). Nine participants had to be excluded due to poor eye-tracking quality.

Classification Analysis. Based on behavioral data, LS and ROP participants were classified with a balanced accuracy of 52.1% (sensitivity = 71.9%; specificity = 32.4%), which was not significant (P = .438, AUC = 0.56).

Univariate Group Comparisons.. Mixed ANCOVA with all four groups revealed main effects of Velocity for all three parameters (gain: $F_{(1,168)}$ = 54.02, P < .001, η_p^2 = .24; RMSE: $F_{(1,168)}$ = 61.46, P < .001, η_p^2 = .27; saccade frequency: $F_{(1,168)}$ = 40.89, P < .001, η_p^2 = .20). Additionally, there was a main effect of Group on RMSE ($F_{(3,168)}$ = 2.92, P = .036, η_p^2 = .05). Post-hoc pair-wise comparisons showed significant differences between the LS and ROP group that did not, however, survive Bonferroni-correction (table 4). For saccade frequency and gain, there were no significant effects of Group, although there was a trend towards a main effect of Group on gain (P = .079). There were no Group by Velocity interactions (all P > .126). Statistical parameters and effect sizes of all pairwise group comparisons are in table 4.

FMRI Results

A total of 180 participants were included for the fMRI analyses. Three participants (2 LS, 1 ROP) had to be excluded due to poor fMRI data quality.

BOLD Task and Group Effects. There were no significant group differences for the SPEM or Velocity contrasts. However, the smooth pursuit task (SPEM contrast) activated areas of the pursuit network (figure 2 and Supplementary tables 2 and 3 for results in the LS group). The Velocity contrast revealed significant activations in visual cortex (figure 2 and Supplementary table 4 for results in the LS group). There were no significant differences for the reverse Velocity contrast.

Table 1. Sociodemographic and clinical variables of the four study groups

Variable	LS (n = 62)	HPS (n = 41)	HNS (n = 46)	ROP (n = 34)	Statistics
Site (n Bonn/Munich)	31/31	28/13	29/17	12/22	$\chi^2_{(3)}$ = 10.07, P = .02
Sex (n female/male)	29/33	26/15	25/21	10/24	$\chi^2_{(3)}$ = 9.28, P = .03
Age (in years; M, SD)	25.94 (4.73)	26.24 (6.33)	26.67 (4.61)	25.09 (4.98)	$F_{(3,179)}$ = 0.65, P = .58, η_p^2 = 0.01
O-LIFE scores (M, SD)					
UE	1.21 (1.19)	9.46 (1.80)	1.48 (1.19)	N/A	$F_{(2,146)}$ = 513.89, P < .001, η_p^2 = 0.88
IA	1.03 (0.75)	1.27 (0.81)	6.33 (1.01)	N/A	$F_{(2,146)}$ = 592.55, P<.001, η_p^2 = 0.89
CD	3.17 (2.52)	5.97 (2.98)	6.00 (2.93)	N/A	$F_{(2,146)}$ = 17.27, P < .001, η_p^2 = 0.21
Total	5.34 (3.46)	16.62 (4.45)	13.67 (3.62)	N/A	$F_{(2,146)}$ = 114.49, P < .001, η_p^2 = 0.63
Years of formal education (M, SD)	16.83 (3.26)	16.32 (3.15)	16.72 (3.45)	15.20 (3.50)	$F_{(3,173)}$ = 1.91, P = .13, η_p^2 = 0.03
Verbal intelligence test score[a] (M, SD)	12.02 (2.98)	10.98 (2.62)	11.59 (2.61)	9.47 (3.33)	$F_{(3,177)}$ = 5.87, P = .001, η_p^2 = 0.09
Nonverbal intelligence test score[b] (M, SD)	11.21 (1.91)	11.24 (1.95)	11.22 (1.82)	9.42 (3.56)	$F_{(3,178)}$ = 5.57, P = .001, η_p^2 = 0.09

Notes: LS, low-schizotypy; HPS, high positive schizotypy; HNS, high negative schizotypy; ROP, recent onset psychosis; O-LIFE, Oxford-Liverpool Inventory of Feelings and Experiences; UE, unusual experiences; IA, introvertive anhedonia; CD, cognitive disorganization; N/A, not available.
[a]Wechsler Adult Intelligence Scale (WAIS) vocabulary subtest.
[b]WAIS matrices subtest.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

Connectivity Analysis. gPPI analyses yielded no significant differences between the four groups for any of the seed regions or contrasts. However, wide-spread connectivity maps for the SPEM contrast for all seed regions could be observed (Supplementary figures 1 and 2 and tables 5–14 for results in the LS group). There were no significant connectivity maps for the Velocity contrasts.

Classification Analysis. Based on the SPEM contrast, LS and ROP participants were separated with a balanced accuracy of 55.6% (sensitivity = 56.7%, specificity = 54.5%) which was not significant (P = .297, AUC = 0.63). Based on the Velocity contrast, classification reached a balanced accuracy of 44.5% (sensitivity = 61.7%; specificity = 27.3%), which was also not significant (P = .392, AUC = 0.47).

Classification results of the gPPI analyses were significant for the SPEM contrast in right FEF (table 5). For this seed region, LS and ROP participants were separated with a balanced accuracy of 62.4% (sensitivity = 73.3%; specificity = 51.5%) which was significant (P = .009; AUC = 0.63) before but not after correcting for multiple testing (FDR; P = .090).

Visualization of the machine-learning results revealed that classification was based on connectivity from right FEF to parahippocampal gyrus and hippocampus, striatum, thalamus, cerebellum, anterior and posterior cingulate gyrus, postcentral gyrus, superior parietal cortex, lateral occipital cortex and fusiform gyrus, supramarginal and angular gyrus, precuneus, temporal pole, inferior temporal gyrus, frontal pole and frontal-medial cortex (Supplementary figure 3).

Stacking Analyses. In the stacking analyses of the SPEM contrast, LS and ROP participants were separated with a balanced accuracy of 55.4% (sensitivity = 68.3%, specificity = 42.4%) which was not significant (P = .748, AUC = 0.56). Based on the Velocity contrast, classification reached a balanced accuracy of 43.3% (sensitivity = 53.3%; specificity = 33.3%), which was not significant (P = .941, AUC = 0.35).

Model Application to Schizotypal Samples. The classification model of the right FEF SPEM gPPI contrast was significant before correction for multiple testing. Therefore, in an explorative analysis, we applied the classification algorithm to the schizotypal samples to determine whether persons with high schizotypy would be classified as LS or ROP. Sixteen HPS and 18 HNS were classified as ROP, and 25 HPS and 28 HNS were classified as LS. Descriptively, decision scores of persons with high schizotypy were in between LS and ROP (Supplementary table 15). However, one-way ANOVA for comparison of decision scores between groups was not significant ($F_{(3,179)} = 1.51$, $P = .214$, $\eta_p^2 = 0.025$).

In an additional regression analysis in both schizotypal samples, lower decision scores were associated with increased gPPI connectivity from right FEF to clusters in angular gyrus, precuneus, hippocampus and parahippocampus, postcentral and precentral gyrus as

Table 2. Clinical characteristics of the ROP group

Variable	ROP (n = 34)
Time since illness onset (in days; M, SD)	281.40 (302.45)
Diagnosis (n)	
Schizophrenia	22
Delusional disorder	2
Brief psychotic disorder	5
Schizoaffective disorder	4
Unspecified nonorganic psychosis	1
PANSS scores (M, SD)	
Positive	20.64 (5.52)
Negative	16.84 (8.37)
General psychopathology	36.96 (16.29)
Medication (n)	
Typical	–
Atypical	19
Both	5
No medication	4
Unknown	6

Notes: ROP, recent onset psychosis; PANSS, Positive and Negative Symptom Scale.

Table 3. Descriptive statistics for SPEM parameters

Target velocity	Variable	LS (n = 57)	HPS (n = 41)	HNS (n = 42)	ROP (n = 34)
0.2 Hz	Gain (%)	91.19 (9.59)	90.73 (11.70)	90.36 (11.49)	86.89 (14.50)
	RMSE (°)	1.45 (0.75)	1.45 (0.54)	1.46 (0.64)	1.93 (1.09)
	Frequency of saccades (N/s)	0.67 (0.38)	0.66 (0.38)	0.75 (0.45)	0.82 (0.45)
0.4 Hz	Gain (%)	75.95 (11.99)	71.77 (15.28)	71.89 (17.00)	68.53 (18.27)
	RMSE (°)	1.99 (0.76)	2.15 (0.67)	2.09 (0.81)	2.23 (0.93)
	Frequency of saccades (N/s)	1.47 (0.44)	1.50 (0.46)	1.56 (0.51)	1.60 (0.49)

Notes: Data represent means (standard deviations). LS, low-schizotypy; HPS, high positive schizotypy; HNS, high negative schizotypy; ROP, recent onset psychosis; RMSE, root mean square error.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

Table 4. Between-group comparison of SPEM performance

Groups	Variables	0.2 Hz	0.4 Hz
LS vs. ROP	Gain (%)	$t_{(89)}$ = 2.01, P = .047, d = 0.44	$t_{(89)}$ = 2.34, P = .021, d = 0.51
	RMSE (°)	$t_{(89)}$ = -2,51, P = .014, d = -0.54	$t_{(89)}$ = -1.32, P =.189, d = -0.29
	Frequency of saccades (N/s)	$t_{(89)}$ = -1.68, P =.096, d = -0.36	$t_{(89)}$ = -1.28, P =.203, d = -0.28
LS vs. HNS	Gain (%)	$t_{(97)}$ = 0.39, P =.695, d = 0.08	$t_{(97)}$ = 1.39, P =.166, d = 0.28
	RMSE (°)	$t_{(97)}$ = -0.10, P =.921, d = -0.02	$t_{(97)}$ = -0.60, P =.550, d = -0.12
	Frequency of saccades (N/s)	$t_{(97)}$ = -0.97, P =.334, d = -0.20	$t_{(97)}$ = -0.90, P =.368, d = -0.18
LS vs. HPS	Gain (%)	$t_{(96)}$ = 0.21, P =.832, d = 0.04	$t_{(96)}$ = 1.52, P =.132, d = 0.31
	RMSE (°)	$t_{(96)}$ = 0.003, P =.997, d = 0.00	$t_{(96)}$ = -1.06, P =.293, d = -0.22
	Frequency of saccades (N/s)	$t_{(96)}$ = 0.20, P =.845, d = 0.04	$t_{(96)}$ = -0.27, P =.784, d = -0.06
HNS vs. ROP	Gain (%)	$t_{(74)}$ = 1.42, P =.159, d = 0.33	$t_{(74)}$ = 0.83, P =.410, d = 0.19
	RMSE (°)	$t_{(74)}$ = -2.34, P =.022, d = -0.54	$t_{(74)}$ = -0.71, P =.481, d = -0.16
	Frequency of saccades (N/s)	$t_{(74)}$ = -0.65, P =.518, d = -0.15	$t_{(74)}$ = -0.36, P = 0.723, d = -0.08
HPS vs. HNS	Gain (%)	$t_{(81)}$ = 0.15, P =.883, d = 0.03	$t_{(81)}$ = -0.03, P =.973, d = -0.01
	RMSE (°)	$t_{(81)}$ = -0.11, P =.910, d = -0.02	$t_{(81)}$ = 0.37, P =.710, d = 0.08
	Frequency of saccades (N/s)	$t_{(81)}$ = -1.05, P =.299, d = -0.23	$t_{(81)}$ = -0.58, P =.565, d = -0.13
HPS vs. ROP	Gain (%)	$t_{(73)}$ = 1.53, P =.131, d = 0.35	$t_{(73)}$ = 0.84, P =.406, d = 0.19
	RMSE (°)	$t_{(73)}$ = -2.50, P =.014, d = -0.58	$t_{(73)}$ = -0.43, P =.665, d = -0.10
	Frequency of saccades (N/s)	$t_{(73)}$ = -1.69, P =.095, d = -0.39	$t_{(73)}$ = -0.94, P =.352, d = -0.22

Notes: LS, low-schizotypy; HPS, high positive schizotypy; HNS, high negative schizotypy; ROP, recent onset psychosis; RMSE, root mean square error.

well as superior medial gyrus and ACC (Supplementary figure 4 and table 16). This indicates that higher probability of being categorized as ROP was associated with increased task-based functional connectivity from right FEF to these clusters. There was no significant effect in the reverse (i.e., positive) contrast.

Discussion

The aim of the present study was to directly compare individuals with high levels of schizotypy and patients with psychotic disorders regarding SPEM performance as well as brain function and connectivity. Using traditional BOLD and connectivity analyses, no group differences could be observed. However, using machine-learning, a model to distinguish patients from controls was delineated for the right FEF seed region.

Differences Between Controls and Patients

Based on behavioral SPEM data, LS and ROP participants could not be classified as distinct groups. However, univariate results revealed higher RMSE in ROP compared to LS, in agreement with previous evidence of reduced SPEM performance in psychosis.[31,33] In contrast to previous investigations, univariate analyses of gain and saccadic frequency were not significant. The small difference in RMSE and the absence of differences in the two other performance measures are surprising considering that the SPEM deficit is a highly reliable marker of psychosis.[31,33] Importantly, at the descriptive level, effects were in the expected direction with small to medium effect sizes, but not significant after Bonferroni-correction (see table 4).

In line with the behavioral results but in contrast to previous investigations[36,41–44] no significant differences between ROP, HPS, HNS and LS groups could be determined at the neural level for the SPEM or Velocity contrasts. The same pattern emerged for the connectivity maps of all seed regions and contrasts. Of note, the task networks associated with the SPEM and Velocity contrasts showed substantial overlap with previous investigations, tightly replicating the neural network underlying SPEM[36,75,84–90] and its modulation by target velocity[36,75,87]. This highlights the validity of our task design and data analytic approach. Similarly, task-related connectivity maps showed substantial overlap with a recent investigation[75] studying pursuit-related functional connectivity in a healthy sample performing the same task employed in this study. However, in the current investigation, SPEM-related connectivity maps were even more widespread, especially from LGN, V1 and V5 seed regions, potentially related to greater statistical power stemming from a larger sample size.

Classification of functional connectivity maps was significant only before correction for multiple comparisons (achieving trend-level significance after correction) for the right FEF seed region. As the analyses did not survive correction for multiple comparison, results should be interpretated with great caution. The PPI seed region was located in right medial FEF. Classification was based on connectivity from there to subcortical (e.g., striatum and thalamus) and cortical structures encompassing early visual areas, cingulate gyrus, parietal cortex (e.g., precuneus, superior parietal cortex), frontal cortex (e.g., superior frontal gyrus and frontal-medial cortex), hippocampus and cerebellum. These areas partially overlap

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

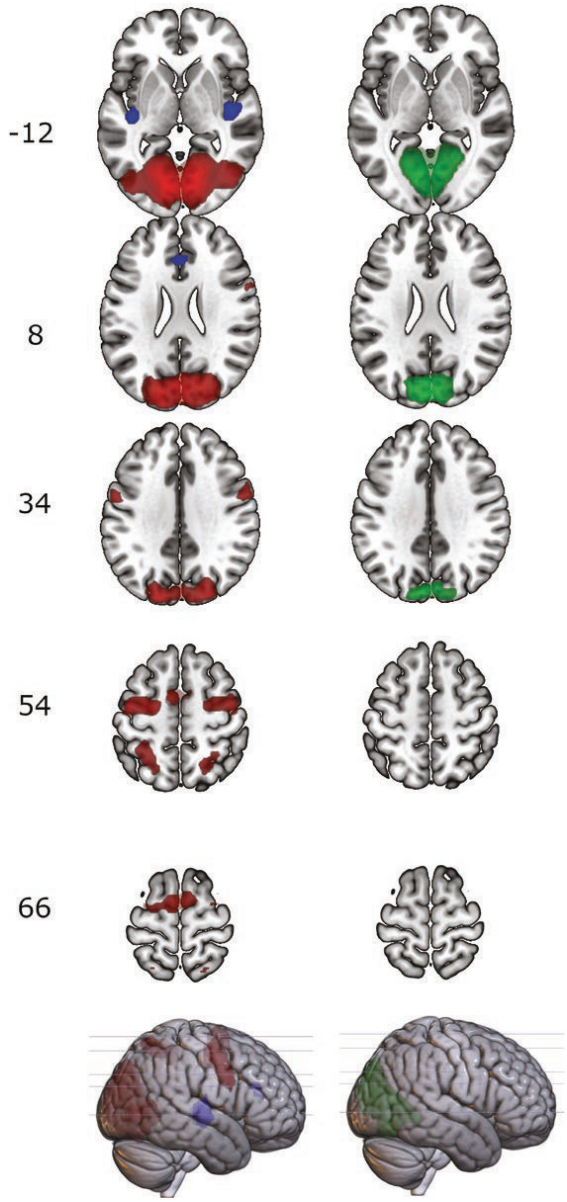

Fig. 2. Results of one-sample *t*-tests of the SPEM vs. fixation contrast (left, higher activation during SPEM is depicted in red, higher activation during fixation is depicted in blue) and high vs. low velocity contrasts (right, higher activation during high velocity SPEM is depicted in green, there was no higher activation during low velocity vs. high velocity SPEM), respectively (n = 60). Results are reported whole-brain family-wise error rate (FWE) corrected (P < .001, peak level) for clusters of at least 25 voxels. Labels on the left refer to the z-coordinate [Montreal Neurological Institute (MNI) space]. Slices were generated in MRIcroGL.

with the known SPEM network but also include additional areas. For example, classification was based in part on connectivity from right FEF to hippocampus, which is in line with previous reports that hyperactivity of that area during SPEM may be related to inhibitory dysfunction in schizophrenia.[44,91]

Three explanations of the absence of group effects using traditional analyses and the rather subtle results combining functional connectivity and machine-learning approaches may be offered. First, the results could be explained by the diagnostic heterogeneity of the ROP group, given that the SPEM deficit is more pronounced in schizophrenia patients compared to patients with other disorders in the psychosis spectrum.[33] The inclusion of a variety of such spectrum disorders into our ROP group might have led to the rather subtle effects. However, the PANSS scores obtained here were similar to those of previous investigations that did find significant differences between patients and controls.[67,91] All patients had ROP with average disorder duration of less than a year which could imply that SPEM deficits may not yet be fully developed. On the other hand, however, it has been demonstrated in a meta-analysis that duration of illness does not significantly influence SPEM dysfunction[31].

A second possibility is insufficient power, which is why we conducted a post-hoc power analysis. According to this analysis, we had sufficient power to detect SPEM differences between controls and patients: Meta-analytical results from studies comparing SPEM performance of schizophrenia patients and controls show large effect sizes (d=.70 for RMSE, d =.78 for saccade frequency, and d = .87 for gain).[31] With our sample size of n = 62 in the LS and n = 34 in the ROP group and an alpha-level of .05 we had a power of 0.94–0.99 to detect effect sizes in this range (t-tests, difference between two independent means). In addition, we used substantially larger samples than all previous BOLD fMRI investigations of SPEM in psychosis spectrum disorders[36,41–44] suggesting that also at the neural level lack of power is not the main driver of the absence of group effects.

Third, it should be noted that behavioral performance in the LS group was lower than in other healthy control groups performing the same task in previous studies.[36,92,93] It is therefore possible that the detection of significant group differences was impeded by the unusually poor performance in the control group. However, it has to be emphasized that control group participants were thoroughly screened and selected based on strict criteria to ensure suitability.

Schizotypy

Descriptively, at the behavioral level, both schizotypal samples showed intermediate SPEM performance levels between patients and control. This pattern of results was not significant, but reflects the expected direction of effects.[35,37,38] At the neural level, in contrast to a previous study[36] traditional BOLD or functional connectivity analyses did not yield any evidence for group differences.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

Table 5. Results of the machine-learning analyses for the gPPI contrasts

Seed region	Hemisphere	Contrast	Sensitivity	Specificity	BAC	AUC	P	P_{corr}
LGN	l	SPEM	63.6	36.4	49.8	0.51	.834	.834
LGN	r		53.3	39.4	46.4	0.54	.633	.707
V1	l		65.0	48.5	56.7	0.63	.184	.368
V1	r		63.3	30.3	46.8	0.49	.636	.707
V5+	l		78.3	27.3	52.8	0.58	.350	.583
V5	r		85.0	27.3	56.1	0.52	.135	.338
PPC+	l		81.7	36.4	59.0	0.61	.096	.338
PPC	r		76.7	33.3	55.0	0.61	.135	.338
FEF	l		63.3	48.5	55.9	0.56	.534	.707
FEF+	r		73.3	51.5	62.4	0.63	.009	.090
LGN	l	Velocity	51.7	48.5	50.1	0.47	.948	.949
LGN	r		46.7	45.5	46.1	0.46	.880	.949
V1	l		71.7	30.3	51.0	0.50	.897	.949
V1+	r		83.3	30.3	56.8	0.56	.117	.949
V5	l		81.7	21.2	51.4	0.50	.517	.949
V5	r		78.3	24.2	51.3	0.44	.685	.949
PPC	l		0	100.0	50.0	0.26	.653	.949
PPC	r		50.0	48.5	49.2	0.45	.949	.949
FEF	l		70.0	39.4	54.7	0.53	.462	.949
FEF	r		11.7	69.7	40.7	0.43	.495	.949

Notes: gPPI, generalized psychophysiological interaction analyses; LGN, lateral geniculate nucleus; PPC, posterior parietal cortex; FEF, frontal eye fields; BAC, balanced accuracy; AUC, area under the curve; P_{corr}, corrected P-value (false discovery rate correction[82]).
+Permutation analyses with all 10 CV2 folds.

However, we also explored similarities and dissimilarities between psychosis and schizotypy by applying a machine-learning algorithm for SPEM seed regions trained on the LS and ROP groups to the schizotypal samples, thereby obtaining evidence of an involvement of right FEF. As the HPS and HNS groups did not differ from each other regarding SPEM performance, and the percentage of participants classified as ROP was virtually the same in both groups (HPS 39.0% vs HNS 39.1%), we treated them as one schizotypy group for subsequent analysis. Machine-learning decision scores for schizotypy groups were in between the LS and ROP groups and thus suggested that persons with high schizotypy could not be reliably classified as either LS or ROP. To identify brain areas that contributed to the assignment of HPS and HNS to ROP or LS, we explored how decision scores in the HPS and HNS samples were related to BOLD activity in those groups. Lower decision scores were associated with increased connectivity from right FEF to clusters in precuneus and angular gyrus, bilateral hippocampi, as well as postcentral and precentral gyrus. This pattern of results suggests that persons with high schizotypy may share some of the features underlying the pursuit deficits in ROP. Specifically, persons with high schizotypy may also show some degree of inhibitory dysfunction in hippocampus.[44,91]

Conclusions

Overall, the present study constitutes a significant first step toward closing a crucial gap in the psychosis literature, which is the lack of direct comparisons between individuals with high schizotypy and patients with psychosis. Critically, however, our data suggest that abnormalities of the pursuit response along the psychosis spectrum may be more subtle than previously reported. The data are partly in line with our initial suggestion that schizotypy is characterized by both similarities and dissimilarities with schizophrenia, which might explain why the SPEM deficit in schizotypy does not seem to be as consistent as may be expected from previous publications. Specifically, our results highlight that more emphasis should be placed on brain connectivity approaches which proved to be the most promising analyses for distinguishing groups along the psychosis spectrum. In summary, we strongly call for more large-scale, well-powered multi-center studies in order to gain a deeper understanding of SPEM-related deficits along the psychosis spectrum at both the behavioral and neural level.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

Funding

This work was supported by Deutsche Forschungsgemeinschaft (ET 31/7-1; KO 3523/7-1; KA 4413/1-1). The PhD project of Rebekka Schröder is

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

funded by the German Academic Scholarship Foundation (Studienstiftung des deutschen Volkes). We acknowledge funding from the Open Access Publication Fund of the University of Bonn. The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgments

We thank Johanna Gröning, Lena Hensel, Erik Lang, Melissa Reinelt, and Santiago Tovar for their help with data collection, and all volunteers for participating in the study.

References

1. Ettinger U, Meyhöfer I, Steffens M, Wagner M, Koutsouleris N. Genetics, cognition, and neurobiology of schizotypal personality: a review of the overlap with schizophrenia. *Front Psychiatry.* 2014;5:18.
2. Tonini E, Quidé Y, Kaur M, Whitford TJ, Green MJ. Structural and functional neural correlates of schizotypy: a systematic review. *Psychol Bull.* 2021;147(8)828–866.
3. Nelson MT, Seal ML, Pantelis C, Phillips LJ. Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neurosci Biobehav Rev.* 2013;37(3)317–327.
4. Thomas EHX, Steffens M, Harms C, Rossell SL, Gurvich C, Ettinger U. Schizotypy, neuroticism, and saccadic eye movements: new data and meta-analysis. *Psychophysiology.* 2021;58(1)e13706.
5. Steffens M, Meyhöfer I, Fassbender K, Ettinger U, Kambeitz J. Association of schizotypy with dimensions of cognitive control: a meta-analysis. *Schizophr Bull.* 2018;44(suppl_2):S512–S524.
6. Liddle PF. The symptoms of chronic schizophrenia. *Br J Psychiatry.* 1987;151(2)145–151.
7. Raine A, Reynolds C, Lencz T, Scerbo A, Triphon N, Kim D. Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull.* 1994;20(1)191–201.
8. Schaefer J, Giangrande E, Weinberger DR, Dickinson D. The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophr Res.* 2013;150(1)42–50.
9. Snitz BE. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull.* 2005;32(1)179–194.
10. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry.* 2006;188:510–518.
11. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull.* 2007;34(2)354–366.
12. Kühn S, Schubert F, Gallinat J. Higher prefrontal cortical thickness in high schizotypal personality trait. *J Psychiatr Res.* 2012;46(7)960–965.
13. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res.* 2001;49(1-2)1–52.
14. Ettinger U, Williams SC, Meisenzahl EM, Möller H-J, Kumari V, Koutsouleris N. Association between brain structure and psychometric schizotypy in healthy individuals. *World J Biol Psychiatry.* 2012;13(7)544–549.
15. Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser MC. Putatively psychosis-prone subjects 10 years later. *J Abnorm Psychol.* 1994;103(2)171–183.
16. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychol Med.* 2009;39(2)179–195.
17. Giakoumaki SG. Cognitive and prepulse inhibition deficits in psychometrically high schizotypal subjects in the general population: relevance to schizophrenia research. *J Int Neuropsychol Soc.* 2012;18(4)643–656.
18. Barrantes-Vidal N, Grant P, Kwapil TR. The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophr Bull.* 2015;41(suppl 2)S408–S416.
19. Ettinger U, Mohr C, Gooding DC, *et al.* Cognition and brain function in schizotypy: a selective review. *Schizophr Bull.* 2015;41(suppl 2)S417–S426.
20. Debbane M, Eliez S, Badoud D, Conus P, Fluckiger R, Schultze-Lutter F. Developing psychosis and its risk states through the lens of schizotypy. *Schizophr Bull.* 2015;41(suppl 2)S396–S407.
21. Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS. Volume of the cingulate and outcome in schizophrenia. *Schizophr Res.* 2005;72(2-3)91–108.
22. Koo MS, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW. A cross-sectional and longitudinal magnetic resonance imaging study of ongulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. *Arch Gen Psychiatry.* 2008;74:6–760.
23. Fornito A, Yücel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr Res.* 2009;108(1-3)104–113.
24. Kasai K, Shenton ME, Salisbury DF, *et al.* Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am J Psychiatry.* 2003;160(1)156–164.
25. Zhou S-Y, Suzuki M, Takahashi T, *et al.* Parietal lobe volume deficits in schizophrenia spectrum disorders. *Schizophr Res.* 2007;89(1-3)35–48.
26. Modinos G, Mechelli A, Ormel J, Groenewold NA, Aleman A, McGuire PK. Schizotypy and brain structure: a voxel-based morphometry study. *Psychol Med.* 2010;40(9)1423–1431.
27. Nenadic I, Lorenz C, Langbein K, *et al.* Brain structural correlates of schizotypy and psychosis proneness in a non-clinical healthy volunteer sample. *Schizophr Res.* 2015;168(1–2)37–43.
28. Batey M, Furnham A. The relationship between measures of creativity and schizotypy. *Personal Individ Differ.* 2008;45(8)816–821.
29. Nelson B, Rawlings D. Relating schizotypy and personality to the phenomenology of creativity. *Schizophr Bull.* 2010;36(2)388–399.
30. Hazlett EA, Goldstein KE, Kolaitis JC. A review of structural MRI and diffusion tensor imaging in schizotypal personality disorder. *Curr Psychiatry Rep.* 2012;14(1)70–78.
31. O'Driscoll GA, Callahan BL. Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993. *Brain Cogn.* 2008;68(3)359–370.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

32. Levy DL, Sereno AB, Gooding DC, O'Driscoll GA. Eye tracking dysfunction in schizophrenia: characterization and pathophysiology. *Curr Top Behav Neurosci.* 2010;4:311–347.
33. Lencer R, Sprenger A, Reilly JL, *et al.* Pursuit eye movements as an intermediate phenotype across psychotic disorders: evidence from the B-SNIP study. *Schizophr Res.* 2015;169(0)326–333.
34. Koychev I, Joyce D, Barkus E, *et al.* Cognitive and oculomotor performance in subjects with low and high schizotypy: implications for translational drug development studies. *Transl Psychiatry.* 2016;6(5)e811–e811.
35. Lenzenweger MF, O'Driscoll GA. Smooth pursuit eye movement and schizotypy in the community. *J Abnorm Psychol.* 2006;115(4)779–786.
36. Meyhöfer I, Steffens M, Kasparbauer A-M, Grant P, Weber B, Ettinger U. Neural mechanisms of smooth pursuit eye movements in schizotypy. *Hum Brain Mapp.* 2015;36(1)340–353.
37. Smyrnis N, Evdokimidis I, Mantas A, *et al.* Smooth pursuit eye movements in 1,087 men: effects of schizotypy, anxiety, and depression. *Exp Brain Res.* 2007;179(3)397–408.
38. Holahan A-LV, O'Driscoll GA. Antisaccade and smooth pursuit performance in positive- and negative-symptom schizotypy. *Schizophr Res.* 2005;76(1)43–54.
39. Gooding DC, Miller MD, Kwapil TR. Smooth pursuit eye tracking and visual fixation in psychosis-prone individuals. *Psychiatry Res.* 2000;93(1)41–54.
40. Meyhöfer I, Steffens M, Faiola E, Kasparbauer A-M, Kumari V, Ettinger U. Combining two model systems of psychosis: the effects of schizotypy and sleep deprivation on oculomotor control and psychotomimetic states. *Psychophysiology.* 2017;54(11)1755–1769.
41. Hong LE, Tagamets M, Avila M, Wonodi I, Holcomb H, Thaker GK. Specific motion processing pathway deficit during eye tracking in schizophrenia: a performance-matched functional magnetic resonance imaging study. *Biol Psychiatry.* 2005;57(7)726–732.
42. Keedy SK, Ebens CL, Keshavan MS, Sweeney JA. Functional magnetic resonance imaging studies of eye movements in first episode schizophrenia: smooth pursuit, visually guided saccades and the oculomotor delayed response task. *Psychiatry Res.* 2006;146(3)199–211.
43. Lencer R, Nagel M, Sprenger A, Heide W, Binkofski F. Reduced neuronal activity in the V5 complex underlies smooth-pursuit deficit in schizophrenia: evidence from an fMRI study. *NeuroImage.* 2005;24(4)1256–1259.
44. Tregellas JR, Tanabe JL, Miller DE, Ross RG, Olincy A, Freedman R. Neurobiology of smooth pursuit eye movement deficits in schizophrenia: an fMRI study. *Am J Psychiatry.* 2004;161(2)315–321.
45. Krishna N, O'Neill H, Sanchez-Morla EM, Thaker GK. Long range frontal/posterior phase synchronization during remembered pursuit task is impaired in schizophrenia. *Schizophr Res.* 2014;157(1–3)198–203.
46. Boksman K, Théberge J, Williamson P, *et al.* A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophr Res.* 2005;75(2-3)247–263.
47. Fogelson N, Litvak V, Peled A, Fernandez-del-Olmo M, Friston KJ. The functional anatomy of schizophrenia: a dynamic causal modeling study of predictive coding. *Schizophr Res.* 2014;158(1–3)204–212.
48. Lynall M-E, Bassett DS, Kerwin R, *et al.* Functional connectivity and brain networks in schizophrenia. *J Neurosci.* 2010;30(28)9477–9487.
49. Wang Y-M, Cai X, Zhang R-T, *et al.* Altered brain structural and functional connectivity in schizotypy. *Psychol Med.* 2020;52(5):1–10. doi:10.1017/S0033291720002445.
50. Nelson MT, Seal ML, Phillips LJ, Merritt AH, Wilson R, Pantelis C. An investigation of the relationship between cortical connectivity and schizotypy in the general population. *J Nerv Ment Dis.* 2011;199(5)348–353.
51. P K, F S, A D, P A. High schizotypy traits are associated with reduced hippocampal resting state functional connectivity. *Psychiatry Res Neuroimaging.* 2021;307:111215.
52. Wang Y, Ettinger U, Meindl T, Chan RCK. Association of schizotypy with striatocortical functional connectivity and its asymmetry in healthy adults. *Hum Brain Mapp.* 2018;39(1)288–299.
53. Waltmann M, O'Daly O, Egerton A, *et al.* Multi-echo fMRI, resting-state connectivity, and high psychometric schizotypy. *Neuroimage Clin.* 2019;21:101603.
54. Wang Y, Yan C, Yin D, *et al.* Neurobiological changes of schizotypy: evidence from both volume-based morphometric analysis and resting-state functional connectivity. *SCHBUL.* 2015;41(Suppl 2)S444–S454.
55. Trajkovic J, Di Gregorio F, Ferri F, Marzi C, Diciotti S, Romei V. Resting state alpha oscillatory activity is a valid and reliable marker of schizotypy. *Sci Rep.* 2021;11(1)10379.
56. Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *NeuroImage.* 2004;23(1)17–20.
57. Fu CH, Mourao-Miranda J, Costafreda SG, *et al.* Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. *Biol Psychiatry.* 2008;63(7)656–662.
58. Koutsouleris N, Meisenzahl EM, Davatzikos C, *et al.* Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Arch Gen Psychiatry.* 2009;66(7)700–712.
59. Orrù G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A. Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. *Neurosci Biobehav Rev.* 2012;36(4)1140–1152.
60. Koutsouleris N, Borgwardt S, Meisenzahl EM, Bottlender R, Möller H-J, Riecher-Rössler A. Disease prediction in the at-risk mental state for psychosis using neuroanatomical biomarkers: results from the FePsy study. *Schizophr Bull.* 2012;38(6)1234–1246.
61. Kaufmann T, Skåtun KC, Alnæs D, *et al.* Disintegration of sensorimotor brain networks in schizophrenia. *SCHBUL.* 2015;41(6)1326–1335.
62. Chyzhyk D, Savio A, Graña M. Computer aided diagnosis of schizophrenia on resting state fMRI data by ensembles of ELM. *Neural Netw.* 2015;68(5)23–33.
63. Kambeitz J, Kambeitz-Ilankovic L, Leucht S, *et al.* Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. *Neuropsychopharmacology.* 2015;40(7)1742–1751.
64. Modinos G, Pettersson-Yeo W, Allen P, McGuire PK, Aleman A, Mechelli A. Multivariate pattern classification reveals differential brain activation during emotional processing in individuals with psychosis proneness. *NeuroImage.* 2012;59(3)3033–3041.
65. Madsen KH, Krohne LG, Cai X, Wang Y, Chan RCK. Perspectives on machine learning for

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022

classification of schizotypy using fMRI data. *Schizophr Bull.* 2018;44(suppl_2)S480–S490.

66. Lencer R, Trillenberg P. Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain Cogn.* 2008;68(3)219–228.
67. Nagel M, Sprenger A, Nitschke M, *et al.* Different extraretinal neuronal mechanisms of smooth pursuit eye movements in schizophrenia: An fMRI study. *NeuroImage.* 2007;34(1)300–309.
68. Grant P, Kuepper Y, Mueller EA, Wielpuetz C, Mason O, Hennig J. Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)—a suitable endophenotype of schizophrenia. *Front Hum Neurosci.* 2013:7(1). doi:10.3389/fnhum.2013.00001.
69. Miller TJ, McGlashan TH, Woods SW, *et al.* Symptom assessment in schizophrenic prodromal states. *Psychiatr Q.* 1999;70(4)273–287.
70. Ackenheil M, Stotz-Ingenlath G, Dietz-Bauer R, Vossen A. MINI Mini International Neuropsychiatric Interview, German version 5.0.0 DSM IV. *Psychiatrische Universitätsklinik München, Germany.* 1999.
71. Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkötter J. *Schizophrenia Proneness Instrument, Adult Version (SPI-a)*. Rome: Giovanni Fioriti Editore; 2007.
72. Wechsler D. Wais-III administration and scoring manual. San Antonio, TX: The Psychological Association 1997.
73. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan R. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage.* 1997;6(3)218–229.
74. McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage.* 2012;61(4)1277–1286.
75. Schröder R, Kasparbauer A-M, Meyhöfer I, Steffens M, Trautner P, Ettinger U. Functional connectivity during smooth pursuit eye movements. *J Neurophysiol.* 2020;124(6)1839–1856.
76. Eickhoff SB, Stephan KE, Mohlberg H, *et al.* A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage.* 2005;25(4)1325–1335.
77. Filzmoser P, Liebmann B, Varmuza K. Repeated double cross validation. *J Chemom.* 2009;23(4)160–171.
78. Koutsouleris N, Meisenzahl EM, Borgwardt S, *et al.* Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. *Brain.* 2015;138(7)2059–2073.
79. Dukart J, Schroeter ML, Mueller K. Age correction in dementia—matching to a healthy brain. *PLoS One.* 2011;6(7)e22193.
80. Kambeitz-Ilankovic L, Meisenzahl EM, Cabral C, *et al.* Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. *Schizophr Res.* 2016;173(3)159–165.
81. Xiao Y, Yan Z, Zhao Y, *et al.* Support vector machine-based classification of first episode drug-naïve schizophrenia patients and healthy controls using structural MRI. *Schizophr Res.* 2019;214(1)11–17.
82. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stati Soc Ser B (Methodological).* 1995;57(1)289–300.
83. Gómez-Verdejo V, Parrado-Hernández E, Tohka J. Sign-consistency based variable importance for machine learning in brain imaging. *Neuroinformatics.* 2019;17(4)593–609.
84. Dieterich M, Muller-Schunk S, Stephan T, Bense S, Seelos K, Yousry TA. Functional magnetic resonance imaging activations of cortical eye fields during saccades, smooth pursuit, and optokinetic nystagmus. *Ann N Y Acad Sci.* 2009;1164:282–292.
85. Kimmig H, Ohlendorf S, Speck O, *et al.* fMRI evidence for sensorimotor transformations in human cortex during smooth pursuit eye movements. *Neuropsychologia.* 2008;46(8)2203–2213.
86. Konen CS, Kleiser R, Seitz RJ, Bremmer F. An fMRI study of optokinetic nystagmus and smooth-pursuit eye movements in humans. *Exp Brain Res.* 2005;165(2)203–216.
87. Nagel M, Sprenger A, Hohagen F, Binkofski F, Lencer R. Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *NeuroImage.* 2008;41(2)483–492.
88. Lencer R, Nagel M, Sprenger A, *et al.* Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *Eur J Neurosci.* 2004;19(5)1430–1436.
89. Ohlendorf S, Sprenger A, Speck O, Glauche V, Haller S, Kimmig H. Visual motion, eye motion, and relative motion: a parametric fMRI study of functional specializations of smooth pursuit eye movement network areas. *J Vis.* 2010;10(14)21.
90. Tanabe J, Tregellas J, Miller D, Ross RG, Freedman R. Brain activation during smooth-pursuit eye movements. *NeuroImage.* 2002;17(3)1315–1324.
91. Tanabe J, Tregellas JR, Martin LF, Freedman R. Effects of nicotine on hippocampal and cingulate activity during smooth pursuit eye movement in schizophrenia. *Biol Psychiatry.* 2006;59(8)754–761.
92. Steffens M, Becker B, Neumann C, *et al.* Effects of ketamine on brain function during smooth pursuit eye movements. *Hum Brain Mapp.* 2016;37(11)4047–4060.
93. Kasparbauer A-M, Meyhöfer I, Steffens M, *et al.* Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. *NeuroImage.* 2016;141:52–59.

Downloaded from https://academic.oup.com/schizbullopen/article/3/1/sgac034/6601468 by guest on 28 July 2022