Oculomotor Biomarkers in Trait and State Model Systems of Psychosis

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"All models are wrong but some are useful"

"Now it would be very remarkable if any system existing in the real world could be exactly represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations. For example, the law PV = RT relating pressure P, volume V and temperature T of an 'ideal' gas via a constant R is not exactly true for any real gas, but it frequently provides a useful approximation and furthermore its structure is informative since it springs from a physical view of the behavior of gas molecules.

For such a model there is no need to ask the question **'Is the model true?'. If 'truth' is to be the 'whole truth' the answer must be 'No'. The only question of interest is 'Is the model illuminating and useful?'**."

[Box, 1979; pages 202-203]

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Our department was divided into the SPEM and the antisaccade camps and I have always been a strong advocate of the SPEM camp. But now that I am leaving I would like to take the high road at last and acknowledge that antisaccades also do have their place in oculomotor research. As Orban de Xivry and Lefèvre (2007) previoulsy have said: "Collaboration between saccades and pursuit gives a good opportunity to investigate how the central nervous system combines different modes of motor control to achieve a common goal. Indeed, saccadic and smooth pursuit systems are clearly much more integrated than has been classically proposed."

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II ABSTRACT

Antipsychotic drugs are highly effective in reducing positive symptoms of psychosis. However, despite major efforts, negative and cognitive symptoms are still not sufficiently treatable. Importantly, these symptoms have been found to be strongly related to psychosocial functioning, thus emphasizing the urgent requirement of new treatments. Model systems are one approach to investigate underlying mechanisms of psychosis and aid the development of new treatments.

In this thesis, I investigated the validity of schizotypy, a multidimensional attribute that includes positive, negative, and disorganized traits, and of sleep deprivation as model systems of psychosis. Furthermore, I combined the two models to evaluate potential interactions between them. In order to validate cognitive performance alterations in schizotypy and after sleep deprivation, I applied widely studied oculomotor biomarkers of psychosis (i.e. smooth pursuit eye movements and antisaccades). To evaluate the usefulness of oculomotor biomarkers as time stable cognitive patterns, I additionally conducted a study on the trait-like nature of saccadic tasks.

The first part of the thesis deals with the research background of psychotic disorders, the foundation of schizotypy and sleep deprivation as valuable model systems, and an introduction to widely studied oculomotor biomarkers of psychosis. The following chapter is a description with introductory information about the methods that I have deployed in the empirical studies. These methods include the recording and analysis of eye movements, latent state-trait modeling, and functional magnetic resonance imaging. Following the presentation of the main findings of the empirical studies, the thesis closes with an integration of the results in the present research literature and with indications to limitations of the studies and ideas for future research.

III ZUSAMMENFASSUNG

Antipsychotika sind wirksam in der Behandlung von Positivsymptomen der Psychose. Negativsymptome und kognitive Symptome sind trotz größter Bemühungen immer noch nicht zufriedenstellend behandelbar. Da die negativen und kognitiven Symptome eng mit dem psychosozialen Funktionsniveau zusammenhängen, werden dringend neue Behandlungsmöglichkeiten gebraucht. Modellsysteme stellen einen vielversprechenden Ansatz dar, um zugrunde liegende Mechanismen der Psychose zu untersuchen und die Entwicklung von neuen Behandlungsmöglichkeiten zu unterstützen.

In der folgenden Dissertation habe ich die Validität von Schizotypie, einem multidimensionalen Persönlichkeitsmerkmal aus positiven, negativen und desorganisierten Eigenschaften und von Schlafentzug als mögliche Modellsysteme der Psychose untersucht. Außerdem habe ich diese beiden Modellsysteme in einer Studie kombiniert, um Interaktionen zwischen ihnen zu erforschen. Zur Validierung der Veränderung von kognitiven Prozessen in hoch schizotypen Probanden und nach Schlafentzug habe ich bekannte okulomotorische Biomarker der Psychose eingesetzt (glatte Augenfolgebewegungen, Antisakkaden). Um die Nützlichkeit von okulomotorischen Biomarkern als reliable kognitive Muster zu evaluieren, habe ich außerdem eine Studie zur Zeitstabilität von Sakkaden durchgeführt.

Im ersten Teil der Dissertation werden der Forschungshintergrund zu psychotischen Störungen und die Grundlagen von Schizotypie und Schlafentzug als Modellsysteme vorgestellt, sowie ein Überblick zu den wichtigsten okulomotorischen Biomarkern der Psychose gegeben. Im folgenden Kapitel werden die empirischen Methoden vorgestellt, die in den Studien eingesetzt worden sind. Diese Methoden umfassen die Aufzeichnung und Auswertung von Augenbewegungen, Latent-State-Trait Analysen und funktionelle Kernspintomographie. Nach der Darstellung der Hauptbefunde werden die Studienergebnisse in der Diskussion in die bisherige Literatur eingeordnet und es werden Limitationen und Ideen für Folgestudien vorgestellt.

IV INTRODUCTION

IV.I Model systems of psychosis

IV.I.I Schizophrenia and the psychosis spectrum

> **"The concept of schizophrenia only covers the 30% poor outcome fraction of a much broader multidimensional psychotic syndrome, yet paradoxically has become the dominant prism through which everything 'psychotic' is observed […]."**
>
> [Guloksuz & Van Os, 2017; page 1]

Psychotic disorders have a lifetime prevalence of about 3.5% (Perälä et al., 2007) and are among the third most expensive brain disorders in Europe with costs of approximately €93 billion per year (DiLuca & Olesen, 2014; Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012). Importantly, two thirds of the costs arise from indirect costs (e.g., lost productivity, social security), mirroring the high rate of unemployment amongst patients with psychosis (Evensen et al., 2016; Olesen et al., 2012). In addition to low employment, further serious problems result from poor social functioning, high rates of physical health problems, and lack of stable housing (Morgan et al., 2017).

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5; American Psychiatric Association, 2013), key features of the schizophrenia spectrum and other psychotic disorders include delusions, hallucinations, disorganized thinking and motor behavior, and negative symptoms (e.g., diminished emotional expression, avolition, anhedonia). Additionally, cognitive deficits are common and appear to play an important role in the functional outcome (Barch et al., 2013; Heckers et al., 2013).

However, although only 30% of the people that meet the criteria of a psychotic disorder suffer from schizophrenia (Perälä et al., 2007), schizophrenia is far more investigated than the other categories and is often suggested to represent a distinct genetic brain disorder (Van Os, 2016).

Therefore, most of the research presented in the current thesis is based on patients with schizophrenia. Nevertheless, there are many reports of psychotic symptoms across diagnostic categories (Mancuso et al., 2015; Murray et al., 2004) as well as the general population (Linscott & Van Os, 2013; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), which question the concept of schizophrenia as a distinct entity and request the conceptualization of a psychosis spectrum ranging from mild symptoms to severe schizophrenia (Guloksuz & Van Os, 2017). Following this rationale, the results of the current thesis are embedded into the context of the spectrum of psychotic disorders.

IV.I.II Model systems and their benefits

Antipsychotic drugs constitute the main approach in the treatment of psychotic features in schizophrenia and other psychotic disorders and they are very effective in reducing positive symptoms such as hallucinations and delusions (Dunlop & Brandon, 2015; Jann, 2014; Köster, Carbon, & Correll, 2014; Rothschild, 2013; Sommer et al., 2012). However, despite major efforts in the development of new compounds, negative and cognitive symptoms are still not sufficiently treatable (Chou, Twamley, & Swerdlow, 2012; Hill, Bishop, Palumbo, & Sweeney, 2010; Keefe et al., 2013; Köster et al., 2014; Nielsen et al., 2015; Remington et al., 2016). Importantly, these symptoms have been found to be strongly related to various social outcome variables (Chang, Hui, Chan, Lee, & Chen, 2016; Green, 2016; Rabinowitz et al., 2012), which underlines the urgent requirement of new treatments.

A substantial problem in the development of new drugs is the high attrition rate due to lack of efficiency in clinical phase 2 (Breier, 2005; Kola & Landis, 2004). Thus, one impactful approach in further the understanding of the pathophysiology of psychosis and in identifying new drugs that are likely to succeed in clinical phase 2 is to create a condition resembling psychosis adding to clinical phase 1, e.g., using model systems. These model systems lack the confounds related to patient research and might be helpful in informing expensive clinical trials in phase 2 (Carpenter & Koenig, 2008; Koychev et al., 2012).

As has been argued elsewhere "[the] ideal model of schizophrenia would faithfully mimic the biological changes driving pathogenesis and carry high predictive value for the efficacy of novel therapeutics" (Steeds, Carhart-Harris, & Stone, 2015). In order to attain this goal, many different model systems have been developed (for an overview with examples see Table IV—1).

Table IV—1.Overview of psychosis model systems

Human models	
Surrogate populations	Schizotypy (Barrantes-Vidal, Grant, & Kwapil, 2015)
	Low performers (Vollenweider, Barro, Csomor, & Feldon, 2006)
Pharmacology	Amphetamine (Bramness et al., 2012)
	Cannabis (Koethe, Hoyer, & Leweke, 2009)
	Lysergic Acid Diethylamide (De Gregorio, Comai, Posa, & Gobbi, 2016)
	Ketamine (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012)
Deprivation	Sleep deprivation (Ettinger & Kumari, 2015)
	Sensory deprivation (Daniel, Lovatt, & Mason, 2014)
Animal models	
Development	Social isolation (Marsden, King, & Fone, 2011)
Pharmacology	Lysergic acid diethylamide (Halberstadt & Geyer, 2013)
Lesions	Ventral hippocampal lesion (Tseng, Chambers, & Lipska, 2009)
Genetics	Dopamine D1 receptor knockout mice (Van Den Buuse, 2010)

Generally, these model systems can be subdivided into long-term trait (e.g., surrogate populations) and short-term state (e.g., pharmacological and experimental interventions) models. However, psychotic disorders are heterogeneous and complex and thus several limitations have been expressed concerning pharmacological model systems, e.g., receptor tautology (Geyer, Olivier, Joëls, & Kahn, 2012) and limited phenomenological specificity for negative or cognitive symptoms (Carhart-Harris, Brugger, Nutt, & Stone, 2013). Furthermore, animal model systems are valuable and have widely been applied in the preclinical phase of pro-cognitive drug development for schizophrenia but their success has been limited so far (Burrows & Hannan, 2016; Mao, Cui, Zhao, & Ma, 2015; Pratt, Winchester, Dawson, & Morris, 2012; Young & Geyer, 2015). Therefore, systematic validation of additional model systems is needed.

Here, I will focus on schizotypy as a trait and sleep deprivation as a non-pharmacological human state model system. These may provide new insights into the underlying mechanisms of psychotic disorders and could be helpful to further the development of effective treatments.

IV.I.III Schizotypy as a trait model of psychosis

> "She reports having a consistently 'uneasy' feeling when around others […]. She has experienced herself as 'different from others' for as long as she can remember […]. She often feels that numbers, symbols, and certain images are imbued with a magical power of sorts […]. When walking down the street, she is especially attentive to the expressions on the faces of those who pass her. To her, a smile on the face of a stranger is often taken to mean that the stranger knows something about her […]."
>
> [Lenzenweger, 2010; pages 6-7]

Schizotypy refers to temporally stable (Chan et al., 2015; Gross, Silvia, Barrantes-Vidal, & Kwapil, 2015; Venables & Raine, 2015) and multidimensional personality traits. There is broad agreement that schizotypal traits can be assigned to positive (e.g., unusual perceptual experiences, ideas of reference), negative (e.g., dislike of emotional and physical intimacy, lack of enjoyment from social sources), and disorganized (e.g., odd speech, eccentric behavior) factors (Mason, Claridge, & Jackson, 1995; Raine et al., 1994). The factors were found to be invariant across cultures (Chan et al., 2015, 2016; Fonseca-Pedrero et al., 2015; Yu, Bernardo, & Zaroff, 2016), time (Venables & Raine, 2015), sex (Fonseca-Pedrero, Paíno, Lemos-Giráldez, Sierra-Baigrie, & Muñiz, 2011; Fossati, Raine, Carretta, Leonardi, & Maffei, 2003; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000), and age (Bora & Baysan Arabaci, 2009; Fonseca-Pedrero et al., 2011). However, the number of factors also depends on the measure of schizotypy, e.g., yielding only positive and negative schizotypy factors in some of the instruments (Gross et al., 2015; Kwapil, Barrantes-Vidal, & Silvia, 2008) and additional factors in others

(Davidson, Hoffman, & Spaulding, 2016; Gross, Mellin, Silvia, Barrantes-Vidal, & Kwapil, 2014; Stefanis et al., 2004).

There are many different self-report and interview instruments that capture the construct of schizotypy (for overviews refer to Fonseca-Pedrero et al., 2008; Kwapil & Chun, 2015; Mason, 2015; Vollema & Van den Bosch, 1995). The most widely used measurements represent the Schizotypal Personality Questionnaire (SPQ; Cohen, Matthews, Najolia, & Brown, 2010; Davidson et al., 2016; Raine, 1991; Raine & Benishay, 1995; Wuthrich & Bates, 2005), the Chapman Scales (Chapman, Chapman, & Raulin, 1976, 1978; Eckblad & Chapman, 1983; Winterstein et al., 2011), and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Grant et al., 2013; Mason & Claridge, 2006; Mason et al., 1995; Mason, Linney, & Claridge, 2005). Most importantly, these different instruments were found to substantially correlate with each other, emphasizing the measurement of one underlying construct (Asai, Sugimori, Bando, & Tanno, 2011; Gross et al., 2014; Rössler et al., 2015; Venables & Raine, 2015).

The distribution of schizotypy in the population can be described by two competing models (Kwapil & Barrantes-Vidal, 2015). The first model, proposed by Meehl (1962, 1989, 1990), inspired by Rado (1953), and further pursued by Lenzenweger (2006, 2010), assumes schizotypy to represent a qualitative latent construct that is either present or absent. Meehl (1990) argued that about 10% of the population is afflicted by schizotaxia, an anomaly of the central nervous system caused by the schizogene, that almost always leads to a schizotypal personality. The second model, developed by Claridge and colleagues (Claridge, 1972, 1987; Claridge & Beech, 1995; Claridge & Broks, 1984), based on the ideas of Eysenck (Eysenck, 1967; Eysenck & Eysenck, 1968), argues that schizotypy constitutes a fully dimensional trait that is continuously distributed in the population. Taxometric analyses provide an ongoing discussion about the distribution of schizotypy across the general population (Beauchaine, Lenzenweger, & Waller, 2008; Everett & Linscott, 2015; Linscott, 2013; Rawlings, Williams, Haslam, & Claridge, 2008a, 2008b). However, the fully dimensional model was found to be superior to the quasi-dimensional view in the explanation of various recent findings on schizotypy and schizophrenia (Grant, Munk, Kuepper, Wielpuetz, & Hennig, 2015; Nelson, Seal, Pantelis, & Phillips, 2013) but the issue has not been resolved (Lenzenweger, 2015; Mason, 2014).

Overlap between schizotypy and psychosis has been found on different levels of measurement (Barrantes-Vidal et al., 2015). The three factors of schizotypy resemble the factors previously found in schizophrenia (Liddle, 1987) and factor analyses revealed similar underlying structures of schizotypy in schizophrenia patients and healthy controls (Chan et al., 2016; Rossi & Daneluzzo, 2002). Additionally and in accordance with the psychosis spectrum, schizotypal traits were also found to be elevated not only in schizophrenia but also in patients with bipolar disorder (Brosey & Woodward, 2015; Chan et al., 2016; Cochrane, Petch, & Pickering, 2010; Dembińska-Krajewska & Rybakowski, 2016; Heron et al., 2003; Rossi & Daneluzzo, 2002). Furthermore, there is evidence for genetic overlap (Walter, Fernandez, Snelling, & Barkus, 2016; however see Stefanis et al., 2007), shared cognitive deficits (Giakoumaki, 2012; Siddi, Petretto, & Preti, 2017; however see Chun, Minor, & Cohen, 2013), and similar deviations in brain structure and function (Ettinger et al., 2015) for high schizotypes and patients with schizophrenia. Together, these findings suggest that schizotypy shares many common features with clinical psychosis in an attenuated form, emphasizing its usefulness as a model system of psychosis.

Studying schizotypy as a model system provides the advantage to examine underlying mechanisms of psychosis without disruptive effects of clinical illness, medication, and hospitalization (Lenzenweger, 2010). Furthermore, conversion rates in high schizotypes were reported to be low (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Gooding, Tallent, & Matts, 2005). Thus, as a trait model, schizotypy offers the possibility to image mechanisms of vulnerability rather than the symptomatic state (Koychev et al., 2011). Schizotypal traits vary in the normal population (Nelson et al., 2013) and can be assessed using self-report instruments that are cheap, reliable, and easy to administer (Kwapil & Chun, 2015; Mason, 2015). Therefore, schizotypy provides a relatively easy available opportunity to study the pathophysiology of psychosis and to support the development of new treatments.

IV.I.IV Sleep deprivation as a state model of psychosis

> "I spent like 10 days sleeping 4 or even just 2 hours, and sometimes not at all. It was sunday and I felt uncredibly well. I did not sleep, or slept only 2 hours...and so, monday I got crazy. […]... then my mind climbed, climbed... I had deliriums, I would be the new president... then I was taken to the hospital believing and saying the most crazy things. A doctor gave me an injection and I finally got asleep."
>
> [M. G., personal communication, 2017]

Randy Gardner's experience of 11 days (264 hours) of sleep deprivation is one of the most cited records of long-term wakefulness (Coren, 1998; Ross, 1965). Symptoms of sleep deprivation began with difficulty focusing the eyes (day 2) and moodiness (day 3). Hallucinations (mistook a street sign for a person) and a first delusional episode (imagined he was a famous football player) followed on day 4 and, together, with fragmented thinking and memory lapses, these experiences became worse until day 11 (Coren, 1998; Ross, 1965). The symptoms were reversible with no physical or mental problems persisting after Gardner had slept again (Coren, 1998).

In addition to Randy Gardner and similar individual case reports, scientific researchers became interested in systematically investigating the effects of sleep deprivation on cognitive and psychological variables. Early studies used descriptive impressions to characterize the consequences of acute sleep deprivation. They found prolonged wakefulness with durations of 90 to 205 hours to evoke experiences similar to hallucinations (smoke issuing from under doors/the walls/objects, humming or ringing noises in the ears, voices while a water tap was running, tingling sensations in the skin), to delusional thinking (feeling threatened by the fellow participants), and to negative (disinterest in the outside world, tendency to withdraw) and disorganized (overt confusion, disorientation, odd speech) psychosis symptoms (Berger & Oswald, 1962; Heinemann, 1966; Kales et al., 1970; Kollar et al., 1969; Luby et al., 1962; Patrick & Gilbert, 1896).

Later studies applied rating scales (Scott, McNaughton, & Polman, 2006) and validated psychological inventories (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007; Killgore et al., 2008) to explore the effects of sleep deprivation. Those studies detected higher paranoia (Kahn-Greene et al., 2007) and greater confidence in formal superstitions and magical thinking processes (Killgore et al., 2008), as well as higher depressed mood (Kahn-Greene et al., 2007; Scott et al., 2006) and reduced positive thinking (Killgore et al., 2008). In addition to experimental induced sleep deprivation, sleep dysfunctions, e.g., symptoms of insomnia, were also found to be associated to increases of psychotic experiences (Barton, Varese, Jones, Kyle, & Haddock, 2017; Reeve, Emsley, Sheaves, & Freeman, 2017).

Beside alterations in mental states, sleep deprivation was reported to induce cognitive deficits such as reduced attention, working memory, and processing speed (Koslowsky & Babkoff, 1992; Lim & Dinges, 2010; Phillips, 2005; Pilcher & Huffcutt, 1996) that are accompanied by widespread changes in brain function (Krause et al., 2017) and overlap with those seen in patients with psychotic disorders (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Hill et al., 2013; Reichenberg & Harvey, 2007; Schaefer, Giangrande, Weinberger, & Dickinson, 2013).

There is an ongoing debate in the literature about the underlying mechanisms of the sleep deprivation induced cognitive deficits (Jackson et al., 2013; Lim & Dinges, 2010). On the one hand, fundamental attentive processes were emphasized to be responsible for the cognitive dysfunctions being present specifically in monotonous tasks. These hypotheses stress lapses (Williams, Lubin, & Goodnow, 1959), state instability (Doran, Van Dongen, & Dinges, 2001), less controlled attention (Pilcher, Band, Odle-Dusseau, & Muth, 2007), and reduced arousal (Wilkinson, 1961) and vigilance (Lim & Dinges, 2008) as relevant factors to explain cognitive impairments after sleep loss. On the other hand, Harrison, Horne and colleagues (Harrison, Horne, & Rothwell, 2000; Horne, 2000; Horne, 1993; Jones & Harrison, 2001) argue that sleep deprivation impacts on higher-order cognitive tasks that are mediated through the prefrontal cortex such as language (Harrison & Horne, 1998) and decision making (Harrison & Horne, 2000) tasks, analogous to a healthy ageing condition (Harrison et al., 2000; Zhou, Wu, Yu, & Lei, 2017; however see Tucker, Stern, Basner, & Rakitin, 2011). To date, there are findings that

point to more integrative approaches, suggesting that cognitive decline through prolonged wakefulness is a result of both a reduction of attentional arousal and impaired central processing (Boonstra, Stins, Daffertshofer, & Beek, 2007; Ratcliff & Van Dongen, 2009).

Additionally, various characteristics and systematic interindividual differences seem to affect how people respond to long-term wakefulness (Van Dongen, Baynard, Maislin, & Dinges, 2004), e.g., age (Brendel et al., 1990; Philip et al., 2004; Smulders, Kenemans, Jonkman, & Kok, 1997; Webb, 1985), sex (Corsi-Cabrera, 2003), genetic variation (Dissel et al., 2015; Holst et al., 2017), perceived sleep quality (Cosgrave et al., 2017), and personality (Killgore, Richards, Killgore, Kamimori, & Balkin, 2007; Rupp, Killgore, & Balkin, 2010; Taylor & McFatter, 2003). Interestingly, evidence for further amplifying factors on the impact of sleep deprivation was found in early studies investigating the effects of psychotomimetic drugs after prolonged wakefulness (Bliss, Clark, & West, 1959; Safer, 1970a, 1970b). Safer studied the effects of lysergic acid diethylamide (1970b) and scopolamine (1970a) and found stronger cognitive impairments and intense hallucinations in the combined drug sleep deprivation groups than the drug alone groups.

Disturbances of sleep are common in schizophrenia patients (Freeman, Pugh, Vorontsova, & Southgate, 2009; Monti & Monti, 2004; Reeve et al., 2017) and symptoms appear to deteriorate under acute sleep deprivation (Koranyi & Lehmann, 1960). Emphasizing the association between sleep disruption, psychosis symptoms, and cognitive dysfunctions from a clinical perspective, sleep dysfunctions seem to be related to the severity of symptoms (Xiang et al., 2009) and poor cognitive functioning in schizophrenia patients (Ferrarelli, 2015; Wilson & Argyropoulos, 2012).

Using sleep deprivation to model psychosis symptoms offers some crucial benefits (for an overview see Ettinger & Kumari, 2015) to existing models. Sleep deprivation is inexpensive, easy to apply, and can be considered as a safe model system as effects have been found to be completely reversible (Everson, 1997). Additionally, prolonged sleep can be combined with nearly any biomarker and can be applied cross-species (Frau et al., 2008).

IV.II Biomarkers and their application in psychosis research

IV.II.I Definition and delimitation

Biological markers, mostly abbreviated as biomarkers, represent characteristics that are "objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001).

In clinical applications, biomarkers are proposed to be helpful with regard to diagnostic (classification of the presence of a disorder), prognostic (prediction of the development of a disorder), and theranostic (prediction of the response to a certain treatment) purposes (Weickert, Weickert, Pillai, & Buckley, 2013). Additionally, in scientific research contexts, biomarkers are beneficial in the development and evaluation of model systems (Ettinger & Kumari, 2015) and drug treatments (De Visser, Van der Post, Pieters, Cohen, & Van Gerven, 2001; Green, Nuechterlein, et al., 2004). Due to their objective measurement they can circumvent the problems of subjectivity and variability that are common in traditional measures such as rating scales and interviews (Koychev et al., 2011; Weickert et al., 2013). Thus, biomarkers might constitute a valuable addition to clinical ratings and interviews (Bender, Weisbrod, & Resch, 2007).

To achieve these goals, a biomarker must be closely associated to a given disorder. In practical terms, a biomarker should be an accurate indicator of the development, the presence or the progression of a specific disorder. Thus, biomarkers can represent persistent deviations, they can occur episodic and symptom-related, or they can be sequelae of the existing disorder (Thibaut et al., 2015). In other words, biomarkers can refer to altered behavioral and biological processes that are associated to the core of a disorder (trait biomarkers) or mirror the status of clinical symptoms (state biomarkers) (Chen, Bidwell, & Norton, 2006). Both, trait and state biomarkers can in principle be addressed by pharmacological compounds. However, modulation of trait biomarkers should be independent from symptom alterations (Chen et al., 2006). When using biomarkers in the context of drug development, a consistent response across specific drugs with a clear response to a therapeutic dose and a dose-response relationship are

required. Additionally, a comprehensible association between the biomarker, the drug pharmacology, and the pathogenesis of the disorder should be obtained (De Visser et al., 2001). Furthermore, test-retest reliability and the utility as a repeated measure are key elements of biomarkers that can be applied in clinical trials (Nuechterlein et al., 2008).

Biomarker is often used as an umbrella term that comprises further concepts such as endophenotypes. Endophenotypes, also referred to as intermediate phenotypes, can be considered as a subset of biomarkers that additionally meet the criteria of heritability and co-segregation (Glahn et al., 2014; Gottesman & Gould, 2003; Gould & Gottesman, 2006; for reviews of the endophenotype rationale and current scientific issues see Braff, 2015; Braff, Greenwood, Swerdlow, Light, & Schork, 2008; Flint & Munafò, 2007; Glahn et al., 2014; Gould & Gottesman, 2006; Insel & Cuthbert, 2009). As the aim of the present thesis does not involve findings on genetic alterations or results from non-affected family members, the preferably used term here is considered to be biomarker.

IV.II.II Importance of cognitive biomarkers

> "[…] cognitive deficits of schizophrenia are a core feature of the illness. A core feature means that the cognitive performance deficits are not simply the result of the symptoms, nor of the current treatments of schizophrenia. Instead, these deficits represent a fundamental aspect of the illness."
>
> [Green et al., 2004; page 302]

Generally, there is a broad literature on many different types of biomarkers that have been found to be relevant in schizophrenia research, e.g., neuropsychological, neurophysiological, neuroendocrine, and neuroimmune assessments (for overviews refer to Allen, Griss, Folley, Hawkins, & Pearlson, 2009; De Visser et al., 2001; Goff et al., 2016; Greenwood et al., 2016; Lai et al., 2016; Rodrigues-Amorim et al., 2017; Schmitt, Martins-de-Souza, et al., 2016;

Schmitt, Rujescu, et al., 2016; Stöber et al., 2009; Thibaut et al., 2015; Tomasik, Rahmoune, Guest, & Bahn, 2016).

However, as cognitive dysfunctions are very common in schizophrenia (Aquila & Citrome, 2015; Bhattacharya, 2015; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs, 2004; Palmer, Dawes, & Heaton, 2009; Schaefer et al., 2013) and the broader psychosis spectrum (Reilly & Sweeney, 2014) and can still not be treated effectively (Keefe et al., 2013; Nielsen et al., 2015; Vingerhoets, Bloemen, Bakker, & Van Amelsvoort, 2013), biomarkers of cognition are particularly valuable in the research of new treatment options. Impairments of cognition were found to play a key role in schizophrenia and represent a much discussed topic among experts in the field (Keefe et al., 2015). Additionally, in order to advance treatment approaches, there is strong effort to develop suitable measures of cognitive processes (Carter & Barch, 2007; Green, Nuechterlein, et al., 2004; Nuechterlein et al., 2008).

Cognitive impairments in schizophrenia include e.g., deficits of processing speed, attention, working memory, and executive functioning (Schaefer et al., 2013). Some of the dysfunctions are already present before the manifestation of the illness, e.g., in subjects with clinical high risk to develop psychosis (Bora & Murray, 2014; Seidman et al., 2016) and remain relatively stable from the first episode over the course of the illness (Bergh et al., 2016; Ekerholm et al., 2012; Hoff, Svetina, Shields, Stewart, & DeLisi, 2005; Rund et al., 2016). Additionally, cognitive deficits have been found regardless of drug treatment, e.g., in medication naïve first episode patients (Fatouros-Bergman et al., 2014) and relatively independent from remission of clinical symptoms (Bergh et al., 2016; Braw et al., 2013; Heilbronner, Samara, Leucht, Falkai, & Schulze, 2016). Impairments in cognition do not only relate to schizophrenia but also to the psychosis spectrum (Bora & Pantelis, 2015; Bora, Yucel, & Pantelis, 2010; Hill et al., 2013; Kuswanto et al., 2016; Lewandowski, Cohen, & Ngur, 2011; Reichenberg et al., 2009; Trotta, Murray, & MacCabe, 2015). In order to account for the important role of cognitive impairments, the latest version of the DSM has included a dimensional assessment of cognitive impairments in the psychotic disorders section (Barch et al., 2013).

Most importantly and emphasizing its impact as a treatment goal, numerous findings have demonstrated that cognitive impairments are associated to psychosocial functioning, outcome, and relapse (Chang et al., 2016; Chen et al., 2005; Fervaha, Foussias, Agid, & Remington, 2014; Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green, Kern, & Heaton, 2004; Nuechterlein et al., 2011). Widely used measures to display cognitive functioning in patients represent neuropsychological tests (e.g., MATRICS Consensus Cognitive Battery; Nuechterlein, Green, et al., 2008) that through their complexity may have problems to detect subtle effects of pharmacological treatments (Reilly & Sweeney, 2014). In contrast to neuropsychological tests, neurophysiological measures, e.g. prepulse inhibition (PPI) and oculomotor measures, are far more specific and may therefore be advantageous in evaluating pharmacological alterations in cognitive functioning (Green et al., 2009; Hill et al., 2010; Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008).

IV.II.III Oculomotor biomarkers

i. Foundations and oculomotor tasks

> "The oculomotor system is a microcosm of the brain -it has sensory input, motor output, and incorporates bits of virtually all the major anatomical structures. In clinical neurological practice, few diagnostic tests discover quite so much quite so quickly as a test of oculomotor function."
>
> [Carpenter, 1994; page 341]

Foundations

Measuring oculomotor control offers some crucial benefits in the assessment of cognitive functions and there has been much progress with many new insights in the last decades. The progress involves technical advances of oculomotor measure methods (Duchowski, 2007) and a lot of practical research on eye movements (Klein & Ettinger, 2008; Kowler, 2011).

Generally, the assessment of oculomotor variables offers a tool to study cognitive functions using highly selective measures and an efficient way as regards to time and personnel resources. Mostly, oculomotor tasks are short and their instructions are straightforward (Klein & Ettinger, 2008). Thus, in accordance with the required criteria of tolerability and practicability (Green, Nuechterlein, et al., 2004), the assessment is relatively simple to implement and feasible even in severely impaired patients (Poletti et al., 2017). Furthermore, oculomotor tasks can be adapted systematically to tap into different cognitive functions very specifically (Barnes, 2008; Hutton, 2008). In addition, the neural underpinnings of the oculomotor systems are well-understood as the use and combination of many different measurement methods have advanced this field, by applying e.g., lesion studies (Müri & Nyffeler, 2008; Sharpe, 2008), assessments in non-human primates (Ilg & Thier, 2008; Johnston & Everling, 2008), and investigations using various imaging and electrophysiological methods in humans (Lencer & Trillenberg, 2008; McDowell, Dyckman, Austin, & Clementz, 2008).

Another strength of measuring oculomotor function is the limited set of types of eye movements that have different properties with regards to their role in vision and their physiological and anatomical characteristics. Leigh and Zee (2015) differentiate vestibular (keep images stable on the retina during brief rotations of the head), vergence (disjunctive eye movements to keep/place images on the fovea), optokinetic (keep images stable on the retina during sustained rotations of the head), and smooth pursuit (SPEM; hold the image of a small moving object on the fovea) eye movements, fixations (hold images of a stationary object on the fovea), quick phases of nystagmus (reposition the eyes during sustained rotation towards the oncoming scene), and saccades (cause objects of interest to be placed on the fovea).

SPEM and saccades have been most widely studied in relation to cognitive and brain functional disturbances of patients with psychotic disorders.

SPEM

SPEM are a mechanism that allows to follow a small moving object solely with the eyes aiming to provide a clear vision of this object (Leigh & Zee, 2015). Two factors are important to attain

this goal (Barnes, 2008). First, as motion of the object's image on the retina adversely affects visual acuity, retinal motion has to be minimized and retinal velocity error/retinal slip velocity (difference between target velocity and eye velocity) is used as sensory input to SPEM. Secondly, the fovea is the area of the retina with the highest acuity and, therefore, the image of the object should ideally be processed close to the fovea. Whenever position error is detected, small saccadic eye movements are used to realign the eyes (see Orban de Xivry & Lefèvre, 2007 for further information on the collaboration network of pursuit and saccades).

Saccadic eye movements that disrupt pursuit are divided into compensatory and intrusive saccades (Levy, Sereno, Gooding, & O'Driscoll, 2010). Compensatory saccades reduce position error by repositioning the eyes on the target (catch-up saccades, back-up saccades). Intrusive saccades increase the position error of the eye by disturbing the correspondence between eye and target (anticipatory saccades, leading saccades, square wave jerks). A full description of the saccade types can be found in Chapter V.I. However, as opposed to saccades towards stationary stimuli, the programming involves not only the position error but also information about the target motion (De Brouwer, Missal, & Lefèvre, 2001).

Generating SPEM can be divided into two successive phases (open-loop, closed-loop; Lisberger, Morris, & Tychsen, 1987). SPEM are initiated roughly 100ms after a stimulus has started to move (Robinson, 1965), presumably due to 70ms processing delay and 30ms initiation time (Wyatt & Pola, 1987). The first 100ms pursuit were found to be guided by the perception of target motion across the retina and do not depend on visual feedback comparable to an open-loop system (Lisberger & Westbrook, 1985). The initiation of pursuit can be investigated using ramp tasks or, in order to avoid the initial saccade that realign the image to the fovea, step-ramp tasks can be applied (Carl & Gellman, 1987; Rashbass, 1961).

After 100ms, retinal slip velocity is deployed as a feedback control and the system works closed-loop (Lisberger et al., 1987), relying on retinal (slip velocity) and (after a short familiarization period) extra-retinal (prediction, anticipation) input. The maintenance of pursuit is commonly studied with triangular or sinusoidal target movements. Thereby, stressing the impact

of predictive mechanisms, these periodic waveforms can be tracked more accurately than predicted from usually existing visual processing delays (Barnes, 2008). Findings that have examined the role of periodicity on prediction reported that unexpected changes to periodic waveforms result in poor adjustment to the novel waveform partly due to maintaining eye velocity consistent with the preceding waveform (Barnes & Asselman, 1991a, 1991b). Furthermore, the use of predictive and anticipatory functions has been explored using target occlusion/blanking (for an overview see Fukushima, Fukushima, Warabi, & Barnes, 2013). SPEM can be sustained, albeit with lower accuracy, during short periods of target disappearance (Becker & Fuchs, 1985) and even recover when expecting the target to reappear (Bennett & Barnes, 2003, 2004). Additionally, SPEM can be generated anticipatorily when the stimulus is blanked initially but reappears shortly afterwards (Barnes & Collins, 2008).

Neural core regions of SPEM include (for overviews refer to Leigh & Zee, 2015; Lencer & Trillenberg, 2008) motion-sensitive area V5 (Dukelow et al., 2001; Mukherjee, Battifarano, Simoncini, & Osborne, 2015), frontal eye fields (Fukushima et al., 2002; Gagnon, Paus, Grosbras, Pike, & O'Driscoll, 2006; Rosano et al., 2002; Tanaka & Lisberger, 2001), supplementary eye fields (Gagnon et al., 2006; Lencer, Nagel, et al., 2004; Missal & Heinen, 2004; Schmid, Rees, Frith, & Barnes, 2001), and parietal eye fields (Lencer, Nagel, et al., 2004; Nagel et al., 2006; Nagel, Sprenger, Hohagen, Binkofski, & Lencer, 2008; Schmid et al., 2001).

Models based on control theory have made a major contribution to the specification of the dynamic characteristics and physiological foundations of SPEM (for overviews refer to Barnes, 2008; Glasauer, 2007; Leigh & Zee, 2015; Lencer & Trillenberg, 2008). A key model proposed by Yasui and Young (1975) is based on the assumption that stable pursuit is obtained by the positive feedback of an efference copy (Von Holst & Mittelstaedt, 1950)/corollary discharge signal (Sperry, 1950) of the oculomotor command. According to this and similar models (e.g., Robinson, Gordon, & Gordon, 1986) the stimulus for SPEM is an internal representation combining retinal slip velocity inferred from the retina and the efference copy of the motor command. However, the models cannot account for findings of e.g., recovery of eye velocity shortly before expected target reappearance (Bennett & Barnes, 2003, 2004). Therefore, more recent methods suggest to add a predictive pathway (second internal loop that stores information

about target velocity similar to a working memory; Fukushima, Fukushima, Warabi, & Barnes, 2013) or use generative models that rely on active inference (sample sensory inputs in order to minimize errors of prediction; Adams, Perrinet, & Friston, 2012).

The main dependent variables can be classified into global and specific measures (for an overview see Smyrnis, 2008). Global measures refer to the full recording of SPEM thus including sections of pursuit as well as sections of saccadic eye movements. Therefore, using global measures (e.g., global error of eye compared to target position, root mean square error; RMSE) to evaluate SPEM yield no clear distinctions between possible inabilities either to pursue the target or to suppress the saccadic system ("abnormalities of pursuit" or "abnormalities during pursuit"; Abel & Ziegler, 1988). However, the RMSE was found to be highly valuable for quantifying deficits in clinical populations (Clementz, Iacono, & Grove, 1996). Specific measures refer either to the pursuit (e.g., velocity gain; how well does eye velocity match target velocity) or to the saccadic system (e.g., number of saccadic intrusions per second). A full description of the measures can be found in Chapter V.I.

Prosaccades and antisaccades

Prosaccades are visually-guided saccades that require the participant to look as fast and as accurately as possible towards a sudden-onset peripheral target (Figure IV—1). The cognitive influences on the generation of saccades can be illustrated using the LATER (Linear Approach to Threshold with Ergodic Rate) model proposed by Carpenter and colleagues (1981; 1995). Briefly summarized, there is a decision signal that increases from baseline with a certain rate until a threshold value is attained and the saccade is triggered. All model parameters can potentially be affected by cognitive processes. Thus, these cognitive modulations can be responsible for whether a saccade and how quickly this saccade is triggered (Hutton, 2008). In addition, the generation of a saccade always requires balancing bottom-up (e.g., stimulus position, size, luminance) and top-down (e.g., goals, intentions) signals (Hutton, 2008).

There is a strong association between saccade execution and attention. In their eye-mind assumption, Just and Carpenter (1980) summarized the relationship as follows: “there is no appreciable lag between what is being fixated and what is being processed” (page 331). Even though there is broad agreement that saccadic eye movements and spatial attention are closely linked to each other (Hutton, 2008), it remains unclear how to describe the relationship itself (e.g., overt and covert shifts of attention are functionally independent, Hunt & Kingstone, 2003; they are loosely functionally connected, Fischer & Weber, 1993; or they are more explicit functionally relate, Schneider, 1995).

In the antisaccade paradigm (Hallett, 1978), the participant is required to perform a saccade to the opposite direction of a sudden-onset peripheral target (Figure IV—1). Antisaccades typically result in a considerable proportion of direction errors (~20%), which in almost all cases (~99%) are immediately followed by a correct antisaccade (Hutton & Ettinger, 2006; Tatler & Hutton, 2007). Prosaccades are often used as a control condition in addition to antisaccades. They represent an elegant and convenient experimental control because both tasks share the same stimuli and they only differ in their task instructions (Hutton, 2008; Munoz & Everling, 2004). Thereby, they can either be presented separately in blocks consisting only of prosaccades or antisaccades or in a mixed design with randomized alternating prosaccades and antisaccades (Cherkasova, Manoach, Intriligator, & Barton, 2002; Dyckman, Camchong, Clementz, & McDowell, 2007). Obtaining prosaccades in addition to antisaccades is strongly recommended in clinical and experimental research (Antoniades et al., 2013) because prosaccade data are helpful to model antisaccades and allow to investigate whether performance impairments are already present in low-level visuomotor control.

The performance of correct antisaccades is thought to consist of two relevant processes: First, the automatic answer towards the peripheral target must be suppressed and second, the location of the peripheral stimulus has to be transformed into a voluntary eye movement away from the target (Cutsuridis, 2017; Everling & Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004). Thereby, previous findings suggest parallel saccade programming and a competition between the exogenously elicited prosaccade and the endogenously activated anti-

saccade starting at stimulus onset (Hutton & Ettinger, 2006; Massen, 2004). Thus active inhibitory processes have been proposed to represent key features in suppressing erroneous prosaccades and executing correct antisaccades (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002; Hutton, 2008). Additional cognitive processes that are relevant to calculate appropriate coordinates and initiate the correct antisaccade include working memory (Mitchell, Macrae, & Gilchrist, 2002) and goal activation (Nieuwenhuis, Broerse, Nielen, & Jong, 2004).

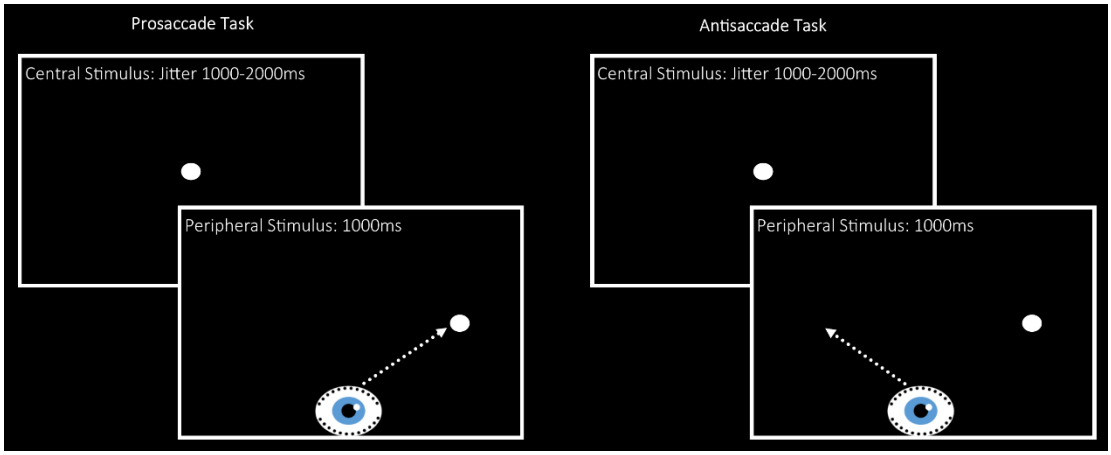

Figure IV—1. Illustration of a correct performed prosaccade (left) and antisaccade (right).

The neural saccade circuit comprises the primary visual and extra-striate cortices, regions of posterior parietal cortex, frontal and supplementary eye fields, striatum, thalamus, and the superior colliculus (Jamadar, Fielding, & Egan, 2013; McDowell et al., 2008). Generally, antisaccades have been shown to elicit more extended brain activation than prosaccades. Differences were most consistently found in parietal and dorsolateral prefrontal cortices and in frontal and supplementary eye fields (DeSouza, Menon, & Everling, 2002; Dyckman et al., 2007; Ettinger et al., 2008; for overvews refer to Cieslik, Seidler, Laird, Fox, & Eickhoff, 2016; Hutton & Ettinger, 2006; Jamadar, Fielding, & Egan, 2013; McDowell et al., 2008; Munoz & Everling, 2004). However, task properties (block/mixed design) may play an important role in explaining divergent results regarding neural differences between prosaccades and antisaccades across studies (Dyckman et al., 2007). Additionally, variation in brain activation between prosaccades

and antisaccades was proposed to stem from preparatory and not from movement related differences (DeSouza et al., 2002).

The main dependent variables for prosaccades and antisaccades (Antoniades et al., 2013; Leigh & Zee, 2015) include percentages of direction errors, latencies (time that is needed to start the saccade), accuracy measures (how accurate does the amplitude of the saccade match the amplitude of the target), and peak velocities. A full description of the measures can be found in Chapter V.I.

ii. Oculomotor dysfunctions in psychosis

> "If one's experience of the sensory consequences of one's action was not attenuated, then when one made an active movement it would feel like a passive movement. It would feel as if one's action was being driven by an external force."
> [Fletcher & Frith, 2009; page 50]

SPEM

Diefendorf and Dodge showed in 1908 that patients with schizophrenia suffer from deteriorated SPEM (Diefendorf & Dodge, 1908). Nearly 70 years later, Holzman and colleagues replicated these deficits (Holzman, Proctor, & Hughes, 1973). Since then numerous studies have been conducted on the performance of SPEM in schizophrenia and findings of impaired performance have widely been replicated (for overviews refer to Franco, De Pablo, Gaviria, Sepúlveda, & Vilella, 2014; Hutton & Kennard, 1998; Levy, Holzman, Matthysse, & Mendell, 1993, 1994; Levy, Sereno, Gooding, & O'Driscoll, 2010; O'Driscoll & Callahan, 2008; Tandon, 1999; Thaker, 2000, 2008; Trillenberg, Lencer, & Heide, 2004).

The most frequently reported deficit in schizophrenia patients is low maintenance gain (Bagary et al., 2004; Boudet et al., 2005; Fabisch et al., 2009; Haraldsson et al., 2008, 2009; Hutton et al., 2004; Ivleva et al., 2014; Kathmann, Hochrein, Uwer, & Bondy, 2003; Lencer et al., 2015; Lencer, Trillenberg, et al., 2004; Louchart-De La Chapelle et al., 2005; Morita et al., 2017; Nagel

et al., 2007; Nkam et al., 2010; Spering, Dias, Sanchez, Schutz, & Javitt, 2013; Sprenger, Trillenberg, Nagel, Sweeney, & Lencer, 2013; Trillenberg et al., 2017).

Furthermore, poor performance in schizophrenia has been detected using global measures such as reduced SPEM quality (Amador et al., 1991; Chen, Levy, et al., 1999), higher signal to noise ratio (Allen, 1997; Benson et al., 2012; Kelly et al., 1990), and increased global position error (Benson et al., 2012; Lee, Williams, Loughland, Davidson, & Gordon, 2001; Sponheim, Iacono, Thuras, Nugent, & Beiser, 2003; Sweeney et al., 1993).

Additionally, schizophrenia patients demonstrate more frequent saccadic intrusions during SPEM (Allen, 1997; Campion et al., 1992; Haraldsson et al., 2008, 2009; Mather, Neufeld, Merskey, & Russell, 1992). More specifically, schizophrenia has been found to be associated to higher frequencies (Abel, Friedman, Jesberger, Malki, & Meltzer, 1991; Friedman et al., 1995; Lencer et al., 2008; Nkam et al., 2001) and amplitudes (Sweeney, Clementz, et al., 1994; Sweeney, Haas, Li, & Weiden, 1994) of catch-up saccades and higher rates of anticipatory (Friedman, Abel, Jesberger, Malki, & Meltzer, 1992; Ross, Olincy, Harris, Sullivan, & Radant, 2000; Spengler et al., 2006; Sweeney et al., 1993) and leading (Martin et al., 2007; Ross et al., 2002, 2000; Ross, Olincy, Harris, et al., 1999) saccades. No differences between patients and controls were reported for square wave jerks (Campion et al., 1992; Clementz, Sweeney, Hirt, & Haas, 1990; Flechtner, Steinacher, Sauer, & Mackert, 1997; Nkam et al., 2001; Sweeney et al., 1993) and back-up saccades (Litman, Hommer, Radant, Clem, & Pickar, 1994; Radant & Hommer, 1992).

In addition to disturbed closed-loop SPEM, patients with schizophrenia display worse pursuit initiation (Chen, Levy, et al., 1999; Chen, Nakayama, Levy, Matthysse, & Holzman, 1999; Hong, Avila, Adami, Elliot, & Thaker, 2003; Lencer et al., 2010, 2015; Sweeney et al., 1999; Trillenberg et al., 2017) and reduced capacities of SPEM prediction during stimulus disappearance (Hong et al., 2003; Ivleva et al., 2014; Thaker, Ross, Buchanan, Adami, & Medoff, 1999; Trillenberg et al., 1998, 2017).

A comprehensive meta-analysis (O'Driscoll & Callahan, 2008) that summarized studies from 1998 to 2008 (k=57, $n_{patients}$=2049, $n_{controls}$=1927) reported high effect sizes for global variables (d=0.70-1.55), maintenance gain (d=0.87), and leading saccade rate (d=1.31).

Neural correlates of SPEM impairments in schizophrenia mainly comprise abnormal activation in frontal and occipital areas. Specifically, most studies have reported lower brain activity during SPEM for schizophrenia patients compared to healthy controls in frontal and supplementary eye fields (Hong et al., 2005; Keedy, Ebens, Keshavan, & Sweeney, 2006; Tregellas et al., 2004). In addition, impaired SPEM were found to be associated to reduced gray matter integrity (Bagary et al., 2004) and lower metabolism (Ross et al., 1995) in frontal areas. However, there are also findings of SPEM related increased activations in dorsolateral prefrontal cortex and frontal eye fields in schizophrenia (Lencer et al., 2011; Nagel et al., 2007). Furthermore, patients with schizophrenia were found to exhibit abnormal brain activation in the motion-sensitive V5 complex (Hong et al., 2005; Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005; Nagel, Sprenger, Steinlechner, Binkofski, & Lencer, 2012). A recent study that combined SPEM recording with electroencephalography found schizophrenia patients to demonstrate reduced frontal/posterior phase synchronization in beta to gamma range frequency bands (Krishna, O'Neill, Sánchez-Morla, & Thaker, 2014).

Emphasizing stability independent from clinical status, most studies revealed no significant associations between SPEM performance and severity of clinical symptoms (Haraldsson et al., 2008; Hutton et al., 2004; Kallimani et al., 2009; Kelly et al., 1990; Lencer et al., 2008, 2015; Louchart-De La Chapelle et al., 2005; Schlenker et al., 1994) or differences between non-deficit and deficit schizophrenia patients (Nkam et al., 2001, 2010). However, some studies reported that higher SPEM deficits were modestly related to more pronounced (predominantly negative) schizophrenia symptoms (Hong et al., 2003; Lee et al., 2001; Lees Roitman, Keefe, Harvey, Siever, & Mohs, 1997; Malaspina et al., 2002; Ross et al., 1996, 1997; Sweeney, Clementz, et al., 1994).

SPEM deficits have been assessed in chronic schizophrenia (Katsanis & Iacono, 1991; Litman et al., 1991), in the residual subtype (Arolt, Teichert, Steege, Lencer, & Heide, 1998), and in first

episode medicated (Bagary et al., 2004; Hutton et al., 1998, 2004; Keedy et al., 2006), untreated (Lencer et al., 2011; Rybakowski & Borkowska, 2002), and medication naïve (Keedy et al., 2006; Lencer et al., 2008; Sweeney, Haas, et al., 1994) patients. Some studies that compared treated and untreated first episode and chronic patients reported rather similar SPEM disturbances in all patient groups compared to healthy controls (Campion et al., 1992; Hutton et al., 2001; Thaker et al., 1999). Additionally, SPEM have been found to be impaired in unaffected first-degree relatives of schizophrenia patients (Lencer et al., 2015). In accordance with these findings, SPEM in schizophrenia patients were found to maintain stable over time (Benson et al., 2012; Calkins, Iacono, & Curtis, 2003; Lencer et al., 2010; Yee, Nuechterlein, & Dawson, 1998), despite improvement of clinical symptoms (Flechtner, Steinacher, Sauer, & Mackert, 2002; Gooding, Iacono, & Beiser, 1994; Kallimani et al., 2009; Schlenker & Cohen, 1995) or commencement of medical treatment (Campion et al., 1992; Sweeney, Haas, et al., 1994). Together, these findings of time stability, independence of clinical symptoms, and presence in unaffected first-degree relatives suggest SPEM impairments to represent a valuable trait biomarker of schizophrenia.

Studies on the impacts of current available antipsychotic medication on SPEM performance in schizophrenia revealed either no/minimal (Flechtner et al., 2002; Sweeney et al., 1998; Sweeney, Haas, et al., 1994) or even adverse (Friedman, Jesberger, & Meltzer, 1992; Lencer et al., 2008; Litman et al., 1994) effects. More specifically, Hutton and colleagues (2001) found that SPEM gain was unaffected by short-term but deteriorated by long-term antipsychotic medication.

Cognitive deficits that play an important role in the explanation of SPEM deficits in schizophrenia cover impairments in motion processing, prediction/anticipation, and attention. Facilitation of attention during SPEM (monitor changes of the stimulus) revealed an improvement of overall performance in patients and controls (Amador et al., 1991; Cegalis & Sweeney, 1981; Schlenker et al., 1994; Sweeney, Clementz, et al., 1994; Sweeney, Haas, et al., 1994; however see Yee et al., 1998). These findings suggest that impairments of attentive processes do not constitute the primary reason of SPEM deficits in schizophrenia (Sweeney, Clementz, et al.,

1994). In accordance with the rather subtle effects of attention enhancement on SPEM performance in schizophrenia patients, Stuve and colleagues (1997) found a strong association between deteriorated SPEM and lower motion perception even after controlling for measures of attention. Additionally, underlining the responsibility of deficient motion perception, many studies have reported impairments of sensorimotor transformation in schizophrenia that are mostly reflected by reduced initial eye velocity/acceleration (Lencer et al., 2010, 2015; Trillenberg et al., 2017). With regard to higher cognitive functions, schizophrenia patients fail to adequately use efference copy/predictive (Spering et al., 2013) and anticipatory (Avila, Hong, Moates, Turano, & Thaker, 2006) information (however see Trillenberg et al., 2017). Furthermore, patients with schizophrenia were found to demonstrate difficulties maintaining SPEM during periods of blanking (Ivleva et al., 2014; Thaker et al., 1999; Trillenberg et al., 2017; however see Sprenger et al., 2013). The use of efference copy information to attenuate sensory experiences is important in distinguishing self-generated from externally-generated actions. Adversely affected efference copy function was found to significantly contribute to explanation approaches of psychosis symptoms (Feinberg, 1978; Ford & Mathalon, 2012; Pynn & DeSouza, 2013) and higher deficits were found to be associated to higher symptom severity in schizophrenia patients (Rösler et al., 2015).

In agreement with the hypothesized overlap between different phenotypes of psychosis (Tamminga et al., 2013), SPEM deficits have been found to be present not only in schizophrenia but also in patients with schizoaffective (Martin et al., 2007) and affective (Ivleva et al., 2014; Kathmann et al., 2003; Lencer et al., 2010; Sponheim et al., 2003; Sweeney et al., 1999; Trillenberg et al., 2017) disorders. However, some findings concluded that impairments in schizophrenia were more severe compared to other disorders of the psychosis spectrum (Amador et al., 1991; Lencer et al., 2015; Lencer, Trillenberg, et al., 2004). Emphasizing diagnostic specificity to psychosis spectrum disorders, rather intact SPEM were found for patients with predominantly non-psychotic affective disorders (Abel et al., 1991; Fabisch et al., 2009; Friedman et al., 1995), substance use disorders (Kathmann, Wagner, Rendtorff, Schöchlin, & Engel, 1995; Radant & Hommer, 1992), and attention-deficit/hyperactivity disorder (Ross et

al., 2000). Additionally minimal or distinct deficits were reported in obsessive compulsive disorder (Damilou, Apostolakis, Thrapsanioti, Theleritis, & Smyrnis, 2016; Farber et al., 1997; Lencer et al., 2004; Spengler et al., 2006; for an overview see Jaafari et al., 2011) and posttraumatic stress disorder with secondary psychotic symptoms (Cerbone et al., 2003).

In summary, many studies have replicated SPEM disturbances in schizophrenia patients (O'Driscoll & Callahan, 2008) and their neural correlates were found to comprise abnormal activation in frontal and motion-sensitive posterior areas (Hong et al., 2005; Nagel et al., 2012). These trait-like deficits remain stable over time (Benson et al., 2012), are rather independent from clinical symptoms (Lencer et al., 2015), pertain the further psychosis spectrum (Lencer et al., 2015), and the beneficial effects of current available medication is low (Lencer et al., 2008). Underlining its importance in every day functioning, impaired SPEM in schizophrenia patients were also found in natural settings (Dowiasch et al., 2016) and to be associated to reduced occupational and social functioning (Beiser et al., 1994; Katsanis, Iacono, & Beiser, 1996).

Prosaccades and antisaccades

In 1988, Fukushima and colleagues first detected disturbances in the control of antisaccades in schizophrenia patients (Fukushima et al., 1988). Since then, numerous studies have replicated increased direction error rates (Ettinger et al., 2006; Ettinger, Kumari, Crawford, et al., 2004; Haraldsson et al., 2008; Mazhari et al., 2011; Nkam et al., 2001; Radant et al., 2010, 2015; Reilly et al., 2014), promoting antisaccades to be a highly valuable biomarker of schizophrenia (Thibaut et al., 2015). Importantly, schizophrenia patients display normal error correction rates underlining adequate task understanding and intact error awareness (Nkam et al., 2001; Polli et al., 2008). Thus, this finding emphasizes that the reasons for deteriorated antisaccade performance are associated to impairments in cognitive control mechanisms and not to deficient understanding of the task instructions or lack of motivational aspects.

In addition to direction errors, schizophrenia patents were found to demonstrate prolonged latencies and reduced spatial accuracy (Haraldsson et al., 2008; Maruff, Danckert, Pantelis, & Currie, 1998; Mazhari et al., 2011; Radant et al., 2015; for an overview, see Gooding & Basso,

2008). When comparing schizophrenia patients and healthy controls in basic saccade generation, e.g., prosaccades, most studies agree that both groups display similarly intact performance (Broerse, Crawford, & den Boer, 2001; Gooding & Basso, 2008).

The neural correlates of antisaccade deficits in schizophrenia include dysfunctions in frontostriatal regions. Schizophrenia patients were found to demonstrate frontal cortical atrophy (Fukushima et al., 1988) and they fail to demonstrate higher brain activity in dorsolateral prefrontal cortex (Fukumoto-Motoshita et al., 2009; McDowell et al., 2002; Nakashima et al., 1994) and further frontal regions (Tu, Yang, Kuo, Hsieh, & Su, 2006) during antisaccades, a neural pattern that is apparent in healthy controls. In addition to reduced activation of prefrontal cortex, Camchong and colleagues (2008) also detected lower brain signal during antisaccades for patients in frontal and supplementary eye fields, middle occipital gyrus, insula, cuneus, and anterior cingulate. Higher antisaccade direction errors were found to be associated to reduced grey matter volume in the medial superior frontal cortex (Bagary et al., 2004) and longer latencies of correct antisaccades were related to smaller prefrontal lobe volume in schizophrenia patients and healthy controls (Schulze et al., 2006).

Recently, deficient antisaccade performance was suggested to be explained by an aberrant pattern in rostral and dorsal anterior cingulate cortices and ventrolateral prefrontal cortex during the preparation of antisaccades (Manoach et al., 2013; Polli et al., 2008). Furthermore, associations between number of antisaccade errors and activation of anterior cingulate cortices were less pronounced in patients than controls (Polli et al., 2008). Further evidence for abnormal response preparation comes from electrophysiological studies: Schizophrenia patients were found to lack higher contingent negative variation when preparing antisaccades compared to prosaccades (Klein, Heinks, Andresen, Berg, & Moritz, 2000; Reuter, Herzog, Endrass, & Kathmann, 2006) and to present neural abnormalities over prefrontal cortex prior to the execution of antisaccades (Kang, Dionisio, & Sponheim, 2011).

Besides frontal alterations, further relevant differences between schizophrenia and healthy controls were found in thalamus (Fukumoto-Motoshita et al., 2009) and striatal regions. Lower

brain activation during antisaccades was shown in striatum (Raemaekers et al., 2002) and lentiform nucleus (Tu et al., 2006) and volume of the caudate was reported to predict antisaccade latency and gain in first episode psychosis (Ettinger, Kumari, Chitnis, et al., 2004). Furthermore, Crawford and colleagues (1996) found schizophrenia patients with high error rates to display lower regional cerebral blood flow in the anterior cingulate, insula, and striatum than patients with normal error rates.

Another conceivably relevant factor in the explanation of schizophrenia dysfunctions includes abnormal timing of hemodynamic responses during antisaccades in schizophrenia. Dyckman and colleagues (2011) found delayed and prolonged hemodynamic responses in frontal eye fields that did not differ in amplitude during antisaccades for patients compared to healthy controls, suggesting that these functions that are necessary to achieve correct antisaccades take longer to implement and are more persistent.

Consistent with intact behavioral performance of prosaccades, no differences in neural activation were found between patients and healthy controls during basic saccade generation (McDowell et al., 2002). Altogether, these findings suggest functionally intact circuit of basic saccades, whereas mechanisms underlying the generation of antisaccades display severe disturbances (for an overview see Gooding & Basso, 2008).

The relationship between antisaccade impairments and severity of schizophrenia symptoms revealed mixed findings. In accordance with trait stability independent from clinical status, most findings demonstrated no/minimal significant correlations between antisaccade measures and schizophrenia symptom severity (Haraldsson et al., 2008; Harris, Reilly, Thase, Keshavan, & Sweeney, 2009; Hutton et al., 2004; Kallimani et al., 2009; Nkam et al., 2001; Reilly et al., 2014). However, some studies found that poorer antisaccade performance was associated to higher clinical (predominantly negative) symptom ratings (Ettinger, Kumari, Chitnis, et al., 2004; Louchart-De La Chapelle et al., 2005; Müller, Riedel, Eggert, & Straube, 1999; Nieman et al., 2000).

Impairments of antisaccade performance have been found in first-episode/recent-onset (De Wilde et al., 2008; Grootens et al., 2008; Hutton, Joyce, Barnes, & Kennard, 2002), medication-

naïve (Harris et al., 2009), and drug-treated (Hutton et al., 1998; Maruff et al., 1998; Nieman et al., 2000) patients as well as in acute (Curtis, Calkins, Grove, Feil, & Iacono, 2001) and remitted (Curtis et al., 2001) schizophrenia. Furthermore, antisaccade deficits have been reported in unaffected first-degree relatives of schizophrenia patients (Reilly et al., 2014). Additionally, emphasizing their role as core features of the illness (Green, Nuechterlein, et al., 2004), longitudinal studies have reported antisaccade deficits in schizophrenia patients to represent high test-retest reliabilities despite fluctuations in clinical states (Calkins et al., 2003; Gooding, Mohapatra, & Shea, 2004; Kallimani et al., 2009; Light et al., 2012). Together, these findings of time stability independent of clinical symptoms and the presence of deficits in unaffected first-degree relatives suggest antisaccade impairments to demonstrate a valuable trait biomarker of schizophrenia.

To date, studies that have examined the effects of antipsychotic medication on antisaccades in schizophrenia patients have mainly detected no or only few beneficial effects (Burke & Reveley, 2002; Harris, Reilly, Keshavan, & Sweeney, 2006; Hill, Reilly, Harris, Khine, & Sweeney, 2008; Larrison et al., 2011; Müller et al., 1999), possibly due to baseline dependency (Babin et al., 2011).

Conceivable explanations for antisaccade deficits in schizophrenia rather point to cognitive than sensory sources (Leonard et al., 2013). Several cognitive functions such as inhibition (Barton, Pandita, Thakkar, Goff, & Manoach, 2008), working memory (Hutton et al., 2004), and attention (Tendolkar et al., 2005) seem to be involved in the deterioration of antisaccade performance in schizophrenia (for an overview see Gooding & Basso, 2008). Additionally, antisaccade deficits can be considered as an essential deficit in goal-directed behavior (Nieuwenhuis et al., 2004; Reuter & Kathmann, 2004), a concept that is closely related to symptoms of schizophrenia (Reuter & Kathmann, 2007; Rinaldi & Lefebvre, 2016).

In addition to antisaccade deficits in patients with schizophrenia, similar impairments have also been found in schizoaffective (Martin et al., 2007; Reilly et al., 2014) and affective disorders with psychotic features (Harris et al., 2009; Katsanis, Kortenkamp, Iacono, & Grove, 1997; Reilly et al., 2014). Furthermore, borderline personality disorder patients with psychotic features had

higher antisaccade error rate that those without these features (Grootens et al., 2008). Underlining its specificity to the psychosis spectrum, rather unimpaired (Fukushima et al., 1990; Harris et al., 2009) and unstable (Gooding et al., 2004) antisaccade performance was reported in affective disorders without psychotic features. Similarly, patients with obsessive compulsive disorder demonstrate low or distinct impairments (Damilou et al., 2016; McDowell & Clementz, 1997; Spengler et al., 2006) compared to patients from the psychosis spectrum (for an overview see Jaafari et al., 2011).

To summarize, schizophrenia is associated with behavioral antisaccade disturbances, specifically increased direction errors (Radant et al., 2015) whereas basic saccade generation circuits seem to be largely intact (Gooding & Basso, 2008). On the brain functioning level, disruption of antisaccades is mainly reflected in abnormal activation of frontal-striatal circuits (Camchong et al., 2008; Raemaekers et al., 2002). The antisaccade performance deficits were reported to be time-stable and independent from fluctuations in clinical symptoms (Light et al., 2012) and current available antipsychotic medication has only minimal beneficial effects (Hill et al., 2008).

iii. Evaluation of SPEM and antisaccades as biomarkers of psychosis

As discussed above, SPEM and antisaccades meet several important criteria for biomarkers of schizophrenia (for a review see Koychev et al., 2011). First, both tasks can be assessed with high objectivity, thereby showing high internal consistency and test-retest reliability (Ettinger et al., 2003). Furthermore, the tasks are short und their instructions are simple which makes them applicable even in severely impaired patients (Klein & Ettinger, 2008). Additionally, in contrast to complex and time-consuming neuropsychological assessments, oculomotor measures are easy to administer and variables can be analyzed in real time (Benson et al., 2012).

Secondly, SPEM and antisaccade measures demonstrate high construct validity. Neural networks of SPEM and antisaccades have been well-established in humans (SPEM: Lencer & Trillenberg, 2008; antisaccades: McDowell et al., 2008) and non-human primates (SPEM: Ilg &

Thier, 2008; antisaccades: Johnston & Everling, 2008). Additionally their cognitive underpinnings have been clearly studied and can be manipulated systematically (SPEM: Barnes, 2008; antisaccades: Hutton, 2008).

Third, SPEM and antisaccade impairments have widely been replicated in schizophrenia and the psychosis spectrum (SPEM: Lencer et al., 2015; antisaccades: Reilly et al., 2014). In order to provide further evidence for using the measures as indicators of pathogenic processes, algorithms to quantify classification accuracies were applied. Using logistic regression approaches, oculomotor variables (in combination with further biomarkers) were found to be useful in the classification of schizophrenia patients with sensitivities between 82%-95% and specificities between 83%-88% (Martin et al., 2007; Millard et al., 2016; Price et al., 2006). Furthermore, applying neural network algorithms on oculomotor data, patients with schizophrenia can be distinguished from controls with high levels of discrimination (80%-98%; Benson et al., 2012; Campana, Duci, Gambini, & Scarone, 1999).

Fourth, underlining the general responsiveness of SPEM and antisaccade measures to pharmacological treatments, both measures were found to display dose-dependent responses to antipsychotic drugs in healthy participants (De Visser et al., 2001; Reilly et al., 2008). Nevertheless, the effects of current available antipsychotic drugs on oculomotor performance in patients with psychosis were found to be of only small benefit or even adverse (Hill et al., 2008; Lencer et al., 2008), emphasizing the importance of the development of new compounds.

Altogether, SPEM and antisaccade measures represent valuable biomarkers that are clearly associated to disorders of the psychosis spectrum. In terms of practical application, they might be highly beneficial in supporting the diagnosis of cognitive disturbances in psychotic disorders (Benson et al., 2012) and in developing alternatives to traditional disorder categories (Clementz et al., 2016; Hudgens-Haney et al., 2017; Insel et al., 2010). Furthermore, the assessment of oculomotor control can be helpful in the evaluation of pharmacological responses to new therapeutic interventions for schizophrenia patients (Reilly et al., 2008).

IV.III Oculomotor biomarkers in the schizotypy and sleep deprivation models

IV.III.I SPEM, saccades, and schizotypy

SPEM

Studies of SPEM in high schizotypes have found performance deficits similar to those reported in studies with psychotic patients. An overview of all studies can be found in Table IV—2 and an exemplary illustration of SPEM in schizotypy is in Figure IV—2b. Reduced performance in schizotypy includes deficits in global measures, e.g., lower quality of SPEM (O'Driscoll, Lenzenweger, & Holzman, 1998), higher percentage of poor eyetrackers (Holahan & O'Driscoll, 2005; Simons & Katkin, 1985), and higher RMSE (Gooding, Miller, & Kwapil, 2000; Smyrnis et al., 2007; Van Kampen & Deijen, 2009). Additionally, performance deficits were reported using specific SPEM measures, e.g., lower velocity gain (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kattoulas, Evdokimidis, et al., 2011; Koychev et al., 2016), and higher frequency of saccade rate (Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007). In most studies, different saccade types were combined to compute the total rate of saccades (Koychev et al., 2016; Schmechtig et al., 2013; Smyrnis et al., 2007). The few studies that have distinguished saccade subtypes, discovered positive associations between schizotypy and catch-up (Lenzenweger & O'Driscoll, 2006) but not anticipatory (Gooding et al., 2000) saccade rate.

Poor SPEM have been found in high schizotypes comprising the positive, negative, and disorganized factors (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kattoulas, Evdokimidis, et al., 2011; Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007), and the total schizotypy score (Koychev et al., 2016; Schmechtig et al., 2013; Van Kampen & Deijen, 2009).

Additionally, schizotypy-related SPEM deficits were found using different methodological approaches. Most studies have examined extreme groups with high schizotypes and average (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Kattoulas, Smyrnis, et al., 2011; Koychev et al., 2016; Smyrnis et al., 2007; Van Kampen & Deijen, 2009) and/or low (Koychev et al., 2016; Simons & Katkin, 1985) control participants. Additionally, few studies have investigated schizotypal traits in participants with high or poor oculomotor accuracy (Kendler et al., 1991; Siever,

1982; Siever et al., 1989). Furthermore, correlative designs have been used to explore associations between schizotypy and SPEM (Kattoulas, Smyrnis, et al., 2011; Kelley & Bakan, 1999; Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007).

However, there are also studies that have not detected any schizotypy-related differences in SPEM (Blackwood et al., 1994; Schmechtig et al., 2013; Thaker, Cassady, Adami, Moran, & Ross, 1996). Reasons for the non-significant findings may include too unspecific and imprecise SPEM measures (Blackwood et al., 1994; Thaker et al., 1996) and extremely strict study inclusion criteria that may have blurred the rather small effects of schizotypy (Schmechtig et al., 2013).

Almost all studies have focused on closed-loop maintenance SPEM. In most of these studies, sinusoidal movement patterns using frequencies ranging from 0.2Hz to 0.8Hz were applied (Holahan & O'Driscoll, 2005; Kelley & Bakan, 1999; Koychev et al., 2016; Lenzenweger & O'Driscoll, 2006). Additionally, some studies have employed triangular movement patterns with velocities ranging from 8°-30°/sec (O'Driscoll et al., 1998; Smyrnis et al., 2007; Van Kampen & Deijen, 2009). Similar to schizophrenia patients (O'Driscoll & Callahan, 2008), performance deficits in schizotypy were found to be largely independent from frequency/velocity (Koychev et al., 2016; Smyrnis et al., 2007; Van Kampen & Deijen, 2009) occurring with different target movement patterns (Koychev et al., 2016; Van Kampen & Deijen, 2009). Until now, there is only one study that has investigated predictive SPEM in schizotypy. Kattoulas and colleagues (2011) found disorganized schizotypy to be related to lower residual gain and, unexpectedly, high negative schizotypes had higher residual gain. These results remain inconclusive and need to be further investigated. Until now, there is no research on the open-loop response in high schizotypal subjects.

A further major issue comprises the neural correlates of SPEM deficits in schizotypy. To date there is no study that has addressed the underlying neural mechanisms of reduced SPEM performance found in high schizotypes.

In summary, schizotypal traits are associated with lower maintenance SPEM, e.g., higher RMSE and lower velocity gain (Gooding et al., 2000; Koychev et al., 2016), compatible with findings

from schizophrenia patients (O'Driscoll & Callahan, 2008). However, the neural mechanisms of these behavioral performance deficits remain unclear.

Prosaccades and antisaccades

Previous research in high schizotypes have reported antisaccade deficits that are similar to those observed in patients with psychotic disorders. An overview of these studies is in Table IV—3. Most importantly, high schizotypes have been found to demonstrate higher rates of direction errors (Aichert, Williams, Möller, Kumari, & Ettinger, 2012; Ettinger et al., 2005; Gooding, Shea, & Matts, 2005; Holahan & O'Driscoll, 2005; Koychev et al., 2016; Schmechtig et al., 2013). Additionally, most studies have applied prosaccade tasks as a control condition. In accordance with psychotic patients (Broerse et al., 2001; Gooding & Basso, 2008), schizotypes were reported to show intact prosaccade performance (Aichert et al., 2012; Gooding, 1999; Gooding, Shea, et al., 2005; Larrison, Ferrante, Briand, & Sereno, 2000). Contrary to schizophrenia (Gooding & Basso, 2008), schizotypy is not associated to prolonged antisaccade latencies (Aichert et al., 2012; Ettinger et al., 2005; Gooding, Shea, et al., 2005; Holahan & O'Driscoll, 2005; Koychev et al., 2016).

Increased antisaccade direction errors have been found to be associated with positive (Aichert et al., 2012; Ettinger et al., 2005, 2017; Gooding, Shea, et al., 2005; Larrison et al., 2000), negative (Gooding, 1999; Gooding, Shea, et al., 2005), as well as to overall high schizotypy (Koychev et al., 2016; Schmechtig et al., 2013). However, in studies that have compared positive and negative schizotypy, antisaccade deficits were found to arise more consistently in positive schizotypes (Ettinger et al., 2005, 2017; Holahan & O'Driscoll, 2005).

Furthermore, schizotypy-related antisaccade deficits have been discovered with different methodological approaches. Most studies used extreme groups using mean deviation criteria with high schizotypes and average (Gooding et al., 2000; Gooding, Shea, et al., 2005; Koychev et al., 2016; Larrison et al., 2000; Schmechtig et al., 2013) and/or low (Koychev et al., 2016; Larrison et al., 2000) control subjects. Additionally, a study of Klein and colleagues (2000) applied a median split to discriminate high and low schizotypy groups. Furthermore, three studies

have investigated larger samples with correlative analyses (Aichert et al., 2012; Ettinger et al., 2005; Smyrnis et al., 2003).

However, there are also studies that revealed no differences in antisaccade performance for high and low schizotypes (Klein et al., 2000; Thaker et al., 2000, 1996). Reasons for the lack of differences may include methodological details. For example, the gap and overlap task variations were used in the study by Klein and colleagues (2000), but not the standard step task. Studies that discovered elevated antisaccade direction error rate in schizotypy have mostly applied a step task design (Aichert et al., 2012; Ettinger et al., 2005; Gooding, Shea, et al., 2005; Koychev et al., 2016; Schmechtig et al., 2013). Additionally, Holahan and O'Driscoll (2005) compared step, gap, and overlap designs in one study and schizotypy-related group differences were only detected using the step design. However, a study by Larrison and colleagues (2000) also reported effects of schizotypy in a gap design antisaccade task. Further reasons for non-significant results may be due to imprecise definitions of schizotypal traits. Despite considerable overlap between schizophrenia spectrum personality symptoms and schizotypy measured with the Chapman Scales (Thaker, Moran, Adami, & Cassady, 1993), Thaker and colleagues (2000, 1996) did not detect any performance differences between healthy subjects with and without schizophrenia spectrum symptoms.

Until today, there is only one study that has examined the neural mechanisms of antisaccade performance in schizotypy. Aichert and colleagues (2012) demonstrated that higher positive schizotypy was associated to less brain activity in putamen, cerebellum, thalamus, and visual cortex during antisaccades compared to fixation, a pattern that overlaps with dysfunctions previously reported in schizophrenia patients (Camchong et al., 2008; Fukumoto-Motoshita et al., 2009; Raemaekers et al., 2002).To summarize, high schizotypes have been found to display elevated antisaccade direction errors, similar to patients with psychotic disorders (Koychev et al., 2016; Reilly et al., 2014). In addition, the neural correlates of poor antisaccade performance were found to overlap between schizotypy (Aichert et al., 2012) and schizophrenia (Raemaekers et al., 2002) which underlines the meaningfulness and utility of schizotypy as a model system for schizophrenia.

Table IV—2. Summary of studies on schizotypy and SPEM.

Authors	Study Design [Sample Size]	Schizotypy Measure [Dimension]	Task Velocity/Frequency [Dependent Variables]	Results
Siever (1982)	*n*=68 good eyetrackers, *n*=9 poor eyetrackers	MMPI [total]	sinusoidal, 0.4Hz	Poor eyetrackers had higher social introversion.
Simons & Katkin (1985)	extreme groups [(a) *n*=17 PhysAn, *n*=16 low controls; (b) *n*=37 PhysAn/PerAb, *n*=14 average controls]	Chapman Scales [positive, negative]	sinusoidal, 0.33Hz/0.4Hz [pursuit quality, % poor eyetrackers]	There were no differences for pursuit quality. High schizotypes had higher % poor eyetrackers.
Siever et al. (1989)	*n*=31 good eyetrackers, *n*=13 poor eyetrackers	Rating Scale for Borderline and Schizotypal Characteristics [positive, negative]	sinusoidal, 0.4Hz	Poor eyetrackers scored higher on various schizotypy characteristics. Additionally, SPEM accuracy was negatively correlated to social isolation.
Kendler et al. (1991)	*n*=52 good eyetrackers, *n*=5 poor eyetrackers [twin study]	Structured Interview for Schizotypy, SRQ [positive, negative]	sinusoidal, 0.3Hz [RMSE]	There were no differences in schizotypy traits and positive symptom schizotypy between the good and poor eyetrackers. Poor eyetrackers had higher negative symptom schizotypy.
Blackwood et al. (1994)	extreme groups [*n*=17 high, *n*=17 controls]	Baron Schedule for Schizotypal Personality Disorder	sinusoidal, 0.4Hz [ln (S/N)]	There were no differences between high and low schizotypes.
Thaker, Cassady, Adami, Moran, & Ross, (1996)	*n*=46 without symptoms, *n*=22 with symptoms	Schizophrenia spectrum symptoms [highly correlated to the Chapman Scales; Thaker et al., 1993]	sinusoidal, 0.5Hz [pursuit quality]	There were group differences on SPEM performance. SPEM performance was not associated to spectrum symptoms.
O'Driscoll, Lenzenweger, & Holzman (1998)	extreme groups [*n*=31 PerAb, *n*=24 average controls]	Chapman Scales [positive]	triangular, 8°/sec [pursuit quality]	High schizotypes had lower quality of pursuit.
Kelley & Bakan (1999)	correlations [*n*=121]	MMPI [total]	sinusoidal, 0.4Hz/0.8Hz [RMSE]	Higher schizotypy was associated to higher RMSE.
Gooding et al. (2000)	extreme groups [*n*=97 PerMag, *n*=54 SocAn, *n*=31 PhysAn, *n*=94 controls]	Chapman Scales [positive, negative]	sinusoidal, 0.4Hz [RMSE, gain, total and anticipatory saccades]	High schizotypy groups had higher RMSE and lower gain. No differences were found for total and anticipatory saccades.

Holahan & O'Driscoll (2005)	extreme groups [*n*=21 PerAb, *n*=20 PhysAn, *n*=29 controls]	Chapman Scales [positive, negative]	sinusoidal, 0.4Hz [% poor eyetrackers, gain]	Both groups had higher % poor eyetrackers and PhysAnh but not PerAb showed lower gain than controls.
Lenzenweger & O'Driscoll (2006)	correlations [*n*=300]	SPQ [total, positive, negative, disorganized]	sinusoidal, 0.4Hz [gain, CUS]	SPQ total score and all sub-scales were associated with lower gain and higher disorganization was correlated with higher CUS.
Smyrnis et al. (2007)	correlations [*n*=1087] and extreme groups [*n*=55 PerAb, *n*=26 SPQ total, *n*=34 cognitive-perceptual, *n*=41 negative, *n*=23 disorganization, *n*=19 paranoia, *n*=1032-1068 controls]	Chapman Scales, SPQ [total, positive, negative, disorganized]	triangular, 10°,20°,30°/sec [RMSE, gain, total saccade frequency]	Negative schizotypy was positively correlated to saccade frequency at 30°/sec. No other associations were found in the whole sample. Using sub-groups with extreme scores, high PerAb had higher RMSE and high disorganized presented lower gain and higher saccade frequency.
Van Kampen & Deijen (2009)	extreme groups [*n*=19 high, *n*=19 average controls]	SSQ [total]	triangular, 5°,10°,20°/sec [RMSE]	High schizotypes showed higher RMSE than controls.
Kattoulas et al. (2011)	correlations [*n*=762-763] and extreme groups [*n*=46 PerAb, *n*=19 SPQ total, *n*=34 cognitive-perceptual, *n*=32 negative, *n*=17 disorganization, *n*=15 paranoia, *n*=717-747 controls]	Chapman Scales, SPQ [total, positive, negative, disorganized]	triangular with blanking, 10°/sec [gain, latency, deceleration time]	Disorganized schizotypy was negatively related to residual gain. Using sub-groups with extreme scores, high negative schizotypes presented higher residual gain. No effects were found for latency and deceleration time.
Schmechtig et al. (2013)	extreme groups separated by three drugs and placebo	SPQ [total]	sinusoidal, 0.25Hz/0.5Hz/0.75Hz [gain, total saccade frequency]	No effects for schizotypy were found.
Koychev et al. (2016)	extreme groups [*n*=30 high, *n*=31 average, *n*=22 low]	SPQ [total]	sinusoidal, 0.25Hz/0.5Hz/0.75Hz [gain, total saccade frequency]	Average schizotypes displayed lower gain compared to low schizotypes. High schizotypes performed intermediate and there were no differences to the low and average schizotypy groups. No differences were found for frequency of saccades.

Notes. Studies are presented in chronological order. Only studies using adult samples are included. SPEM=smooth pursuit eye movements. SRQ=self-report questionnaire for schizotypy. PhysAn=physical anhedonia scale. SocAn=social anhedonia scale. PerAb=perceptual aberration scale. PerMag=perceptual aberration/magical ideation scale. MMPI=Minnesota multiphasic personality inventory. SPQ=schizotypal personality questionnaire. SSQ=schizotypic syndrome questionnaire. RMSE=root mean square error. CUS=catch-up saccade.

Table IV—3. Summary of studies on schizotypy and saccades.

Authors	Study Design [Sample Size]	Schizotypy Measure [Dimension]	Task Design [Dependent Variables]	Results
Thaker et al. (1996)	*n*=45 without symptoms, *n*=23 with symptoms	Schizophrenia spectrum symptoms [highly correlated to the Chapman Scales; Thaker et al., 1993]	PS, AS [step]	There were no group differences on PS and AS performance. Saccade performance was not associated to spectrum symptoms.
O'Driscoll, Lenzenweger, & Holzman (1998)	extreme groups [*n*=31 high, *n*=24 average controls]	Chapman Scales [positive]	AS [step, 12°] [% correct, latency, perseverative errors, non-perseverative errors]	High schizotypes had lower % correct AS and a higher rate of perseverative errors. The groups did not differ in latencies to correct antisaccades or errors and non-perseverative errors.
Gooding (1999)	extreme groups [*n*=90 PerMag, *n*=39 SocAnh, *n*=89 controls]	Chapman Scales [positive, negative]	PS, AS [step, 4°, 8°, 12°] [direction errors, latency]	Both high schizotypy groups had higher AS error rate than controls. No group differences were found for PS error rates and PS and AS latencies.
Klein, Brügner, Foerster, Müller, & Schweickhardt (2000)	extreme groups using median split [*n*=20 high, *n*=21 average controls]	SPQ [total]	PS, AS [gap, overlap, 4°] [direction errors, latency, % anticipatory saccades, % express saccades]	There were no differences between the two groups.
Larrison, Ferrante, Briand, & Sereno, (2000)	extreme groups [*n*=16 high, *n*=7 average, *n*=13 low]	RISC [positive]	PS, AS [gap, non-gap, 7.2°] [direction errors, latency]	High schizotypes had higher error rate in the AS gap condition compared to low schizotypes. No other effects were significant.
Thaker et al. (2000)	*n*=37 without symptoms, *n*=25 with symptoms	Schizophrenia spectrum symptoms [highly correlated to the Chapman Scales; Thaker et al., 1993]	PS, AS [step, 10°-150°] [direction errors, latency, gain, peak velocity]	There were no group differences and associations between saccade measures and spectrum symptoms.
Smyrnis et al. (2003)	correlations [*n*=1273] and extreme groups [*n*=68 PerAb, *n*=39 SPQ, *n*=1205-1234 controls]	Chapman Scales, SPQ [positive, total]	AS [step, 2-10°] [direction errors, mean and SDs of latency]	Schizotypy was only weakly associated to AS performance. High PerAb group had higher direction error rate and SD of AS latency than controls. No significant differences were found for the SPQ group.

Ettinger et al. (2005)	correlations [*N*=115]	RISC, PSQ-80 [positive, negative, thought disorder]	PS, AS [step, 6°, 12°] [direction errors, latency, spatial error]	AS direction errors and PS spatial error were positively associated with positive schizotypy. Additionally, PS latency was negatively correlated to a measure of thought disorder.
Gooding, Shea, & Matts (2005)	extreme groups [*n*=50 PerMag, *n*=32 SocAnh, *n*=39 controls]	Chapman Scales [positive, negative]	PS, AS [step, 4°, 8°, 12°] [direction errors, latency]	Both high schizotypy groups had higher AS direction errors than controls and, additionally, at follow-up, the SocAnh group produced more error than the PerMag group. No group differences were found for PS and AS latencies.
Holahan & O'Driscoll (2005)	extreme groups [*n*=21 PerAb, *n*=20 PhysAn, *n*=29 controls]	Chapman Scales [positive, negative]	AS [step, gap, overlap, 10°] [direction errors, latency]	The PerAb group showed higher AS direction error rates in the step task compared to controls and the PhysAnh group were found to score intermediate. No group differences were found for latencies and the gap and overlap tasks.
Aichert, Williams, Möller, Kumari, & Ettinger (2012)	correlations [*N*=54]	RISC [positive]	PS, AS [step, 8°] [direction errors, latency]	AS error rate was related to higher schizotypy. No associations were found for latencies. Furthermore, higher schizotypy was associated to less activation in putamen, cerebellum, thalamus, and visual cortex during AS and less activity in posterior IPS, SEF, and visual cortex during PS.
Schmechtig et al. (2013)	extreme groups separated by three drugs and placebo	SPQ [total]	PS, AS [step, 7.25°, 14.5°] [direction errors, latency, amplitude gain, peak velocity]	High schizotypes made more direction errors than medium schizotypes in the placebo condition. No effects for schizotypy were found for the other variables.
Koychev et al. (2016)	extreme groups [*n*=30 high, *n*=31 average, *n*=22 low]	SPQ [total]	AS [step, 7.25°, 14.5°] [direction errors, latency, saccade amplitude, peak velocity]	High schizotypes had higher direction error rates than low schizotypy controls. No effects were found for the other variables.

Notes. Studies are presented in chronological order. Only studies using adult samples are included. PS=prosaccades. AS=antisaccades PhysAn=physical anhedonia scale. SocAn=social anhedonia scale. PerAb=perceptual aberration scale. PerMag=perceptual aberration/magical ideation scale. SPQ=schizotypal personality questionnaire. RISC=Rust inventory of schizotypal cognitions. PSQ-80=personality syndrome questionnaire. For further overviews, see also Myles, Rossell, Phillipou, Thomas, & Gurvich (2017) and Wan, Thomas, Pisipati, Jarvis, & Boutros (2017).

IV.III.II SPEM, saccades, and sleep deprivation

SPEM

Healthy subjects have been found to show sleep deprivation-related impairments on SPEM performance that are similar to those seen in patients with psychotic disorders. An overview of all studies can be found in Table IV—4 and an exemplary illustration of SPEM after sleep deprivation is in Figure IV—2d. The performance deficits mainly comprised reduced maintenance gain (De Gennaro, Ferrara, Urbani, & Bertini, 2000; Fransson et al., 2008; Tong, Maruta, Heaton, Maule, & Ghajar, 2014). Additionally, there are findings of reduced accuracy (Fransson et al., 2008) and elevated anticipatory but not catch-up saccade rate (Tong et al., 2014).

Durations of sleep deprivation ranged from 7 hours (Porcu, Ferrara, Urbani, Bellatreccia, & Casagrande, 1998) to 40 hours (De Gennaro et al., 2000). All studies examined closed-loop SPEM and most of them used sinusoidal tasks (De Gennaro et al., 2000; Tong et al., 2014) with frequencies between 0.2Hz-1.1Hz. Additionally, there is one study that has applied stimuli moving with different constant velocities (10°-40°/sec; Fransson et al., 2008). Until now, there is no study that has investigated the effects of sleep deprivation in open-loop and predictive SPEM tasks.

Furthermore, there are also studies that did not find any sleep deprivation-related differences in the performance of SPEM (Quigley, Green, Morgan, Idzikowski, & King, 2000; Van Steveninck et al., 1999). Both studies compared the performance of subjects after a normal sleep night and a night of sleep deprivation, a design that has been successfully applied in other studies (Fransson et al., 2008; Tong et al., 2014). However, both studies failed to provide information on their measures and, additionally, Quigley and colleagues (2000) did not describe the parameters of the task. Therefore, it is difficult to guess any reasons for the non-significant results.

In summary, there is evidence for sleep deprivation to deteriorate the maintenance of SPEM (Fransson et al., 2008; Tong et al., 2014) in a similar way to disturbances that are present in schizophrenia patients (O'Driscoll & Callahan, 2008). However, further studies are needed to characterize these deficits in more detail using additional measures and task variations.

Prosaccades and antisaccades

Consistent with increased antisaccade error rates and latencies in psychosis, sleep deprivation was found to disrupt antisaccade performance in healthy subjects (see Table IV—5 for an overview). Total sleep deprivation was reported to increase antisaccade direction errors and latencies (Bocca, Marie, & Chavoix, 2014). Additionally, a recent study displayed higher antisaccade error rates even after partial sleep deprivation (Lee, Manousakis, Fielding, & Anderson, 2015). However, other studies failed to find sleep deprivation-related increases in antisaccade impairments (Crevits, Simons, & Wildenbeest, 2003; Gais et al., 2008; Zils, Sprenger, Heide, Born, & Gais, 2005). As time-of-day was found to impact on response control (Manly, Lewis, Robertson, Watson, & Datta, 2002; Wachowicz et al., 2015), reasons for the inconsistent findings may include confounding with circadian effects (Crevits et al., 2003; Fimm & Blankenheim, 2016).

In contrast to largely intact prosaccade performance in schizophrenia (Gooding & Basso, 2008), sleep deprivation was additionally found to impair prosaccade performance, e.g., increase direction errors (Porcu et al., 1998) and latencies (Bocca & Denise, 2006; De Gennaro et al., 2000; Van Steveninck et al., 1999) and reduce spatial accuracy (Bocca & Denise, 2006; Porcu et al., 1998; Zils et al., 2005).

Sleep deprivation in these experimental settings was carried out once, with durations varying between 7 hours (Porcu et al., 1998) and 72 hours (Thomas et al., 2003). Additionally there are studies that have examined the effects of chronic sleep deprivation and of wakefulness due to working conditions. Persistent partial sleep deprivation with seven days of only 3 to 5 hours sleep per night was shown to prolong saccadic peak velocities (Russo et al., 2003; however see: Wachowicz et al., 2015). Another study compared the saccade performance of physicians during a 24 hours on-call shift to a routine working day (non on call). They found that the on-call shift yielded in increased time awake and longer latencies of saccades (lower rates of saccades with latencies below 150ms; Ernst et al., 2014).

Overall, prolonged wakefulness adversely affects the performance of both antisaccades and prosaccades. The disturbances of antisaccade control (Bocca et al., 2014; Lee et al., 2015) correspond to findings of patients with psychotic disorders (Radant et al., 2015). Until now, there

are only few studies that have explicitly compared antisaccades and prosaccades within one study (Crevits et al., 2003; Gais et al., 2008; Lee et al., 2015; Zils et al., 2005) and only one of these studies did not compare morning and evening data (Lee et al., 2015). Thus, further studies are needed to allow direct comparisons of sleep deprivation effects on these tasks.

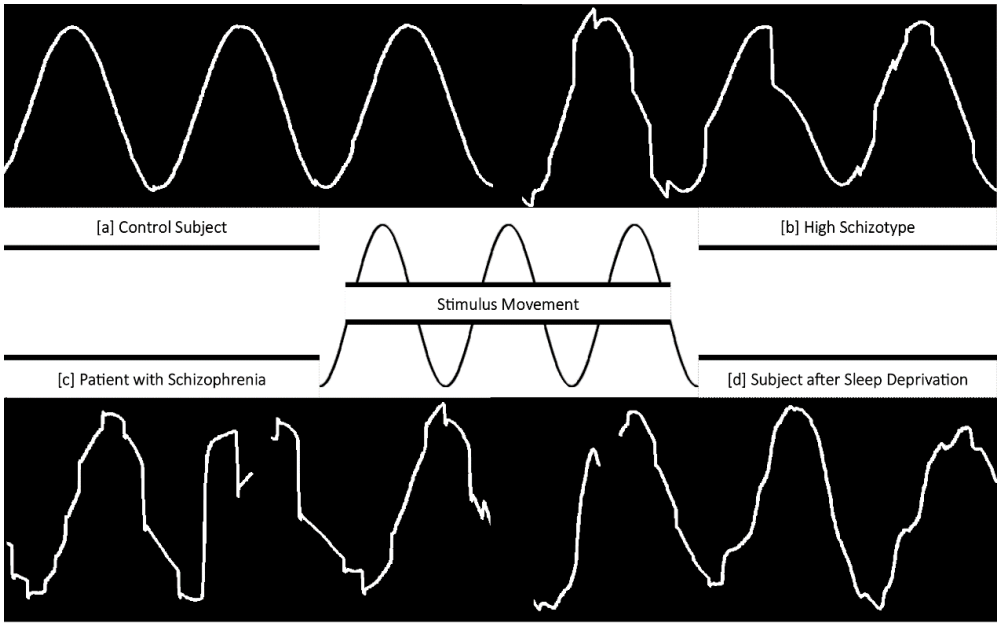

Figure IV—2. Illustration of sinusoidal SPEM at 0.4Hz (eye position plotted against time).

Table IV—4. Summary of studies on sleep deprivation and SPEM in healthy humans.

Author	Sample Size	Task Design	Measures	Duration of SD	Study Design	Results
Porcu et al. (1998)	*N*=5 males	sinusoidal movement pattern with 6 frequencies between 0.2-0.7Hz	velocity gain, phase shift	up to 7h	Measurements were conducted at 12pm, after NSC, and later at midnight, 2am, 4am, and 6 am with intermediate day sleep [2:30pm-11:00pm].	For velocity gain the performance decreased at the end of the night. There were no effects of SD for phase shift.
van Steveninck et al. (1999)	*N*=9 [*n*=5 females, *n*=4 males]	sinusoidal movement pattern with 9 frequencies between 0.3-1.1Hz	not specified	1 night	Measurements were conducted after NSC, during SD, and after SD. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 1 week apart.	There were no significant effects of SD on SPEM variables.
De Gennaro et al. (2000); Ferrara et al. (2000)	*N*=9 males	sinusoidal movement pattern with 6 frequencies between 0.2-0.7Hz	velocity gain, phase shift	up to 40h	Measurements were taken every 2h from 10am in the pre-deprivation day to 10pm of the day following SD.	Velocity gain was reduced on measurements after SD compared to NSC. There were no effects of SD for phase shift.
Quigley et al. (2000)	*N*=16 [*n*=8 females, *n*=8 males]	not specified	not specified	1 night	Measurements were taken before/after NSC/SD on two consecutive test days on the same time of day [between-subjects].	There were no significant effects of SD.
Fransson et al. (2008)	*N*=18 [*n*=8 females, *n*=10 males]	constant velocity [10-40°/sec]	velocity gain, accuracy	24h, 36h	Participants were measured after NSC and after 24h and 36h of SD. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 1 week apart.	Velocity gain was reduced after 36h of SD and accuracy was lower after 24h SD but recovered at 36h of SD.
Tong et al. (2014)	*N*=87 [*n*=19 females, *n*=68 males]	sinusoidal clockwise movement pattern at 0.4Hz	phase/radial/tangential error, gain, average powers of radial and tangential velocities, saccade rate	up to 26h	Measurements were taken at 6:30am after NSC and at 2:00am and 6:30am after SD.	SD reduced velocity gain and average power of tangential velocity and increased standard deviations and anticipatory saccade rate. No effects were found for phase error, radial error, average power of radial velocity, and catch-up saccades.

Notes: *NSC*=normal sleep control night. *SD*=sleep deprivation. Unless otherwise indicated, studies included healthy participants. Studies are presented in chronological order. Table is adapted from Meyhöfer and colleagues (2016).

Table IV—5. Summary of studies on sleep deprivation and saccades in healthy humans.

Author	Sample	Task Design [Target Eccentricity]	Measures	Duration of SD	Study Design	Results
Porcu et al. (1998)	*N*=5 males	PS [5-30°]	latency, gain, error rate	up to 7h	Measurements were conducted at 12pm after NSC and later at midnight, 2am, 4am, and 6am with intermediate day sleep [2:30pm-11:00pm].	For gain and error rate the performance decreased at the end of the night. There were no SD effects for latency.
van Steveninck et al. (1999)	*N*=9, age [*n*=5 females, *n*=4 males]	PS [15°, 20°]	latency, peak velocity	1 night	Measurements were conducted after NCS, during SD, and after SD. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 1 week apart.	After SD there was a decrease in peak velocity and an increase in saccadic latency.
De Gennaro et al. (2000); Ferrara et al. (2000)	*N*=9 males	PS [5-30°]	latency, gain, peak velocity	up to 40h	Measurements were taken every 2h from 10am in the pre-deprivation day to 10pm of the day following the SD.	Performance for latency and peak velocity was worsened on measurements after the day following SD. No SD effects for gain were found.
Quigley et al. (2000)	*N*=16 [*n*=8 females, *n*=8 males]	not specified	e.g. peak velocity, acceleration	1 night	Measurements were taken before/after NSC/SD on two consecutive test days on the same time of day [between-subjects].	Peak velocity and acceleration were significantly decreased after SD.
Crevits et al. (2003)	*N*=21 [*n*=11 females, *n*=10 males]	block design, fixed order: PS [14°], voluntary saccades [14°], AS [14°]	latency, error rate	20h	Measurements were conducted on the evening before SD [9:30pm] and on the morning after SD [6am].	There were no significant differences between the measurements.
Thomas et al. (2000;2003)	*N*=17 males	PS [20°]	saccadic velocity	24h, 48h, 72h	Measurements were conducted on baseline and after the next consecutive days of SD.	There was a decrease in saccadic velocity with prolonged SD.
Rowland et al. (2005)	*N*=12 [*n*=6 females, *n*=6 males]	PS [20°]	peak velocity	64h	Measurements were conducted at baseline [every 3 h], after partial sleep deprivation [every 3h], and after total sleep deprivation [every 3h].	Saccadic peak velocity decreased with duration of total SD.

Zils et al. (2005)	*N*=15 males	block design: PS [gap, 10° and 20°], AS [gap, 10° and 20°], MGS [10° and 20°]	latency, peak velocity, gain, Error Rate [AS]	24.5h	Measurements were conducted in the evening before the NSC/SD night [8pm], in the morning [7:30am] after NSC/SD, and in the morning after a recovery night [7:30am]. Order of NSC and SD was randomized [within-subjects] and nights were scheduled at least 4 weeks apart.	PS: Gain and peak velocity were reduced after SD. No SD effect for latency. AS: Peak velocity was reduced after SD. No SD effects for latency, gain, and error rate. MGS: There were longer latencies and reduced peak velocity after SD. No SD effects for gain were found.
Bocca and Denise (2006)	*N*=10 males	block design: PS [gap, 15°], PS [overlap, 15°]	latency, gain, peak velocity	1 night	Measurements were conducted in the morning [10:00am] after NSC and after a night of SD. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 2 weeks apart.	Latency was increased after SD especially for the gap task and gain after SD was reduced for both tasks. There were no SD effects for peak velocity.
Fransson et al. (2008)	*N*=18 [*n*=8 females, *n*=10 males]	PS [10°-30°]	gain, peak velocity, ratio velocity divided by amplitude	24h, 36h	Participants were measured after NSC and after 24h and 36h of SD. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 1 weeks apart.	Peak velocity decreased after SD [24h and 36h], gain was higher after 36h of SD, and the ratio between saccade velocity and amplitude was reduced after SD [24h and 36h].
Gais et al. (2008)	*N*=20 [*n*=10 females, *n*=10 males]	block design: PS [gap, 10°,20°], AS [gap, 10°,20°]	latency, gain, peak velocity, error rate [AS]	1 night	Measurements were taken in the evening before the NSC/SD night [8pm], in the morning after NSC/SD [7:30am], and in the following morning after a night of recovery sleep [7:30am]. Subjects were randomly assigned to one of the groups [between-subjects].	PS and AS latencies were reduced only after sleep [for the NSC group after the first sleep night, for the SD group after the recovery night] and peak velocity was decreased after SD. There were no SD effects for gain and error rate.
Goldich et al. (2010)	*N*=13 [*n*=8 females, *n*=5 males]	PS [26.8°]	saccade velocity	up to 28h	Measurements were taken every hour after two nights of sleep [8am-1pm], the day before SD [8am, 10am, 12am], and the night during SD [11pm, 1am, 3am, 5am, 8am, 10am, 12am].	Saccade velocity was decreased during SD [for measurements at 8am-12am].

Grace et al. (2010)	*N*=10 healthy participants [*n*=2 females, *n*=8 males]	PS [35°]	peak velocity	1 night	Healthy participants either received intravenous morphine or saline placebo infusion, both before and after SD. Measurements were taken pre- and post-dose [two-way crossover, randomized, double-blind, placebo-controlled].	Peak velocity was decreased both after SD and morphine infusion and there was an additive effect of SD and morphine infusion.
Hirvonen et al. (2010)	*N* =11 males	block design: PS [gap and overlap, 10°]	peak velocity	up to 60h	Measurements were taken every six hours during SD.	Peak velocity decreased during SD.
McClelland et al. (2010)	*N*=23 non-sleep deprived [*n*=15 females, *n*=8 males]; *N*=26 sleep- deprived [*n*=12 females, *n*=14 males]	PS	saccadic velocity	up to 26h	Non sleep-deprived subjects had two measurements before and three measurements after NSC [between 8am-8pm]. Participants in the SD condition completed five testing sessions between 8pm and 10am during the SD.	Peak velocity remained stable in the NSC but decreased in the SD condition.
Bocca et al. (2014)	*N*=12 [*n*=4 females, *n*=8 males]	AS [gap, 15°]	latency, ICV latency, error rate	30h	Participants were measured after NSC [2pm] and after 30h of SD [2pm]. Order of NSC and SD was randomized [within-subjects] and nights were scheduled 2 weeks apart.	SD increased AS mean latency, ICV of latency, and error rate.
Lee et al. (2015)	*N*=16 males	block design, order was counterbalanced: PS [step, 5°, 10°], AS [step, 5°, 10°]	latency, error rate	Participants' sleep was restricted to 5h [2am-7am].	Participants either received a drink with or without alcohol. Measurements were taken after NSC and sleep restriction [1pm] [4 conditions, within-subjects]. Conditions took place at least 5 days apart.	PS: After sleep restriction alone, there was a reduction of saccadic latency. AS: There was an increase in saccadic latency for the combined alcohol and sleep restriction condition. Error rate was increased after sleep restriction alone.
Fimm & Blankenheim, 2016s	*N*=13 males	block design, fixed order: PS [gap, 6°, 12°; gap/overlap, 10°], AS [gap, 6°, 12°]	latency, peak velocity	up to 24h	Measurements were taken every four hours during the SD.	There were no significant effects of SD.

Notes: *NSC*=normal sleep control night. *SD*=sleep deprivation. *PS*=prosaccades. *AS*=antisaccades. *MGS*=memory-guided saccades. ICV= intra-individual coefficient of variation. Unless otherwise indicated, studies included healthy participants. Studies are presented in chronological order. Table is adapted from Meyhöfer and colleagues (2016).

IV.IV Open questions and goals of the current thesis

Current antipsychotic drugs have little beneficial effects on cognitive disturbances in patients with psychotic disorders (Nielsen et al., 2015). However, as cognitive impairments have widely been emphasized as a core feature of schizophrenia (Green, Nuechterlein, et al., 2004), new treatments are urgently needed (Reilly & Sweeney, 2014).

Model systems of psychosis are one approach in further investigating the pathophysiology of psychosis and aiding the development of new treatments (Carpenter & Koenig, 2008), especially when combined with well-studied and symptom-related biomarkers. Due to short and specific tasks, oculomotor biomarkers are particularly suitable to aid further investigation on model systems and drug development (Klein & Ettinger, 2008).

Antisaccades have been found to represent well-validated trait biomarkers of psychosis (Reilly et al., 2014). Due to repeated measurements, high time stability is required to apply antisaccades as biomarkers in clinical trials (Nuechterlein et al., 2008). However, a detailed description of situational (state) and time-stable (trait) aspects in the antisaccade tasks in standard laboratory settings is missing **(study 1)**.

Based on previous research, schizotypy constitutes a useful model systems of psychotic disorders (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2015), especially when combined with oculomotor biomarkers. However, until now, there is no research on the underlying neural mechanisms of SPEM in schizotypy **(study 2)**.

Furthermore, sleep deprivation has been proposed as a model system of psychosis in rats (Frau et al., 2008). Further research to validate the model system in humans is needed **(study 3)**. Additionally, the combination of a trait (schizotypy) and a state (sleep deprivation) model might be especially valuable in modelling psychotic symptoms **(study 4)**.

To investigate the outlined goals, the work reported in this dissertation combined recording of eye movement data, latent-state-trait (LST) modeling, and functional magnetic resonance imaging (fMRI).

V METHODS

The following chapter includes a brief description of the methods applied in the current dissertation. The first part introduces the recording and analysis of oculomotor data. In the second part is a short outline of LST theory and the models that can be used to compute the amount of trait and state variation in a given measure. The third part deals with the basic assumptions of fMRI as a powerful tool to study the neural mechanisms of cognitive processes.

V.I Recording and analysis of eye movements

> "The eyes have it!"
> [Gegenfurtner, 1999]

A number of methods are available to record changes in eye and/or gaze position. Commonly used eye movement measurement methodologies comprise the electro-oculography, scleral contact lens/search coil, video-oculography, and video-based combined pupil and corneal reflection (VCPCR) techniques (for extensive overviews refer to Duchowski, 2007; Young & Sheena, 1975). The VCPCR method is the most frequently applied approach and provides an opportunity to measure the point of regard (eye position with relation to its orientation in the space). To be able to separate eye movements from head rotation, two reference points on the eye, namely pupil center and corneal reflection from an infra-red light source, are recorded and brought into relation. Thus, the method is based on the observation that eye movements lead to rotation of the pupil whereas the corneal reflection (typically the first Purkinje image) remains relatively stable (Duchowski, 2007).

The calculation of the gaze position can be divided into subsequent steps of image acquisition, image analysis, and gaze estimation (Holmqvist et al., 2011). First, images of the eye are recorded by the camera, with the number of images depending on the sampling frequency (specified in Hz; corresponds to number of images taken per second). Then, pupil and corneal reflection are segmented mostly by applying either feature-based or model-based algorithms.

Finally, geometric computations together with the calibration procedure are used to map the position of the eye to the stimulus. Therefore, the distance between the centers of pupil and corneal reflection is calculated, and, together with the exemplary position data gained through calibration, the gaze position can be estimated.

The raw recording of eye movements typically results in eye position coordinates (x, y; expressed in pixels) with associated time stamps and is commonly transferred to degrees of visual angle. Thus, events (fixations, saccades, blinks) have to be detected in the raw data samples applying appropriate position (°), velocity (°/sec), and acceleration (°/sec²) criteria (Holmqvist et al., 2011). Finally, dependent variables are computed from the stream of data samples based on the classification of the oculomotor events and details of the task that was accomplished.

As there are hardly any freely available computer programs to analyze SPEM data, a major part within the framework of the current thesis was to develop analytic routines to compute SPEM measures in a fast and efficient way.

Widely used algorithms for dependent measures of SPEM, prosaccade, and antisaccade tasks are summarized in Table V—1 and Table V—2.

Table V—1. Overview of SPEM and saccade variables

Variable	Definition	Computation Details
SPEM		
Root mean square error [RMSE] [°]	Deviation between eye and target position including segments of pursuit and saccades	RMSE scores are computed using the sum of the squared differences between eye and target position for each point in the SPEM segment. Finally, the square root of this sum divided by the number measurement points is the RMSE.
Velocity gain [%]	Ratio between eye and target velocity including only segments of pursuit (mostly time-weighted)	[eye velocity / target velocity] × 100
Saccade frequency [*N*/sec]	Number of saccadic intrusions interrupting pursuit (there are different types of saccades that can either be combined or calculated separately)	For further details see Table V—2.
Pursuit latency [sec]	Time that elapses between onset of stimulus movement and onset of eye acceleration (used to examine the initiation of SPEM)	The beginning of eye acceleration is specified when eye velocity exceeds baseline velocity by a certain factor. Then eye velocity is modelled by linear regression whereas the slop represents the initial eye acceleration and the intercept with the abscissa (time) is the latency.
Initial eye acceleration [°/sec²]	Degree of eye acceleration in response to the start of the stimulus movement (used to examine the initiation of SPEM)	See above
Prosaccades and Antisaccades		
Direction errors [%]	Initial saccade after peripheral stimulus onset is executed away from (prosaccade error)/towards (antisaccade error) the stimulus	% errors = number of errors / [number of correct responses + number of errors] × 100
Latency [ms]	Time that elapses between onset of the peripheral stimulus and start of the saccade in correct trials	
Amplitude gain [%]	Accuracy of the initial saccade compared to the target amplitude in correct trials (note that given two saccades that show inaccurate gain values, these inaccuracies can average out resulting in a mean of 100% (e.g., (80%+120%)/2=100%))	% gain = $\text{amplitude}_{\text{saccade}}$ / $\text{amplitude}_{\text{target}}$ × 100
Spatial error [%]	Inaccuracy of the initial saccade compared to the target amplitude in correct trials	|[$\text{amplitude}_{\text{saccade}}$ - $\text{amplitude}_{\text{target}}$] / $\text{amplitude}_{\text{target}}$ × 100|
Peak velocity [°/sec]	Peak eye velocity during a saccade in correct trials	

Notes. For further information on computation algorithms refer to Ettinger et al., 2003; Lencer & Trillenberg, 2008; Smyrnis, 2008.

Table V—2. Overview of definitions used to characterize saccades during SPEM.

Name	Function	Direction	Description	Amplitude	Pursuit after Saccade	Relevant Studies
CUS	compensatory	in target direction	reduces eye position error; starts and ends behind target; if starts behind and ends ahead of the target, post-saccadic position error must be ≤50% of pre-saccadic position error			Ettinger et al., 2003; Ross et al., 1998, 2002, 2000; Ross, Olincy, Harris, et al., 1999
BUS	compensatory	opposite of target direction	reduces eye position error; starts and ends ahead of the target; if starts ahead and ends behind the target, post-saccadic position error must be ≤50% of pre-saccadic position error			Lencer et al., 1999; Levy et al., 2000; Radant & Hommer, 1992
Anticipatory Saccade	intrusive	in target direction, takes the eye ahead of the target	starts and ends ahead of target location; if starts behind and ends ahead of the target, the distance ahead of the target must be at least twice the distance the eye started behind the target	>4°	followed by 50ms of eye velocity ≤50% of target velocity	Ettinger et al., 2003; Olincy, Johnson, & Ross, 2003; Ross et al., 1998, 2002; Ross, Olincy, Zerbe, & Radant, 2001; Ross, Olincy, & Radant, 1999
Leading Saccade	intrusive	see anticipatory saccades	see anticipatory saccades	1°-4°	see anticipatory saccades	Olincy et al., 2003; Ross et al., 2002, 2001
SWJ	intrusive		two saccades in opposite directions, the first saccade increases and the second saccade reduces eye position error; duration between the two saccades can range from 50 to 500ms	1°-5°	eye velocity between saccades must be >65% of target velocity	Abel & Ziegler, 1988; Clementz et al., 1990; Friedman, Jesberger, Abel, & Meltzer, 1992; Lencer et al., 1999; Levy et al., 2000; Radant & Hommer, 1992; Shallo-Hoffmann, Perersen, & Muhlendyck, 1989

Notes. SPEM=smooth pursuit eye movements. CUS=catch-up saccade. BUS=back-up saccade. SWJ=square wave jerks. See Smyrnis (2008) for an overview.

V.II Latent-state-trait modeling

LST theory is based on an extension of classical test theory and was proposed by Steyer and colleagues (Steyer, Ferring, & Schmitt, 1992; Steyer, Mayer, Geiser, & Cole, 2015; Steyer, Schmitt, & Eid, 1999; Steyer & Schmitt, 1990). Compared to classical test theory, which does not take into account any influences of situational aspects, LST theory assumes that not only the person itself but also the situation and the interaction between the person and the situation are valuable sources of variance during a measurement. Thus, "measurement does not take place in a situational vacuum" (Steyer et al., 1999; page 392) and variations between measurements are presumed to represent state differences that include person, situation, and person-situation interactions. LST assumes that a cross-sectional measure assesses a "person-in-the-situation" score (Steyer et al., 2015). Furthermore, tools are provided that allow to disentangle the different sources of variance (person/trait; situation, interaction between person and situation/state) using longitudinal study designs.

There are several different classes of models that can be applied (e.g., multistate models, multistate-singletrait models, multistate-multitrait models) depending on the particular research question (Steyer et al., 2015). In order to estimate the proportion of state and trait variance in a multistate-singletrait model (several measurement occasions assuming a single underlying trait) a two-step decomposition is used: In the first step, the observed variables at each measurement occasion (k) are subdivided in two test sets (i) and dismantled into latent states (S_k) and measurement errors ($\varepsilon_{k,i}$). In the second step, the latent states are decomposed into a latent trait variable (T) and occasion-specific state residuals (SR_k) (Steyer et al., 1999). An example is depicted in Figure VI—1a (for further fundamental assumptions that pertain to the methodological framework of LST refer to Steyer et al., 2015, 1999). States and traits are specified in terms of probability theory as latent random variables that can be estimated but not directly measured from the observed variables (Steyer et al., 2015). Structural equation modeling (SEM) can be used to test the model and compute the relevant parameters.

The components of an LST model can be conceptually identified as follows (Schermelleh-Engel, Keith, Moosbrugger, & Hodapp, 2004; Steyer et al., 1999): Latent state variables estimate the

attributes of the person and the situation during a single measurement occasion. The latent trait variable includes the amount of variation that is common across all measurement occasions and therefore is supposed to constitute an attribute of the person itself. Finally, the occasion-specific state residuals characterize the situational effects and the interactions between the person and the situation during a single measurement.

After testing the model with SEM and evaluating the model fit (recommended indices: chi-square statistic, comparative-fit index, root mean square error of approximation, and standardized root mean residual; Beauducel & Wittmann, 2005; Bentler, 2007; Hu & Bentler, 1999), parameters of the accepted models can be used to calculate the proportions of variances that quantify the situation specific and the stable trait influences of the examined measure (Steyer et al., 1992, 2015, 1999; Steyer & Schmitt, 1990). Common consistency [$Con(X_{k,i})=Var(T)/Var(X_{k,i})$] displays how well the observed variable ($X_{k,i}$) estimates the trait variable (T). Occasion specificity [$Spe(X_{k,i})=Var(SR_k)/ Var(X_{k,i})$] indicates how much variance of the observed variable ($X_{k,i}$) can be explained by the state residuals (SR_k). Both common consistency and occasion specificity can be summed up to the coefficient of reliability [$Rel(X_{k,i})=Con(X_{k,i})+Spe(X_{k,i})$]. Therefore, reliability [$Rel(X_{k,i})=Var(S_k)/Var(X_{k,i})$] represents the amount of variance of the observed variable ($X_{k,i}$) due to the latent state (S_k).

V.III Functional magnetic resonance imaging

fMRI allows to measure brain activation non-invasively and with relatively high spatial resolution (Logothetis, 2008). Therefore, this method has widely been used to study neural mechanisms of cognitive processes (Niendam et al., 2012) and can additionally be combined with recording of eye movements to investigate the neural underpinnings of the oculomotor system (Jamadar et al., 2013).

The fMRI method was introduced in the early 1990s (Bandettini, 2012) and is based on magnetization differences in different types of tissue (Huettel, Song, & McCarthy, 2008; Logothetis, 2002). Whenever a strong magnetic field is applied to the protons of hydrogen atoms, they either align parallel (low-energy level) or antiparallel (high-energy level) to the field. The net

magnetization (difference between number of atoms in the parallel and the antiparallel state) provides the basis for the signal generation. Pulses of radiofrequency energy lead some nuclei to change from low- to high-energy states (excitation). Once these pulses are turned off, the equilibrium between nuclei in low- and high-energy levels is restored. The subsequent energy is measured (reception) and constitutes the MR signal. The MR signal changes over time (relaxation), resulting in the recovery of the longitudinal (T1) and the decay of the transverse (T2, T2*) components of net magnetization. Importantly, different types of tissues can be distinguished by their properties regarding the relaxation process. In order to create an image, superimposed gradient magnetic fields that code spatial information are needed and Fourier transform is used to decode the signal.

The most frequently used form is blood-oxygenation-level dependent (BOLD) fMRI. BOLD fMRI estimates brain activation indirectly from changes in blood oxygenation using T2* weighted scans (Ogawa, 2012; Ogawa, Lee, Kay, & Tank, 1990). The underlying assumption is that neural activity produces regional metabolic consequences that are linked to increases in blood flow in the same region, probably due to the demand for oxygen and glucose (Huettel et al., 2008; Logothetis & Wandell, 2004). Oxygen is delivered through hemoglobin and, importantly, deoxygenated hemoglobin was found to exhibit greater magnetic properties than oxygenated hemoglobin (Pauling & Coryell, 1936). Thus, whenever the brain becomes active, more oxygenated blood than needed is provided and the following decrease in the proportion of deoxygenated hemoglobin results in a higher MR signal (hemodynamic response). Brain activation can therefore not be measured directly (Heeger & Ress, 2002). However, previous findings document a close relationship between the BOLD signal and intra-cortical recordings of neural activity (Goense & Logothetis, 2008; Logothetis, 2007; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001) emphasizing that fMRI is a powerful tool to investigate neural processes spatially accurately and non-invasively.

VI STUDIES

Table VI—1. Overview of studies included in the current thesis.

Relevant publications for the present thesis	
1	**Meyhöfer, I.**, Bertsch, K., Esser, M., & Ettinger, U. (2015). Variance in saccadic eye movements reflects stable traits. *Psychophysiology, 53*, 566–578. http://doi.org/10.1111/psyp.12592
2	**Meyhöfer, I.**, Steffens, M., Kasparbauer, A., Grant, P., Weber, B., & Ettinger, U. (2015). Neural mechanisms of smooth pursuit eye movements in schizotypy. *Human Brain Mapping, 36*, 340–353. http://doi.org/10.1002/hbm.22632
3	**Meyhöfer, I.**, Kumari, V., Hill, A., Petrovsky, N., & Ettinger, U. (2016). Sleep deprivation as an experimental model system for psychosis: Effects on smooth pursuit, prosaccades, and antisaccades. *Journal of Psychopharmacology, 31*(4), 418-433. http://doi.org/10.1177/0269881116675511
4	**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,* 1-15. http://doi.org/10.1111/psyp.12917
Further relevant publications	
	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), 1–16. http://doi.org/10.3389/fpsyt.2014.00018
	Steffens, M., Becker, B., Neumann, C., Kasparbauer, A. M., **Meyhöfer, I.**, Weber, B., Mehta, M.A., Hurlemann, R, & Ettinger, U. (2016). Effects of ketamine on brain function during smooth pursuit eye movements. *Human Brain Mapping, 37*(11), 4047–4060. http://doi.org/10.1002/hbm.23294
	Petrovsky, N., Ettinger, U., Hill, A., Frenzel, L., **Meyhöfer, I.**, Wagner, M., Backhaus, J., & Kumari, V. (2014). Sleep deprivation disrupts prepulse inhibition and induces psychosis-like symptoms in healthy humans. *The Journal of Neuroscience, 34*(27), 9134–9140. http://doi.org/10.1523/JNEUROSCI.0904-14.2014
	Meyhöfer, I., Ettinger, U., Faiola, E., Petrovsky, N., & Kumari, V. (to be submitted). The effects of schizotypy and sleep deprivation on prepulse inhibition.

Notes. The studies are sorted according to their relevance in the main text.

VI.I Study 1. Reliability of oculomotor tasks

Meyhöfer, I., Bertsch, K., Esser, M., & Ettinger, U. (2015). Variance in saccadic eye movements reflects stable traits. *Psychophysiology, 53*, 566–578. http://doi.org/10.1111/psyp.12592

Saccadic tasks have widely been studies in psychiatric disorders and are particularly useful as biomarkers of psychosis (Gooding & Basso, 2008). Furthermore, saccades have been studied in genetic research (Calkins, Iacono, & Ones, 2008; Mazhari et al., 2011), suggesting antisaccades to demonstrate a valuable endophenotype of psychotic disorders (Reilly et al., 2014). A requirement of endophenotypes is temporal stability (Glahn et al., 2014). However, there are only few studies that have examined the trait-like nature, i.e., the temporal stability, of saccadic measures (Ettinger et al., 2003).

The aim of the current study was to provide a detailed examination of the reliability of the most widely applied saccadic tasks in psychosis research. A special aim was to separate the amount of variance that is trans-situationally stable (trait) from variance that is situations-specific (state). As most oculomotor measures have previously been found to display moderate to high test-retest reliability (Ettinger et al., 2003), we hypothesized that high proportions of variance can be explained by a stable trait component.

A sample of *N*=68 healthy participants performed prosaccades, antisaccades, and memory-guided saccades on three measurement occasions with an interval of one week between the sessions and each testing session was conducted at the same time of day. In order to investigate the influences of state and trait in the saccade measures, formulas based on LST theory (Steyer et al., 2015, 1999) were applied. In addition to multistate-singletrait (LST) models, we also performed models that only assume a single underlying trait with no situations-specific contributions at all (singletrait models; LT models). An illustration of the models can be found in Figure VI—1.

All saccadic variables could be modelled by assuming that each measurement occasion includes situations-specific variance and additionally the three occasions can be characterized

by a single underlying trait (LST models that include parallel or at least τ-equivalent measurements for each of the three measurement occasions; Figure VI—1a). Furthermore, for some of the measures simpler LT models (Figure VI—1b) could be accepted. Mean saccadic variables of all tasks were found to represent high to excellent reliabilities. Intraindividual standard deviations were slightly less reliable. Most importantly, the largest part of the variance of the measure could be explained by the trans-situationally stable trait component and the role of situational aspects and person × situation interactions were rather negligible.

In summary, prosaccade, antisaccade, and memory-guided saccade variables can be measured with high reliability. Additionally, the data collected in a single measurement occasion strongly reflect an underlying trait emphasizing its value in genetic research. Furthermore, oculomotor performance is stable (i.e. trait-like) in standard laboratory settings under constant conditions. This finding provides convincing evidence for the usefulness of antisaccades as a biomarker in repeated measurements, e.g., clinical trials to evaluate pharmacological treatments for cognitive impairments in psychotic disorders.

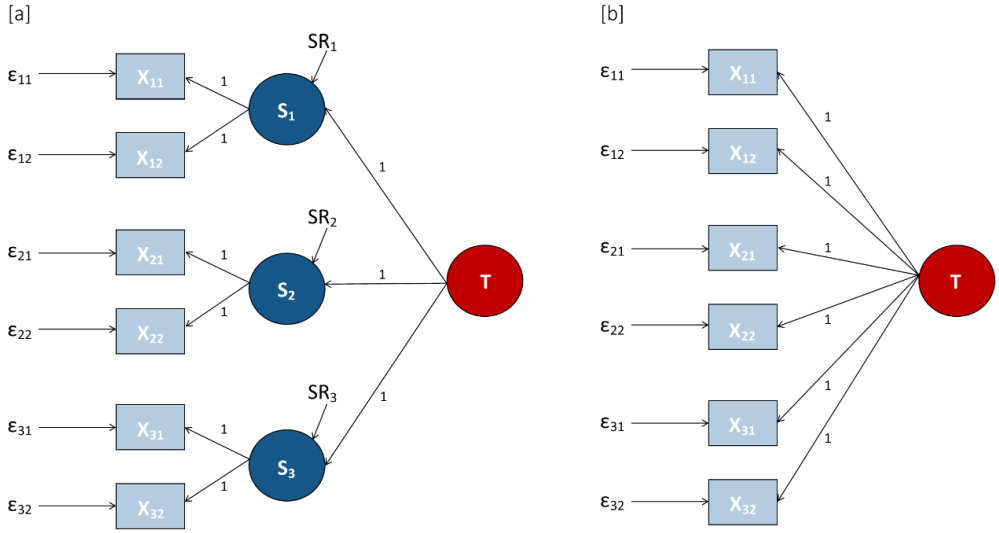

Figure VI—1. Schematic diagram of latent state-trait [a] and latent trait [b] models.
$X_{k,i}$ depict the observed [dependent] variables for each of the tasks [prosaccades, antisaccades, memory-guided saccades]. k=measurement occasion. i=test set. $\varepsilon_{k,i}$=measurement errors. S_k=latent states. SR_k=latent state residuals. T=latent trait.

VI.II Study 2. Schizotypy and the neural mechanisms of SPEM

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

Due to considerable overlap on different levels of measurement (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014), schizotypy is reported to represent a valuable model system of psychosis (Barrantes-Vidal et al., 2015). SPEM have intensively been investigated as a biomarker of psychosis and performance deficits are widely replicated (Lencer et al., 2015; O'Driscoll & Callahan, 2008). Furthermore, studies on the neural correlates of SPEM impairments in patients report abnormal brain activation in frontal and motion-sensitive posterior areas (Hong et al., 2005; Lencer et al., 2011; Nagel et al., 2012). Similarly, high schizotypes were found to demonstrate SPEM abnormalities (Table IV—2). However, no study has investigated the neural mechanisms underlying the SPEM deficits in schizotypy.

Therefore, the aim of the current study was to bridge the gap on the neural correlates of SPEM in schizotypy. We hypothesized that high schizotypes display lower SPEM performance than controls and, additionally, that the differences between schizotypes and controls will overlap with abnormalities seen in patients with psychotic disorders.

To do so, *n*=12 schizotypes and *n*=19 controls underwent fMRI at 3T with concurrent oculographic recording while performing SPEM. An online version of the O-LIFE was applied to establish extreme groups of high and low schizotypes based on their overall schizotypy score.

The key results of the study are shown in Figure VI—2. Behaviorally, high schizotypes demonstrated higher frequency of saccadic intrusions in the slow (0.2Hz) but not the fast (0.4Hz) SPEM condition. At the same time, the high schizotypy group was found to display lower brain activation in different regions of the occipital lobe that was independent of target frequency. These regions (V3A, middle occipital gyrus, and fusiform gyrus) are associated with early sensory/attentional processing and motion perception (Culham, He, Dukelow, & Verstraten,

2001). However, unlike previous studies of psychotic patients, no abnormal brain activation was found in frontal oculomotor areas.

Together, these results replicate, as expected, altered SPEM performance in schizotypy (Table IV—2) that overlaps with impairments seen in psychotic patients (O'Driscoll & Callahan, 2008). Additionally, the posterior brain activation differences during SPEM are broadly in line with evidence of motion processing deficits from schizophrenia patients (Lencer et al., 2011; Nagel et al., 2012). However, in contrast to schizophrenia patients (Hong et al., 2005; Keedy et al., 2006), we did not find any abnormalities in frontal motor areas, possibly indicating the operation of further genetic and/or illness-related influences in clinical patients.

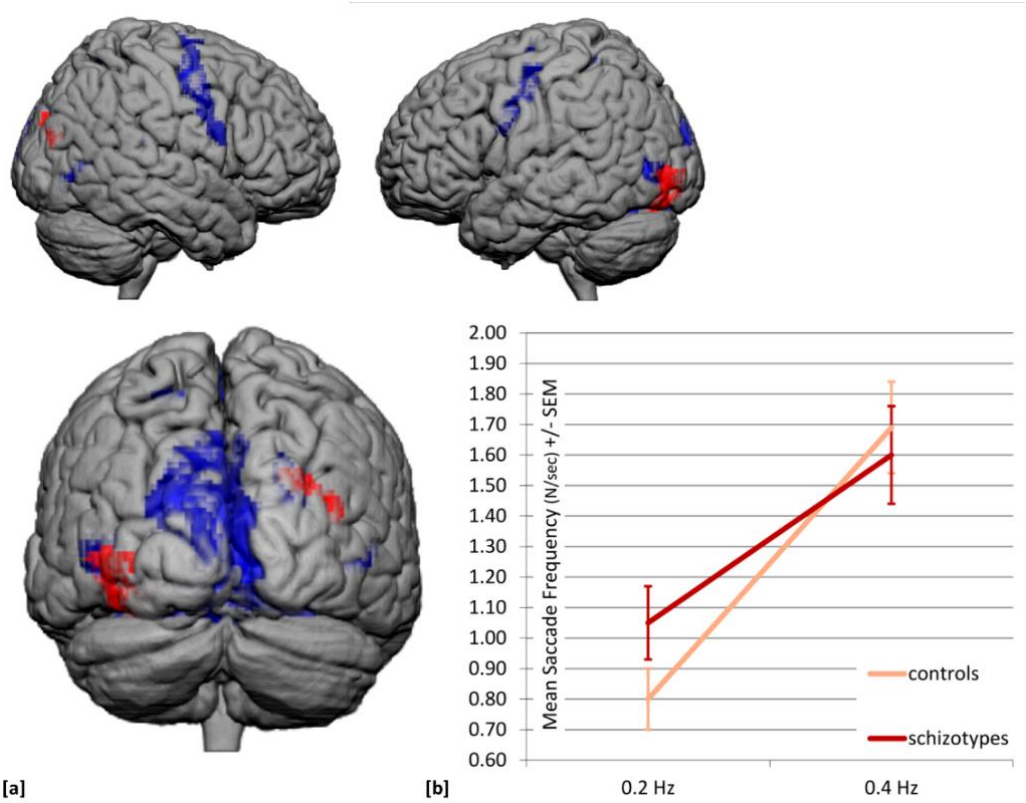

Figure VI—2. Illustration of the key findings of study 2.

[a] Brain activation pattern during SPEM>baseline across all subjects (blue) and differences between groups (controls>schizotypes, red). Whole brain FWE corrected for SPEM>baseline across all subjects, FWEc corrected with cluster threshold k=306 for group differences (peak voxel threshold<.001, uncorrected). *n*=19 controls, *n*=12 schizotypes. [b] Interaction group × target frequency for frequency of saccadic intrusions during SPEM. *n*=14 controls; *n*=10 schizotypes.

VI.III Study 3. Sleep deprivation and oculomotor control

Meyhöfer, I., Kumari, V., Hill, A., Petrovsky, N., & Ettinger, U. (2016). Sleep deprivation as an experimental model system for psychosis: Effects on smooth pursuit, prosaccades, and antisaccades. *Journal of Psychopharmacology, 31*(4), 418-433. http://doi.org/10.1177/0269881116675511

Sleep deprivation has been found to cause deficits in cognitive functions (Lim & Dinges, 2010), e.g., oculomotor control (Table IV—4 and Table IV—5). Furthermore, sleep deprivation has been reported to induce psychotomimetic states (Kahn-Greene et al., 2007; Killgore et al., 2008). Together, these discoveries suggest that studying sleep deprivation may be an experimental model systems for psychosis (Ettinger & Kumari, 2015).

Therefore, in the current study, we aimed investigate the effects of short-term sleep deprivation on psychosis-like experiences and performance in the most widely used oculomotor biomarkers of psychosis, i.e. SPEM and antisaccades. We expected that 24h of sleep deprivation would deteriorate SPEM and antisaccade measures and concurrently increase psychosis-like experiences.

To do so, *N*=32 participants (*n*=16 males, *n*=16 females) were examined after both a normal sleep night and a night of total sleep deprivation. The order of the sessions (normal sleep first, sleep deprivation first) was counterbalanced and participants were randomly assigned to one of the orders. The testing sessions were conducted with one week in between. Oculomotor control and other tasks (e.g., PPI; Petrovsky et al., 2014) were measured in the mornings after normal sleep and sleep deprivation (08:00 am-09:30am). Psychotomimetic states were quantified with the Psychotomimetic States Inventory (PSI; Mason, Morgan, Stefanovic, & Curran, 2008) in the evenings before and the mornings after normal sleep and sleep deprivation.

The main results can be found in Figure VI—3. As expected, sleep deprivation adversely affected numerous SPEM (e.g., velocity gain) and antisaccade (e.g., % direction errors) variables. Furthermore, sleep deprivation also impacted on prosaccade measures. However, some of the

variables were found to show influences of the order of testing, broadly suggesting stronger effects of sleep deprivation when this was the first night. Additionally, sleep deprivation induced psychosis-like states covering the key symptom domains of psychosis. Specifically, scores on perceptual distortion, cognitive disorganization, and anhedonia were higher in the morning after sleep deprivation compared to the evening before and the morning after the normal sleep night. There were no significant associations between oculomotor measures and psychotomimetic states.

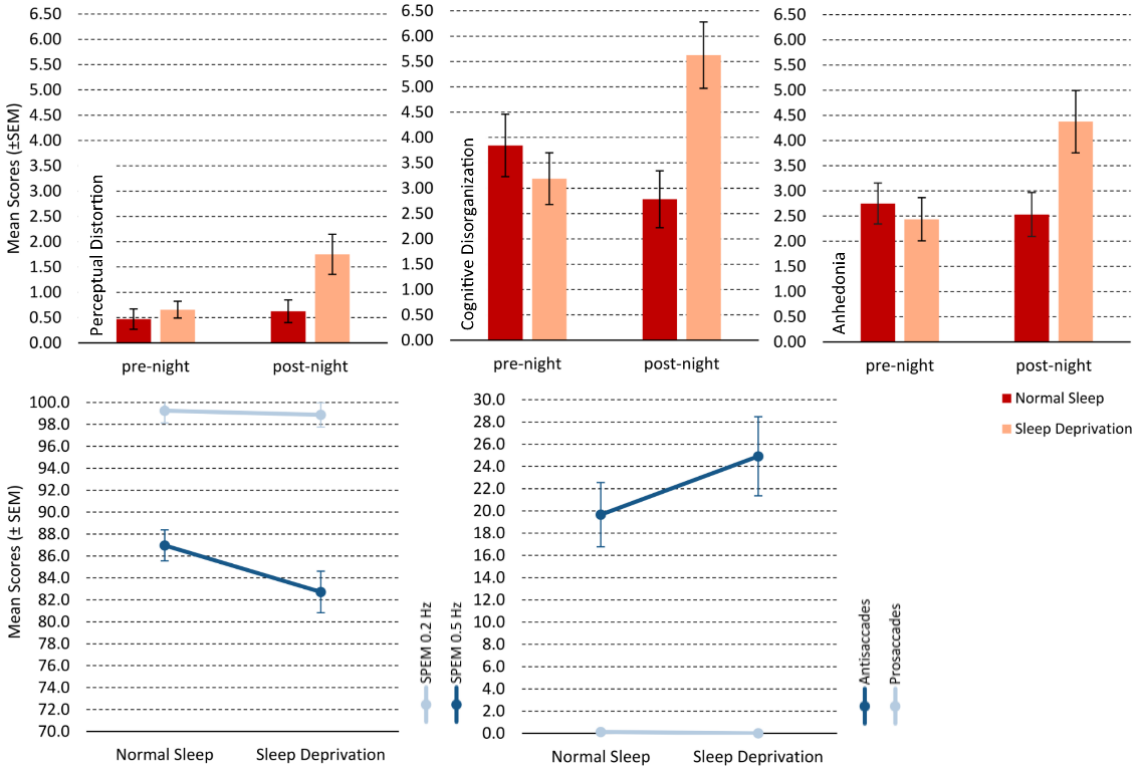

Figure VI—3. Illustration of the key findings of study 3.

In summary, as hypothesized, sleep deprivation resulted in impairments of oculomotor control and increases of psychosis like states. The findings of impaired SPEM and antisaccade measures are in line with findings from psychosis patients with psychotic disorders (Lencer et al., 2015; Reilly et al., 2014).

VI.IV Study 4. Schizotypy, sleep deprivation, and oculomotor control

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,* 1-15. http://doi.org/10.1111/psyp.12917

Schizotypy has been found to constitute a valuable approach in gaining further understanding of the underlying mechanism of psychosis and has commonly been investigated as a trait model system of psychotic disorders (Barrantes-Vidal et al., 2015). Overlaps between schizotypy and psychosis were found on different levels of measurement (Ettinger et al., 2014) and Study 2 reported schizophrenia-like SPEM and BOLD correlates of schizotypy. Additionally, in Study 3, it was found that one night of sleep deprivation induces psychotomimetic states and deteriorates oculomotor measures (Meyhöfer, Kumari, et al., 2017), emphasizing its role as a promising state model system of psychosis.

As psychotic disorders are very complex and heterogeneous, a single model system will possibly not be sufficient in modelling all aspects of psychosis. Therefore, the purpose of the present study was (1) to replicate the SPEM impairments in schizotypy from Study 2, (2) to replicate the effects of sleep deprivation from Study 3, and (3) to combine a trait and a state model of psychosis in one study to closer examine potential interactions between the model systems.

In order to investigate the role of schizotypy, an online version of the O-LIFE (Grant et al., 2013; Mason et al., 2005) was used to establish extreme groups based on the positive schizotypy dimension. Furthermore, to study the impact of sleep deprivation, the two groups (n=17 high schizotypes, n=19 controls) were measured after both a normal sleep night and a night of sleep deprivation. The study procedure is largely the same following the previous sleep deprivation study (Meyhöfer, Kumari, et al., 2017; Petrovsky et al., 2014). In addition to measures of psychotomimetic states (Mason et al., 2008), we also applied state measures of anxiety (Laux,

Glanzmann, Schaffner, & Spielberger, 1981), depression (Chiappelli, Nugent, Thangavelu, Searcy, & Hong, 2014), and stress (Fliege et al., 2005).

An overview of the key results can be found in Figure VI—4. High schizotypes were found to demonstrate worse SPEM performance (e.g., RMSE) and higher scores on psychotomimetic states, anxiety, depression, and stress than the control subjects, irrespective of sleep condition. However, there were no differences between the two groups with regard to antisaccade performance. Sleep deprivation resulted in impairments in numerous SPEM (e.g., RMSE), antisaccade (e.g., % direction errors), and prosaccade variables, irrespective of schizotypy group. Additionally, sleep deprivation led to increased levels of perceptual distortion, cognitive disorganization, anhedonia, anxiety, and depression. Most importantly, both model systems interacted on SPEM velocity gain. High schizotypes but not controls displayed deteriorated gain after sleep deprivation compared to normal sleep.

In summary, as expected, we replicated the SPEM impairments in schizotypy. Furthermore, we replicated the effects of sleep deprivation on oculomotor control and psychosis-like experiences, further strengthening sleep deprivation as a reliable and valid model system of psychosis (Ettinger & Kumari, 2015). Additionally, the evidence of the interaction between sleep deprivation and schizotypy demonstrates that the closest approximation to psychosis can be discovered in high schizotypy after sleep deprivation. This finding underlines that the combination of the two model systems are particularly valuable in modelling psychosis and assisting the development of new treatments.

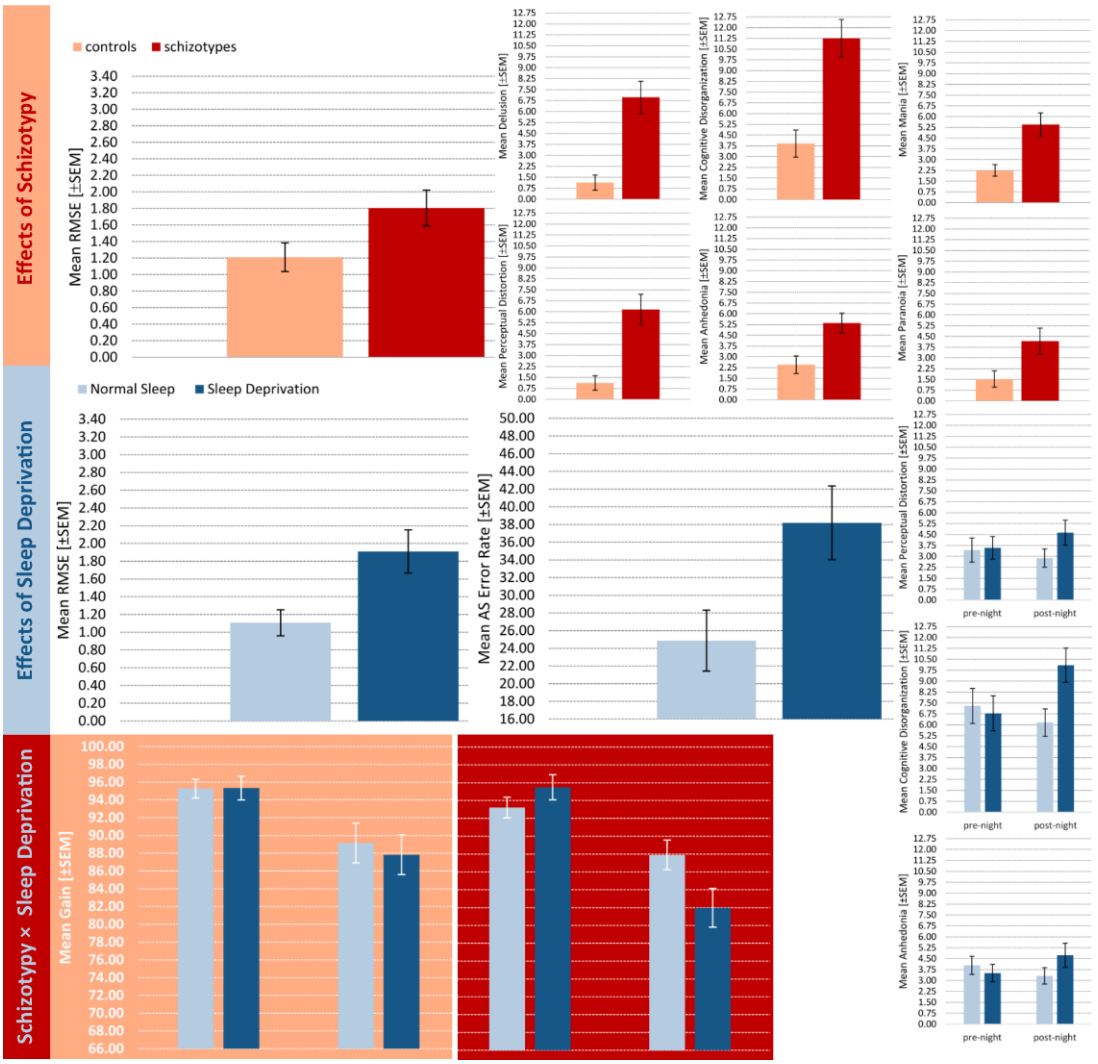

Figure VI—4. Illustration of the key findings of study 4.

VII DISCUSSION

The current thesis is a summary of four studies that (1) examined the time stability and trait-like nature of widely used oculomotor biomarkers of psychosis (Study 1) and (2) applied these biomarkers to evaluate schizotypy and sleep deprivation as two non-pharmacological human model systems of psychosis (Studies 2 and 4).

VII.I Integration

Cognitive dysfunctions are common in psychotic disorders and are closely related to several psychosocial functioning variables (Chapter IV.II.II). Unfortunately, there are no effective treatment options until now (Köster et al., 2014; Nielsen et al., 2015). Oculomotor tasks provide a solid foundation to study cognitive and neural dysfunctions in patient samples (Bey et al., 2017; Lencer et al., 2015; Reilly et al., 2014) and the cognitive effects of pharmacological interventions (Kasparbauer et al., 2016; Reilly et al., 2008).

Test-retest reliability and the utility as a repeated measure are key elements in the selection of tasks that can be applied in clinical trials, e.g., to study the effects of new antipsychotic drugs on cognitive functions (Nuechterlein et al., 2008). Until now, there were only few studies that have examined parameters of reliability for oculomotor performance, mainly reporting good stability over time for most of the variables (Ettinger et al., 2003; Wöstmann et al., 2013). However, no study has clearly investigated how much variance of a saccade variable either refers to a time stable trait or to situations-specific state influences. Therefore, we conducted a study of commonly used saccadic tasks and applied LST analyses (Meyhöfer, Bertsch, Esser, & Ettinger, 2016). We were able to demonstrate that mean saccadic measures exhibit high to excellent reliabilities and, additionally, the largest part of the variance could be explained due to trans-situationally stable consistency. In summary, one measurement occasion is sufficient to quantify saccade performance thereby strongly reflecting the underlying trait. Thus, oculomotor measures are highly valuable in study designs involving e.g., single measurement group comparisons. Furthermore, oculomotor performance is stable (i.e. trait-like) in standard laboratory settings under constant conditions. This finding underlines that saccadic tasks are useful in repeated measurements because the performance is stable over time under regular conditions and alterations are most likely associated to e.g., pharmacological or experimental interventions.

Together with research on practicability (Klein & Ettinger, 2008), cognitive foundations (Hutton, 2008), neural mechanisms (Herweg et al., 2014; McDowell et al., 2008; Talanow et

al., 2016), and disturbances in psychosis disorders (Chapter IV.II.III–ii), our findings further support that antisaccades are highly valuable to evaluate the validity of cognitive alterations in psychosis model systems.

Animal model systems are commonly applied in the development of novel antipsychotic compounds (Pratt et al., 2012). However, modeling cognitive impairments in rats/mice and cross-species translatability is challenging (Burrows & Hannan, 2016). Therefore, human model systems might significantly advance this field. The most studied human model systems include pharmacological interventions (e.g., ketamine; Steffens et al., 2016) and personality traits (e.g., schizotypy; Chapter IV.I.III). Schizotypy is a time-stable (Venables & Raine, 2015), multidimensional attribute that includes positive, negative, and disorganized dimensions (Mason et al., 1995; Raine et al., 1994). There are many findings of considerable overlap between schizotypy and patients with schizophrenia on different levels of measurement (Ettinger et al., 2014), e.g., both groups share impairments in the performance of SPEM (Chapters IV.II.III—ii and IV.III.I).

To further investigate the potential overlaps in brain activation that behaviorally result in SPEM deficits, a high schizotypy and a control group attended an fMRI session with concurrent oculographic recording (Meyhöfer et al., 2015). The high schizotypy group was found to display worse SPEM together with reduced activity in occipital regions. These neural abnormalities are broadly in line with findings of deficits in motion processing from schizophrenia patients (Lencer et al., 2011; Nagel et al., 2012) and ,therefore, further stress the value of schizotypy as a model system of psychosis. However, in contrast to patients with schizophrenia (Chapter IV.II.III—ii), we did not observe any differences in frontal brain areas.

A further promising model system of psychosis, representing a main focus of the current thesis, is sleep deprivation (Chapter IV.I.IV). Sleep deprivation can be applied cross-species and has previously been found to disrupt PPI in rats. Interestingly, the PPI disturbance could be reversed through the administration of antipsychotic but not anxiolytic or antidepressant drugs (Frau et al., 2008). Based on these results, a following study of our group replicated PPI reductions after 24 hours of sleep deprivation in healthy humans (Petrovsky et al., 2014).

To further validate the sleep deprivation model, we examined oculomotor functions in healthy participants after both a night of sleep deprivation and a night of normal sleep (Meyhöfer, Kumari, et al., 2017). Sleep deprivation was found to disrupt SPEM and antisaccade performance, in line with previous studies on oculomotor function after sleep deprivation (Table IV—4 and Table IV—5) and deteriorations reported in patients with psychosis disorders (Chapter IV.II.III—ii). Additionally, sleep deprivation increased psychotomimetic states comprising the positive, negative, and disorganized spectrum, thus validating its striking resemblance to psychosis on the perceptual level.

In order to meet the complexity of psychotic disorders, we aimed to combine the two model systems and investigated potential interaction between them. To do so, a high schizotypy and a control group participated in a night of total sleep deprivation and a night of normal sleep (Meyhöfer, Steffens, et al., 2017). In line with former studies (Table IV—2; Takahashi et al., 2010), the high schizotypy group demonstrated lower SPEM performance (Meyhöfer, Steffens, et al., 2017) and reduced PPI (Meyhöfer et al., to be submitted; Appendix D). Sleep deprivation disrupted several measures of SPEM and saccade tasks and increased psychotomimetic states (Meyhöfer, Kumari, et al., 2017). However, the sleep deprivation induced reduction of PPI failed to reach statistical significance (p=.07, Meyhöfer et al., to be submitted; Appendix D). Most importantly, sleep deprivation reduced SPEM gain in high schizotypes but not controls. Thus sleep deprived high schizotypes demonstrated the closest approximation to psychosis, illustrating the substantial value of combining the two model systems. However, the interactions between schizotypy and sleep deprivation were limited to SPEM performance. The combination of the two model systems is a demanding approach and, therefore, to increase its significance, it would have been desirable to observe additional interactive effects on further important biomarkers of psychosis (i.e. antisaccades, PPI).

Schizotypy as a well-established trait psychosis model and sleep deprivation as a promising non-pharmacological intervention to induce psychosis states are different conceptual approaches, with each of them possessing individual advantages. Due to low correlations between the facets (Grant et al., 2013), positive and negative levels of schizotypy can be investigated fairly independently. Thereby, the distinction of the positive and the negative dimension

provides a useful tool to shed light on the underlying mechanisms of psychotic disorders (Grant, 2015). Sleep deprivation was found to cause psychotomimetic alterations that cover the positive, negative, and disorganized symptom spectrum of psychosis (Studies 3 and 4). Therefore, sleep deprivation might become a valuable alternative choice to pharmacological interventions, allowing the investigation of the effects of innovative treatment options for psychosis in translational study designs.

Overall, the sleep deprivation model offers crucial benefits compared to other often applied model systems (for overviews see Ettinger & Kumari, 2015; Everson, 1997). First, sleep deprivation can be employed cross-species (Frau et al., 2008; Petrovsky et al., 2014). Secondly, sleep deprivation was found to induce psychosis-like experiences mirroring the whole spectrum of symptom dimensions (Chapter IV.I.IV, Studies 3 and 4). Thirdly, cognitive deficits provoked by sleep deprivation overlap with impairments reported in patients with psychotic disorders (Chapter IV.I.IV, Studies 3 and 4). Fourthly, the effects of short-term sleep deprivation are completely reversible, supporting the safety of the model system (Azizi et al., 2017; Elmenhorst et al., 2017). Lastly, sleep deprivation can be administered easily and inexpensively.

Importantly, there are also some caveats concerning the application of sleep deprivation to model symptoms of psychosis that need to be mentioned. Though hallucinations in psychosis can occur in any sensory modality, they most frequently arise in the auditory domain (American Psychiatric Association, 2013). In contrast, sleep deprivation rather induces visual and less strong auditory hallucinations (Berger & Oswald, 1962; Coren, 1998; Kollar et al., 1969). Furthermore, sleep deprivation studies are not double-blind. Due to the level of drowsiness related to sleep loss and the subject's awareness of his sleep state, both the investigator and the participant know the experimental condition.

More broadly, there are also caveats that arise from restrictions of the concept of model systems in principle. Psychosis disorders are heterogeneous and complex, thus leading to a virtually impossible challenge to mimic all aspects in a single model system. Accordingly, schizotypy and sleep deprivation have been found to demonstrate striking overlaps on cognitive and per-

ceptual levels but they certainly do not exhibit/produce the full picture of psychosis. Furthermore, the cognitive and perceptual overlaps between schizotypy, sleep deprivation, and psychosis do not prove that they share the same etiological foundation. In principle it would also be conceivable that these conditions have distinct underlying molecular and cellular mechanisms resulting in a similar phenotype.

VII.II Study limitations

The results shown in the current thesis also have limitations that need to be addressed. The first concerns the size and comparisons of study samples. In Studies 2 and 4, only a small number of males could be included due to low availability of males that were interested in participating. Thus, further research is needed to investigate sex differences in relation to the effects of schizotypy and sleep deprivation found in these studies. However, the effects of sleep deprivation were generally found to be independent from sex (Study 3). Additionally, in order to account for differences in schizotypy scores between males and females (Fonseca-Pedrero et al., 2011), we applied sex-specific inclusion criteria in Study 4, but unfortunately failed to use this criterion in Study 2.

In Studies 3 and 4, the participants spent a normal sleep night and a night of sleep deprivation in our laboratory. Some participants had problems getting to sleep in the unfamiliar stetting. Therefore, additional studies would profit from implementing a familiarization night.

We observed effects of the order of testing (either normal sleep first or sleep deprivation first) for psychotomimetic states and oculomotor measures, broadly indicating stronger effects of sleep deprivation when this was the first testing occasion (Studies 3 and 4). Thus, future studies might benefit from deploying a between-subjects design.

Furthermore, in order to directly draw comparisons between schizotypy, sleep deprived participants, and psychosis patients, prospective studies should additionally include a patient group.

VII.III Future studies

In the current thesis we have investigated the time stability and trait-like nature of saccadic tasks thereby demonstrating their usefulness as endophenotypes in genetic research and as variables in repeated measures designs. As SPEM have been proven a valuable biomarker/endophenotype of psychosis, we have applied SPEM in addition to saccadic tasks to evaluate the validity of the schizotypy and sleep deprivation psychosis model systems. However, until now there is only few research on the time stability of SPEM (Ettinger et al., 2003) and further research is needed to explore the reliability of different SPEM tasks and its trait-like nature.

Sleep deprivation was previously explored as a translational model system of psychosis (Ettinger & Kumari, 2015) and reduced PPI could be restored through antipsychotic drugs in rates (Frau et al., 2008). Building upon our findings of cognitive impairments and increases of psychotomimetic states after sleep deprivation (Study 3 and 4), future research might benefit from the investigation of antipsychotic drug effects on cognition in sleep deprived humans.

In order to discover psychosis-like alterations after sleep deprivation, we have applied the PSI questionnaire (Mason et al., 2008). However, this instrument does not allow to separate auditory and visual hallucinatory-like experiences. As psychotic patients mostly suffer from auditory hallucinations (American Psychiatric Association, 2013), future studies should have a closer look on the types of hallucinatory-like experiences induced through sleep deprivation.

VII.IV Conclusions

Overall, schizotypy and sleep deprivation were found to demonstrate considerable overlaps with psychosis, both on symptom and on cognitive functioning levels. The combination of the two models provided the closest approximation to psychosis. It may thus be concluded that these non-pharmacological model systems when combined with oculomotor biomarkers demonstrate a valuable source to investigate the underlying mechanisms of cognitive deficits in psychosis and to evaluate new treatment approaches. Lastly, framing the findings in the words of Box (1979): Schizotypy and sleep deprivation are illuminating models whose usefulness is highly promising.

VIII REFERENCES

Abel, L. A., Friedman, L., Jesberger, J., Malki, A., & Meltzer, H. Y. (1991). Quantitative assessment of smooth pursuit gain and catch-up saccades in schizophrenia and affective disorders. *Biological Psychiatry*, *29*(11), 1063–1072. http://doi.org/10.1016/0006-3223(91)90248-K

Abel, L. A., & Ziegler, A. S. (1988). Smooth pursuit eye movements in schizophrenics—What constitutes quantitative assessment? *Biological Psychiatry*, *24*(7), 747–761. http://doi.org/10.1016/0006-3223(88)90250-8

Adams, R. A., Perrinet, L. U., & Friston, K. (2012). Smooth pursuit and visual occlusion: active inference and oculomotor control in schizophrenia. *PloS ONE*, *7*(10), 47502–47502. http://doi.org/10.1371/journal.pone.0047502

Aichert, D. S., Williams, S. C. R., Möller, H.-J., Kumari, V., & Ettinger, U. (2012). Functional neural correlates of psychometric schizotypy: An fMRI study of antisaccades. *Psychophysiology*, *49*(3), 345–56. http://doi.org/10.1111/j.1469-8986.2011.01306.x

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. http://doi.org/10.1016/j.schres.2009.01.016

Allen, J. S. (1997). Smooth pursuit eye movements in schizophrenia in New Zealand. *Australian & New Zealand Journal of Psychiatry*, *31*(4), 582–591. http://doi.org/10.3109/00048679709065081

Amador, X. F., Sackeim, H. A., Mukherjee, S., Halperin, R., Neeley, P., Maclin, E., & Schnur, D. (1991). Specificity of smooth pursuit eye movement and visual fixation abnormalities in schizophrenia. *Schizophrenia Research*, *5*(2), 135–144. http://doi.org/10.1016/0920-9964(91)90040-X

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington, VA: Author.

Antoniades, C., Ettinger, U., Gaymard, B., Gilchrist, I., Kristjánsson, A., Kennard, C., … Carpenter, R. H. S. (2013). An internationally standardised antisaccade protocol. *Vision Research*, *84*, 1–5. http://doi.org/10.1016/j.visres.2013.02.007

Aquila, R., & Citrome, L. (2015). Cognitive impairment in schizophrenia: the great unmet need. *CNS Spectrums*, *20*(S1), 32–40. http://doi.org/10.1017/S109285291500070X

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. http://doi.org/10.1016/S0006-3223(97)00479-4

Asai, T., Sugimori, E., Bando, N., & Tanno, Y. (2011). The hierarchic structure in schizotypy and the five-factor model of personality. *Psychiatry Research*, *185*, 78–83. http://doi.org/10.1016/j.psychres.2009.07.018

Avila, M. T., Hong, E. L., Moates, A., Turano, K. A., & Thaker, G. K. (2006). Role of anticipation in schizophrenia-related pursuit initiation deficits. *Journal of Neurophysiology*, *95*(2), 593–601. http://doi.org/10.1152/jn.00369.2005

Azizi, H., Hwang, J., Suen, V., Kang, N. Z., Somvanshi, R., Tadavarty, R., … Sastry, B. R. (2017). Sleep deprivation induces changes in 5-HT actions and 5-HT1A receptor expression in the rat hippocampus. *Neuroscience Letters*, *655*, 151–155. http://doi.org/10.1016/j.neulet.2017.06.053

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 and Biological Psychiatry*, *35*(7), 1753–1764. http://doi.org/10.1016/j.pnpbp.2011.06.004

Bagary, M. S., Hutton, S. B., Symms, M. R., Barker, G. J., Mutsatsa, S. H., Barnes, T. R. E., … Ron, M. A. (2004). Structural neural networks subserving oculomotor function in first-episode schizophrenia. *Biological Psychiatry*, *56*(9), 620–627. http://doi.org/10.1016/j.biopsych.2004.08.017

Bandettini, P. A. (2012). Twenty years of functional MRI: The science and the stories. *NeuroImage*, *62*(2), 575–588. http://doi.org/10.1016/j.neuroimage.2012.04.026

Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Heckers, S., Malaspina, D., … Carpenter, W. (2013). Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: Relevance to DSM-5. *Schizophrenia Research*, *150*(1), 15–20. http://doi.org/10.1016/j.schres.2013.04.027

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

Barnes, G. R., & Asselman, P. T. (1991a). The assessment of predictive effects in smooth eye movement control. *Acta Oto-Laryngologica*, *111*(sup481), 343–347. http://doi.org/10.3109/00016489109131418

Barnes, G. R., & Asselman, P. T. (1991b). The mechanism of prediction in human smooth pursuit eye movements. *Journal of Physiology*, *439*, 439–461.

Barnes, G. R., & Collins, C. J. S. (2008). Evidence for a link between the extra-retinal component of random-onset Pursuit and the anticipatory pursuit of predictable object motion. *Journal of Neurophysiology*, *100*(2), 1135–1146. http://doi.org/10.1152/jn.00060.2008

Barrantes-Vidal, N., Grant, P., & Kwapil, T. R. (2015). The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophrenia Bulletin*, *41*, 408–416. http://doi.org/10.1093/schbul/sbu191

Barton, J. J. S., Pandita, M., Thakkar, K., Goff, D. C., & Manoach, D. S. (2008). The relation between antisaccade errors, fixation stability and prosaccade errors in schizophrenia. *Experimental Brain Research*, *186*(2), 273–282. http://doi.org/10.1007/s00221-007-1235-2

Barton, J., Varese, F., Jones, S. H., Kyle, S., & Haddock, G. (2017). Are sleep disturbances causally linked to the presence and severity of psychosis-like experiences in non-clinical populations? A systematic review. *Sleep*, *40*. http://doi.org/10.1093/sleepj/zsx050.1123

Beauchaine, T. P., Lenzenweger, M. F., & Waller, N. G. (2008). Schizotypy, taxometrics, and disconfirming theories in soft science. *Personality and Individual Differences*, *44*(8), 1652–1662. http://doi.org/10.1016/j.paid.2007.11.015

Beauducel, A., & Wittmann, W. W. (2005). Simulation Study on Fit Indexes in CFA Based on Data With Slightly Distorted Simple Structure. *Structural Equation Modeling*, *12*(1), 41–75. http://doi.org/10.1207/s15328007sem1201_3

Becker, W., & Fuchs, A. F. (1985). Prediction in the oculomotor system: smooth pursuit during transient disappearance of a visual target. *Experimental Brain Research*, *57*(3), 562–575. http://doi.org/10.1007/BF00237843

Beiser, M., Bean, G., Erickson, D., Zhang, J., Iacono, W. G., & Rector, N. A. (1994). Biological and psychosocial predictors of job performance following a first episode of psychosis. *American Journal of Psychiatry*, *151*(6), 857–863. http://doi.org/10.1176/ajp.151.6.857

Bender, S., Weisbrod, M., & Resch, F. (2007). Which perspectives can endophenotypes and biological markers offer in the early recognition of schizophrenia? *Journal of Neural Transmission*, *114*(9), 1199–1215. http://doi.org/10.1007/s00702-007-0742-4

Bennett, S. J., & Barnes, G. R. (2003). Human ocular pursuit during the transient disappearance of a visual target. *Journal of Neurophysiology*, *90*(4), 2504–20. http://doi.org/10.1152/jn.01145.2002

Bennett, S. J., & Barnes, G. R. (2004). Predictive smooth ocular pursuit during the transient disappearance of a visual target. *Journal of Neurophysiology*, *92*(1), 578–90. http://doi.org/10.1152/jn.01188.2003

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. http://doi.org/10.1016/j.biopsych.2012.04.019

Bentler, P. M. (2007). On tests and indices for evaluating structural models. *Personality and Individual Differences*, *42*(5), 825–829. http://doi.org/10.1016/j.paid.2006.09.024

Berger, R. J., & Oswald, I. (1962). Effects of sleep deprivation on behaviour, subsequent sleep, and dreaming. *The Journal of Mental Science*, *108*, 457–465. http://doi.org/10.1192/bjp.108.455.457

Bergh, S., Hjorthøj, C., Sørensen, H. J., Fagerlund, B., Austin, S., Secher, R. G., … Nordentoft, M. (2016). Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders, 10 years after baseline: The OPUS study. *Schizophrenia Research*, *175*(1–3), 57–63. http://doi.org/10.1016/j.schres.2016.03.025

Bey, K., Kloft, L., Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., … Wagner, M. (2017). Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives. *Psychophysiology*, 1–11. http://doi.org/10.1111/psyp.12884

Bhattacharya, K. (2015). Cognitive function in schizophrenia: A review. *Journal of Psychiatry*, *18*(1), 1–8. http://doi.org/10.4172/Psychiatry.1000187

Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics*, *69*(3), 89–95. http://doi.org/10.1067/mcp.2001.113989

Blackwood, D. H., Muir, W. J., Roxborough, H. M., Walker, M. R., Townshend, R., Glabus, M. F., & Wolff, S. (1994). "Schizoid" personality in childhood: auditory P300 and eye tracking responses at follow-up in adult life. *Journal of Autism and Developmental Disorders*, *24*(4), 487–500. http://doi.org/10.1007/BF02172130

Bliss, E., Clark, L., & West, C. (1959). Studies of sleep deprivation—relationship to schizophrenia. *Archives of Neurology And Psychiatry*, *81*(3), 348. http://doi.org/10.1001/archneurpsyc.1959.02340150080009

Bocca, M. L., & Denise, P. (2006). Total sleep deprivation effect on disengagement of spatial attention as assessed by saccadic eye movements. *Clinical Neurophysiology*, *117*(4), 894–899. http://doi.org/10.1016/j.clinph.2006.01.003

Bocca, M. L., Marie, S., & Chavoix, C. (2014). Impaired inhibition after total sleep deprivation using an antisaccade task when controlling for circadian modulation of performance. *Physiology & Behavior*, *124*, 123–8. http://doi.org/10.1016/j.physbeh.2013.10.024

Boonstra, T. W., Stins, J. F., Daffertshofer, A., & Beek, P. J. (2007). Effects of sleep deprivation on neural functioning: An integrative review. *Cellular and Molecular Life Sciences*, *64*(7–8), 934–946. http://doi.org/10.1007/s00018-007-6457-8

Bora, E., & Baysan Arabaci, L. (2009). Effect of age and gender on schizotypal personality traits in the normal population. *Psychiatry and Clinical Neurosciences*, *63*(5), 663–669. http://doi.org/10.1111/j.1440-1819.2009.02011.x

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin*, *40*(4), 744–755. http://doi.org/10.1093/schbul/sbt085

Bora, E., & Pantelis, C. (2015). Meta-analysis of cognitive impairment in first-episode bipolar disorder: Comparison with first-episode schizophrenia and healthy controls. *Schizophrenia Bulletin*, *41*(5), 1095–1104. http://doi.org/10.1093/schbul/sbu198

Bora, E., Yucel, M., & Pantelis, C. (2010). Cognitive impairment in schizophrenia and affective psychoses: Implications for DSM-V criteria and beyond. *Schizophrenia Bulletin*, *36*(1), 36–42. http://doi.org/10.1093/schbul/sbp094

Boudet, C., Bocca, M. L., Chabot, B., Delamillieure, P., Brazo, P., Denise, P., … Dollfus, S. (2005). Are eye movement abnormalities indicators of genetic vulnerability to schizophrenia? *European Psychiatry*, *20*(4), 339–45. http://doi.org/10.1016/j.eurpsy.2004.12.010

Box, G. E. P. (1979). Robustness in the strategy of scientific model building. In R. L. Launer & G. N. Wilkinson (Eds.), *Robustness in Statistics* (pp. 201–236). Academic Press: New York San Francisco London.

Braff, D. L. (2015). The importance of endophenotypes in schizophrenia research. *Schizophrenia Research*, *163*(1–3), 1–8. http://doi.org/10.1016/j.schres.2015.02.007

Braff, D. L., Greenwood, T. A., Swerdlow, N. R., Light, G. A., & Schork, N. J. (2008). Advances in endophenotyping schizophrenia. *World Psychiatry*, *7*(1), 11–18. http://doi.org/10.1002/j.2051-5545.2008.tb00140.x

Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E., … Franck, J. (2012). Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*, *12*, 221. http://doi.org/10.1186/1471-244X-12-221

Braw, Y., Sitman, R., Cohen, M., Berger, U., Lev-Ran, S., Segev, A., … Levkovitz, Y. (2013). Remission of positive symptoms according to the "remission in Schizophrenia Working Group" criteria: A longitudinal study of cognitive functioning. *European Psychiatry*, *28*(5), 282–287. http://doi.org/10.1016/j.eurpsy.2012.04.003

Breier, A. (2005). Developing drugs for cognitive impairment in schizophrenia. *Schizophrenia Bulletin*, *31*(4), 816–822. http://doi.org/10.1093/schbul/sbi051

Brendel, D. H., Reynolds, C. F., Jennings, J. R., Hoch, C. C., Monk, T. H., Berman, S. R., … Kupfer, D. J. (1990). Sleep Stage Physiology, Mood, and Vigilance Responses to Total Sleep Deprivation in Healthy 80-Year-Olds and 20-Year-Olds. *Psychophysiology*. http://doi.org/10.1111/j.1469-8986.1990.tb03193.x

Broerse, A., Crawford, T. J., & den Boer, J. A. (2001). Parsing cognition in schizophrenia using saccadic eye movements: a selective overview. *Neuropsychologia*, *39*(7), 742–756. http://doi.org/10.1016/S0028-3932(00)00155-X

Brosey, E., & Woodward, N. D. (2015). Schizotypy and clinical symptoms, cognitive function, and quality of life in individuals with a psychotic disorder. *Schizophrenia Research*, *166*(1–3), 92–97. http://doi.org/10.1016/j.schres.2015.04.038

Burke, J. G., & Reveley, M. A. (2002). Improved antisaccade performance with risperidone in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, *72*(4), 449–454. http://doi.org/10.1136/jnnp.72.4.449

Burrows, E. L., & Hannan, A. J. (2016). Cognitive endophenotypes, gene-environment interactions and experience-dependent plasticity in animal models of schizophrenia. *Biological Psychology*, *116*, 82–89. http://doi.org/10.1016/j.biopsycho.2015.11.015

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*, *49*(2), 139–46.

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. http://doi.org/10.1016/j.bandc.2008.09.001

Camchong, J., Dyckman, K. A., Austin, B. P., Clementz, B. A., & McDowell, J. E. (2008). Common neural circuitry supporting volitional saccades and its disruption in schizophrenia patients and relatives. *Biological Psychiatry*, *64*(12), 1042–1050. http://doi.org/10.1016/j.biopsych.2008.06.015.Common

Campana, A., Duci, A., Gambini, O., & Scarone, S. (1999). An artificial neural network that uses eye-tracking performance to identify patients with schizophrenia. *Schizophrenia Bulletin*, *25*(4), 789–799.

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. http://doi.org/10.1016/0006-3223(92)90178-3

Carhart-Harris, R., Brugger, S., Nutt, D. J., & Stone, J. (2013). Psychiatry's next top model: cause for a re-think on drug models of psychosis and other psychiatric disorders. *Journal of Psychopharmacology*, *27*(9), 771–778. http://doi.org/10.1177/0269881113494107

Carl, J. R., & Gellman, R. S. (1987). Human smooth pursuit: Stimulus-dependent responses. *Journal of Neurophysiology*, *57*(5), 1446–63.

Carpenter, R. H. S. (1981). Oculomotor procrastination. In D. F. Fisher, R. A. Monty, & J. W. Senders (Eds.), *Eye movements: Cognition and visual perception* (pp. 237–246). Hillsdale: Lawrence Erlbaum.

Carpenter, R. H. S. (1994). Choosing where to look. *Current Biology*, *4*(4), 341–343.

Carpenter, R. H. S., & Williams, M. L. L. (1995). Neural computation of log likelihood in control of saccadic eye movements. *Nature*, *377*, 59–62.

Carpenter, W. T., & Koenig, J. I. (2008). The evolution of drug development in schizophrenia: Past issues and future opportunities. *Neuropsychopharmacology*, *33*(9), 2061–79. http://doi.org/10.1038/sj.npp.1301639

Carter, C. S., & Barch, D. M. (2007). Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: The CNTRICS initiative. *Schizophrenia Bulletin*, *33*(5), 1131–1137. http://doi.org/10.1093/schbul/sbm081

Cegalis, J. A., & Sweeney, J. A. (1981). The effect of attention on smooth pursuit eye movements of schizophrenics. *Journal of Psychiatric Research*, *16*(3), 145–161. http://doi.org/10.1016/0022-3956(81)90001-7

Cerbone, A., Sautter, F. J., Manguno-Mire, G., Evans, W. E., Tomlin, H., Schwartz, B., & Myers, L. (2003). Differences in smooth pursuit eye movement between posttraumatic stress disorder with secondary psychotic symptoms and schizophrenia. *Schizophrenia Research*, *63*(1–2), 59–62. http://doi.org/10.1016/S0920-9964(02)00341-9

Chan, R. C. K., Gooding, D. C., Shi, H., Geng, F., Xie, D., Yang, Z.-Y., … Cheung, E. F. C. (2016). Evidence of structural invariance across three groups of Meehlian schizotypes. *Npj Schizophrenia*, *2*(1), 16016. http://doi.org/10.1038/npjschz.2016.16

Chan, R. C. K., Shi, H., Geng, F. lei, Liu, W., Yan, C., Wang, Y., & Gooding, D. C. (2015). The Chapman psychosis-proneness scales: Consistency across culture and time. *Psychiatry Research*, *228*(1), 143–149. http://doi.org/10.1016/j.psychres.2015.04.031

Chang, W. C., Hui, C. L. M., Chan, S. K. W., Lee, E. H. M., & Chen, E. Y. H. (2016). Impact of avolition and cognitive impairment on functional outcome in first-episode schizophrenia-spectrum disorder: A prospective one-year follow-up study. *Schizophrenia Research*, *170*(2–3), 318–321. http://doi.org/10.1016/j.schres.2016.01.004

Chapman, L. J., Chapman, J. P., Kwapil, T. R., Eckblad, M., & Zinser, M. C. (1994). Putatively psychosis-prone subjects 10 years later. *Journal of Abnormal Psychology*, *103*(2), 171–83. http://doi.org/10.1037/0021-843X.103.2.171

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1976). Scales for physical and social anhedonia. *Journal of Abnormal Psychology*, *85*(4), 374–82. http://doi.org/10.1037/0021-843X.85.4.374

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1978). Body-image aberration in schizophrenia. *Journal of Abnormal Psychology*, *87*(4), 399–407. http://doi.org/10.1037/0021-843X.87.4.399

Chen, E. Y. H., Hui, C. L. M., Dunn, E. L. W., Miao, M. Y. K., Yeung, W. S., Wong, C. K., … Tang, W. N. (2005). A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophrenia Research*, *77*(1), 99–104. http://doi.org/10.1016/j.schres.2005.02.020

Chen, Y., Bidwell, L. C., & Norton, D. (2006). Trait vs. state markers for schizophrenia: Identification and characterization through visual processes. *Current Psychiatry Reviews*, *2*(4), 431–438. http://doi.org/10.2174/157340006778699729

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), 155–61. http://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. http://doi.org/10.1073/pnas.96.8.4724

Cherkasova, M. V, Manoach, D. S., Intriligator, J. M., & Barton, J. J. S. (2002). Antisaccades and task-switching: Interactions in controlled processing. *Experimental Brain Research*, *144*(4), 528–537. http://doi.org/10.1007/s00221-002-1075-z

Chiappelli, J., Nugent, K. L., Thangavelu, K., Searcy, K., & Hong, E. L. (2014). Assessment of trait and state aspects of depression in schizophrenia. *Schizophrenia Bulletin*, *40*(1), 132–142. http://doi.org/10.1093/schbul/sbt069

Chou, H.-H., Twamley, E., & Swerdlow, N. R. (2012). Towards medication-enhancement of cognitive interventions in schizophrenia. In *Novel Antischizophrenia Treatments* (Vol. 213, pp. 81–111). Berlin Heidelberg: Springer. http://doi.org/10.1007/978-3-642-25758-2_4

Chun, C. A., Minor, K. S., & Cohen, A. S. (2013). Neurocognition in psychometrically defined college Schizotypy samples: we are not measuring the "right stuff". *Journal of the International Neuropsychological Society*, *19*(3), 324–37. http://doi.org/10.1017/S135561771200152X

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. http://doi.org/10.1016/j.neubiorev.2016.05.012

Claridge, G. (1972). The schizophrenias as nervous types. *The British Journal of Psychiatry*, *121*(1), 1–17. http://doi.org/10.1192/bjp.121.1.1

Claridge, G. (1987). "The schizophrenias as nervous types" revisited. *The British Journal of Psychiatry*, *151*(6), 735–743. http://doi.org/10.1192/bjp.151.6.735

Claridge, G., & Beech, T. (1995). Fully and quasi-dimensional constructions of schizotypy. In A. Raine, T. A. Lencz, & S. Mednick (Eds.), *Schizotypal Personality* (pp. 192–218). Cambridge, UK: Cambridge University Press.

Claridge, G., & Broks, P. (1984). Schizotypy and hemisphere function—I. *Personality and Individual Differences*, *5*(6), 633–648. http://doi.org/10.1016/0191-8869(84)90111-9

Clementz, B. A., Iacono, W. G., & Grove, W. M. (1996). The construct validity of root-mean-square error for quantifying smooth-pursuit eye tracking abnormalities in schizophrenia. *Biological Psychiatry*, *39*(6), 448–50.

Clementz, B. A., Sweeney, J. A., Hamm, J. P., Ivleva, E. I., Ethridge, L. E., Pearlson, G. D., … Tamminga, C. A. (2016). Identification of distinct psychosis biotypes using brain-based biomarkers. *American Journal of Psychiatry*, *173*(4), 373–384. http://doi.org/10.1176/appi.ajp.2015.14091200

Clementz, B. A., Sweeney, J. A., Hirt, M., & Haas, G. (1990). Pursuit gain and saccadic intrusions in first-degree relatives of probands with schizophrenia. *Journal of Abnormal Psychology*, *99*(4), 327–335. http://doi.org/10.1037/0021-843X.99.4.327

Cochrane, M., Petch, I., & Pickering, A. D. (2010). Do measures of schizotypal personality provide non-clinical analogues of schizophrenic symptomatology? *Psychiatry Research*, *176*(2–3), 150–4. http://doi.org/10.1016/j.psychres.2009.01.031

Cohen, A. S., Matthews, R. a, Najolia, G. M., & Brown, L. A. (2010). Toward a more psychometrically sound brief measure of schizotypal traits: introducing the SPQ-Brief Revised. *Journal of Personality Disorders*, *24*(4), 516–537. http://doi.org/10.1521/pedi.2010.24.4.516

Coren, S. (1998). Sleep Deprivation, psychosis and mental efficiency. *Psychiatric Times*, *15*(3), 5–7.

Corsi-Cabrera, M. (2003). Effect of 38 h of total sleep deprivation on the waking EEG in women: sex differences. *International Journal of Psychophysiology*, *50*(3), 213–224. http://doi.org/10.1016/S0167-8760(03)00168-5

Cosgrave, J., Haines, R., Van Heugten-Van der Kloet, D., Purple, R., Porcheret, K., Foster, R., & Wulff, K. (2017). The interaction between subclinical psychotic experiences, insomnia and objective measures of sleep. *Schizophrenia Research*, 4–8. http://doi.org/10.1016/j.schres.2017.06.058

Crawford, T. J., Bennett, D., Lekwuwa, G., Shaunak, S., & Deakin, J. F. W. (2002). Cognition and the inhibitory control of saccades in schizophrenia and Parkinson's disease (Vol. 140, pp. 449–466). http://doi.org/10.1016/S0079-6123(02)40068-4

Crawford, T. J., Puri, B. K., Nijran, K. S., Jones, B., Kennard, C., & Lewis, S. W. (1996). Abnormal saccadic distractibility in patients with schizophrenia: a 99mTc-HMPAO SPET study. *Psychological Medicine*, *26*(2), 265. http://doi.org/10.1017/S0033291700034668

Crevits, L., Simons, B., & Wildenbeest, J. (2003). Effect of sleep deprivation on saccades and eyelid blinking. *European Neurology*, *50*(3), 176–180. http://doi.org/10.1159/000073060

Culham, J., He, S., Dukelow, S., & Verstraten, F. A. (2001). Visual motion and the human brain: What has neuroimaging told us? *Acta Psychologica*, *107*(1–3), 69–94. http://doi.org/10.1016/S0001-6918(01)00022-1

Curtis, C. E., Calkins, M. E., Grove, W. M., Feil, K. J., & Iacono, W. G. (2001). Saccadic disinhibition in patients with acute and remitted schizophrenia and their first-degree biological relatives. *American Journal of Psychiatry*, *158*(1), 100–106. http://doi.org/10.1176/appi.ajp.158.1.100

Cutsuridis, V. (2017). Behavioural and computational varieties of response inhibition in eye movements. *Philosophical Transactions of the Royal Society*, *372*(1718), 20160196. http://doi.org/10.1098/rstb.2016.0196

Damilou, A., Apostolakis, S., Thrapsanioti, E., Theleritis, C., & Smyrnis, N. (2016). Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. *Psychophysiology*, *53*(6), 796–805. http://doi.org/10.1111/psyp.12630

Daniel, C., Lovatt, A., & Mason, O. J. (2014). Psychotic-like experiences and their cognitive appraisal under short-term sensory deprivation. *Frontiers in Psychiatry*, *5*(August), 106. http://doi.org/10.3389/fpsyt.2014.00106

Davidson, C. A., Hoffman, L., & Spaulding, W. D. (2016). Schizotypal personality questionnaire – brief revised (updated): An update of norms, factor structure, and item content in a large non-clinical young adult sample. *Psychiatry Research*, *238*(7), 345–355. http://doi.org/10.1016/j.psychres.2016.01.053

De Brouwer, S., Missal, M., & Lefèvre, P. (2001). Role of retinal slip in the prediction of target motion during smooth and saccadic pursuit. *Journal of Neurophysiology*, *86*(2), 550–558.

De Gennaro, L., Ferrara, M., Urbani, L., & Bertini, M. (2000). Oculomotor impairment after 1 night of total sleep deprivation: A dissociation between measures of speed and accuracy. *Clinical Neurophysiology*, *111*, 1771–1778. http://doi.org/10.1016/S1388-2457(00)00393-X

De Gregorio, D., Comai, S., Posa, L., & Gobbi, G. (2016). D-Lysergic Acid Diethylamide (LSD) as a model of psychosis: Mechanism of action and pharmacology. *International Journal of Molecular Sciences*, *17*(11), 1–20. http://doi.org/10.3390/ijms17111953

De Visser, S. J., Van der Post, J., Pieters, M. S., Cohen, A. F., & Van Gerven, J. M. (2001). Biomarkers for the effects of antipsychotic drugs in healthy volunteers. *British Journal of Clinical Pharmacology*, *51*(2), 119–32. http://doi.org/bcp308 [pii]

De Wilde, O. M., Bour, L. J., Dingemans, P. M., Koelman, J. H. T. M., Boerée, T., & Linszen, D. H. (2008). P300 deficits are present in young first-episode patients with schizophrenia and not in their healthy young siblings. *Clinical Neurophysiology*, *119*(12), 2721–2726. http://doi.org/10.1016/j.clinph.2008.08.024

Dembińska-Krajewska, D., & Rybakowski, J. (2016). The assessment of schizotypy by the O-LIFE (Oxford-Liverpool Inventory for Feelings and Experiences) in patients with schizophrenia and affective disorders. *Psychiatria Polska*, *50*(6), 1147–1156. http://doi.org/10.12740/PP/62335

DeSouza, J. F. X., Menon, R. S., & Everling, S. (2002). Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related fMRI. *Journal of Neurophysiology*, *89*(2), 1016–1023. http://doi.org/10.1152/jn.00562.2002

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

DiLuca, M., & Olesen, J. (2014). The cost of brain diseases: A burden or a challenge? *Neuron*, *82*(6), 1205–1208. http://doi.org/10.1016/j.neuron.2014.05.044

Dissel, S., Seugnet, L., Thimgan, M. S., Silverman, N., Angadi, V., Thacher, P. V., … Shaw, P. J. (2015). Differential activation of immune factors in neurons and glia contribute to individual differences in resilience/vulnerability to sleep disruption. *Brain, Behavior, and Immunity*, *47*, 75–85. http://doi.org/10.1016/j.bbi.2014.09.019

Doran, S. M., Van Dongen, H. P. A., & Dinges, D. F. (2001). Sustained attention performace during sleep deprivation: Evidence of state instability. *Archives Italiennes de Biologie*, *139*, 253–267.

Dowiasch, S., Backasch, B., Einhäuser, W., Leube, D., Kircher, T., & Bremmer, F. (2016). Eye movements of patients with schizophrenia in a natural environment. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(1), 43–54. http://doi.org/10.1007/s00406-014-0567-8

Duchowski, A. T. (2007). *Eye tracking methodology: Theory and practice.* (2nd ed.). London: Springer-Verlag London Ltd.

Dukelow, S. P., Desouza, J. F. X., 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*, 1991–2000.

Dunlop, J., & Brandon, N. J. (2015). Schizophrenia drug discovery and development in an evolving era: are new drug targets fulfilling expectations? *Journal of Psychopharmacology*, *29*(2), 230–8. http://doi.org/10.1177/0269881114565806

Dyckman, K. A., Camchong, J., Clementz, B. A., & McDowell, J. E. (2007). An effect of context on saccade-related behavior and brain activity. *NeuroImage*, *36*(3), 774–784. http://doi.org/10.1016/j.neuroimage.2007.03.023

Dyckman, K. A., Lee, A. K. C., Agam, Y., Vangel, M., Goff, D. C., Barton, J. J. S., & Manoach, D. S. (2011). Abnormally persistent fMRI activation during antisaccades in schizophrenia: A neural correlate of perseveration? *Schizophrenia Research*, *132*(1), 62–68. http://doi.org/10.1016/j.schres.2011.07.026

Eckblad, M., & Chapman, L. J. (1983). Magical ideation as an indicator of schizotypy. *Journal of Consulting and Clinical Psychology*, *51*(2), 215–25. http://doi.org/10.1037/0022-006X.51.2

Ekerholm, M., Firus Waltersson, S., Fagerberg, T., Söderman, E., Terenius, L., Agartz, I., … Nyman, H. (2012). Neurocognitive function in long-term treated schizophrenia: A five-year follow-up study. *Psychiatry Research*, *200*(2–3), 144–152. http://doi.org/10.1016/j.psychres.2012.05.008

Elmenhorst, D., Elmenhorst, E.-M., Hennecke, E., Kroll, T., Matusch, A., Aeschbach, D., & Bauer, A. (2017). Recovery sleep after extended wakefulness restores elevated A $_1$ adenosine receptor availability in the human brain. *Proceedings of the National Academy of Sciences*, *114*(16), 201614677. http://doi.org/10.1073/pnas.1614677114

Ernst, F., Rauchenzauner, M., Zoller, H., Griesmacher, A., Hammerer-Lercher, A., Carpenter, R., … Joannidis, M. (2014). Effects of 24h working on-call on psychoneuroendocrine and oculomotor function: A randomized cross-over trial. *Psychoneuroendocrinology*, *47*, 221–231. http://doi.org/10.1016/j.psyneuen.2014.05.019

Ettinger, U., Aichert, D. S., Wöstmann, N., Dehning, S., Riedel, M., & Kumari, V. (2017). Response inhibition and interference control: Effects of schizophrenia, genetic risk, and schizotypy. *Journal of Neuropsychology*. http://doi.org/10.1111/jnp.12126

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*(5), 1148–1159. http://doi.org/10.1093/cercor/bhm147

Ettinger, U., & Kumari, V. (2015). Effects of sleep deprivation on inhibitory biomarkers of schizophrenia: implications for drug development. *The Lancet Psychiatry*, *2*(11), 1028–1035. http://doi.org/10.1016/S2215-0366(15)00313-2

Ettinger, U., Kumari, V., Chitnis, X. A., Corr, P. J., Crawford, T. J., Fannon, D. G., … Sharma, T. (2004). Volumetric neural correlates of antisaccade eye movements in first-episode psychosis. *American Journal of Psychiatry*, *161*(10), 1918–1921. http://doi.org/10.1176/appi.ajp.161.10.1918

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. http://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. http://doi.org/10.1111/1469-8986.00063

Ettinger, U., Kumari, V., Crawford, T. J., Flak, V., Sharma, T., Davis, R. E., & Corr, P. J. (2005). Saccadic eye movements, schizotypy, and the role of neuroticism. *Biological Psychology*, *68*(1), 61–78. http://doi.org/10.1016/j.biopsycho.2004.03.014

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), 1–16. http://doi.org/10.3389/fpsyt.2014.00018

Ettinger, U., Mohr, C., Gooding, D. C., Cohen, A. S., Rapp, A., Haenschel, C., & Park, S. (2015). Cognition and brain function in schizotypy: A selective review. *Schizophrenia Bulletin*, *41*, 417–426. http://doi.org/10.1093/schbul/sbu190

Ettinger, U., Picchioni, M., Hall, M., Schulze, K., Toulopoulou, T., Landau, S., … Murray, R. M. (2006). Antisaccade performance in monozygotic twins discordant for schizophrenia: The Maudsley Twin Study. *American Journal of Psychiatry*, *163*(3), 543–545. http://doi.org/10.1176/appi.ajp.163.3.543

Evensen, S., Wisløff, T., Lystad, J. U., Bull, H., Ueland, T., & Falkum, E. (2016). Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: A population-based study using comprehensive health and welfare registers. *Schizophrenia Bulletin*, *42*(2), 476–483. http://doi.org/10.1093/schbul/sbv141

Everett, K. V., & Linscott, R. J. (2015). Dimensionality vs taxonicity of schizotypy: Some new data and challenges ahead. *Schizophrenia Bulletin*, *41*(2), 465–474. http://doi.org/10.1093/schbul/sbu221

Everling, S., & Fischer, B. (1998). The antisaccade: a review of basic research and clinical studies. *Neuropsychologia*, *36*(9), 885–899. http://doi.org/10.1016/S0028-3932(98)00020-7

Everson, C. A. (1997). Clinical manifestations of prolonged sleep deprivation. In W. J. Schwartz (Ed.), *Sleep Science: Integrating Basic Research and Clinical Practice.* (p. 34–59.). Basel: Karger.

Eysenck, H. J. (1967). *The biological basis of personlity.* Springfield, IL: Thomas.

Eysenck, S. B. G., & Eysenck, H. J. (1968). The measurement of psychoticism: a study of factor stability and reliability. *British Journal of Social and Clinical Psychology*, *7*(4), 286–294. http://doi.org/10.1111/j.2044-8260.1968.tb00571.x

Fabisch, K., Fitz, W., Fabisch, H., Haas-Krammer, A., Klug, G., Zapotoczky, S., & Kapfhammer, H.-P. (2009). Sinusoidal smooth pursuit eye tracking at different stimulus frequencies: position error and velocity error before catch-up saccades in schizophrenia and in major depressive disorder. *The Australian and New Zealand Journal of Psychiatry*, *43*(9), 855–65. http://doi.org/10.1080/00048670903107542

Farber, R. H., Clementz, B. A., & Swerdlow, N. R. (1997). Characteristics of open- and closed loop smooth pursuit responses among obsessive-compulsive disorder, schizophrenia, and nonpsychiatric individuals. *Psychophysiology*, *34*, 157–162.

Fatouros-Bergman, H., Cervenka, S., Flyckt, L., Edman, G., & Farde, L. (2014). Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. *Schizophrenia Research*, *158*(1–3), 156–162. http://doi.org/10.1016/j.schres.2014.06.034

Feinberg, I. (1978). Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophrenia Bulletin*, *4*(4), 636–640. http://doi.org/10.1093/schbul/4.4.636

Ferrara, M., De Gennaro, L., & Bertini, M. (2000). Voluntary oculomotor performance upon awakening after total sleep deprivation. *Sleep*, *23*(6), 801–811.

Ferrarelli, F. (2015). Sleep in patients with schizophrenia. *Current Sleep Medicine Reports*, *1*(2), 150–156. http://doi.org/10.1007/s40675-015-0010-3

Fervaha, G., Foussias, G., Agid, O., & Remington, G. (2014). Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. *Acta Psychiatrica Scandinavica*, *130*(4), 290–299. http://doi.org/10.1111/acps.12289

Fimm, B., & Blankenheim, A. (2016). Effect of sleep deprivation and low arousal on eye movements and spatial attention. *Neuropsychologia*, *92*, 115–128. http://doi.org/10.1016/j.neuropsychologia.2016.03.021

Fioravanti, M., Carlone, O., Vitale, B., Cinti, M. E., & Clare, L. (2005). A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review*, *15*(2), 73–95. http://doi.org/10.1007/s11065-005-6254-9

Fischer, B., & Weber, H. (1993). Express saccades and visual attention. *Behavioral and Brain Sciences*, *16*(3), 553. http://doi.org/10.1017/S0140525X00031575

Flechtner, K. M., Steinacher, B., Sauer, R., & Mackert, A. (1997). Smooth pursuit eye movements in schizophrenia and affective disorder. *Psychological Medicine*, *27*(6), 1411–1419.

Flechtner, K. M., Steinacher, B., Sauer, R., & Mackert, A. (2002). Smooth pursuit eye movements of patients with schizophrenia and affective disorder during clinical treatment. *European Archives of Psychiatry and Clinical Neuroscience*, *252*(2), 49–53. http://doi.org/10.1007/s004060200011

Fletcher, P. C., & Frith, C. D. (2009). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature Reviews. Neuroscience*, *10*(1), 48–58. http://doi.org/10.1038/nrn2536

Fliege, H., Rose, M., Arck, P., Walter, O. B., Kocalevent, R.-D., Weber, C., & Klapp, B. F. (2005). The Perceived Stress Questionnaire (PSQ) reconsidered: Validation and reference values from different clinical and healthy adult samples. *Psychosomatic Medicine*, *67*(1), 78–88. http://doi.org/10.1097/01.psy.0000151491.80178.78

Flint, J., & Munafò, M. R. (2007). The endophenotype concept in psychiatric genetics. *Psychological Medicine*, *37*(2), 163–180. http://doi.org/10.1017/S0033291706008750

Fonseca-Pedrero, E., Ortuño-Sierra, J., Sierro, G., Daniel, C., Cella, M., Preti, A., … Mason, O. J. (2015). The measurement invariance of schizotypy in Europe. *European Psychiatry*, *30*(7), 837–844. http://doi.org/10.1016/j.eurpsy.2015.07.005

Fonseca-Pedrero, E., Paíno, M., Lemos-giráldez, S., García-cueto, E., Campillo-álvarez, Á., Villazón-García, U., & Muñiz, J. (2008). Schizotypy assessment: State of the art and future prospects 1. *International Journal of Clinical and Health Psychology*, *8*(2), 577–593.

Fonseca-Pedrero, E., Paíno, 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), 309–15. http://doi.org/10.1016/j.psychres.2011.05.021

Ford, J. M., & Mathalon, D. H. (2012). Anticipating the future: Automatic prediction failures in schizophrenia. *International Journal of Psychophysiology*, *83*(2), 232–239. http://doi.org/10.1016/j.ijpsycho.2011.09.004

Fossati, A., Raine, A., Carretta, I., Leonardi, B., & Maffei, C. (2003). The three-factor model of schizotypal personality: invariance across age and gender. *Personality and Individual Differences*, *35*(5), 1007–1019. http://doi.org/10.1016/S0191-8869(02)00314-8

Franco, J. G., De Pablo, J., Gaviria, A. M., Sepúlveda, E., & Vilella, E. (2014). Smooth pursuit eye movements and schizophrenia: Literature review. *Archivos de La Sociedad Española de Oftalmología*, *89*(9), 361–367. http://doi.org/10.1016/j.oftale.2014.02.009

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*, *18*(4), 209–22.

Frau, R., Orrù, M., Puligheddu, M., Gessa, G. L., Mereu, G., Marrosu, F., & Bortolato, M. (2008). Sleep deprivation disrupts prepulse inhibition of the startle reflex: reversal by antipsychotic drugs. *The International Journal of Neuropsychopharmacology*, *11*, 947–955. http://doi.org/10.1017/S1461145708008900

Freeman, D., Pugh, K., Vorontsova, N., & Southgate, L. (2009). Insomnia and paranoia. *Schizophrenia Research*, *108*(1–3), 280–284. http://doi.org/10.1016/j.schres.2008.12.001

Friedman, L., Abel, L. A., Jesberger, J. A., Malki, A., & Meltzer, H. Y. (1992). Saccadic intrusions into smooth pursuit in patients with schizophrenia or affective disorder and normal controls. *Biological Psychiatry*, *31*(11), 1110–1118. http://doi.org/10.1016/0006-3223(92)90155-S

Friedman, L., Jesberger, J. A., Abel, L. A., & Meltzer, H. Y. (1992). Catch-up saccade amplitude is related to square wave jerk rate. *Investigative Ophthalmology and Visual Science*, *33*(1), 228–233.

Friedman, L., Jesberger, J. A., & Meltzer, H. Y. (1992). Effect of typical antipsychotic medications and clozapine on smooth pursuit performance in patients with schizophrenia. *Psychiatry Research*, *41*(1), 25–36. http://doi.org/10.1016/0165-1781(92)90015-U

Friedman, L., Jesberger, J. A., Siever, L. J., Thompson, P. A., Mohs, R., & Meltzer, H. Y. (1995). Smooth pursuit performance in patients with affective disorders or schizophrenia and normal controls: analysis with specific oculomotor measures, RMS error and qualitative ratings. *Psychological Medicine*, *25*(2), 387–403. http://doi.org/10.1017/S003329170003628X

Fukumoto-Motoshita, M., Matsuura, M., Ohkubo, T., Ohkubo, H., Kanaka, N., Matsushima, E., … Matsuda, T. (2009). Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: A study with fMRI. *Psychiatry and Clinical Neurosciences*, *63*(2), 209–217. http://doi.org/10.1111/j.1440-1819.2009.01941.x

Fukushima, J., Fukushima, K., Chiba, T., Tanaka, S., Yamashita, I., & Kato, M. (1988). Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biological Psychiatry*, *23*(7), 670–677. http://doi.org/10.1016/0006-3223(88)90050-9

Fukushima, J., Morita, N., Fukushima, K., Chiba, T., Tanaka, S., & Yamashita, I. (1990). Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *Journal of Psychiatric Research*, *24*(1), 9–24. http://doi.org/10.1016/0022-3956(90)90021-H

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*(March), 4. http://doi.org/10.3389/fnsys.2013.00004

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*, 157–62. http://doi.org/10.1038/nature00953

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. http://doi.org/10.1523/JNEUROSCI.2789-05.2006

Gais, S., Köster, S., Sprenger, A., Bethke, J., Heide, W., & Kimmig, H. (2008). Sleep is required for improving reaction times after training on a procedural visuo-motor task. *Neurobiology of Learning and Memory*, *90*(4), 610–5. http://doi.org/10.1016/j.nlm.2008.07.016

Gegenfurtner, K. R. (1999). The eyes have it! *Nature*, *398*, 291–292.

Geyer, M. A., Olivier, B., Joëls, M., & Kahn, R. S. (2012). From antipsychotic to anti-schizophrenia drugs: role of animal models. *Trends in Pharmacological Sciences*, *33*(10), 515–521. http://doi.org/10.1016/j.tips.2012.06.006

Giakoumaki, S. G. (2012). Cognitive and prepulse inhibition deficits in psychometrically high schizotypal subjects in the general population: Relevance to schizophrenia research. *Journal of the International Neuropsychological Society*, *18*(4), 643–56. http://doi.org/10.1017/S135561771200029X

Glahn, D. C., Knowles, E. E., 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*, *165*(2), 122–130. http://doi.org/10.1002/ajmg.b.32221

Glasauer, S. (2007). Current models of the ocular motor system. In *Neuro-Ophthalmology* (Vol. 40, pp. 158–174). Basel: KARGER. http://doi.org/10.1159/000100485

Goense, J. B. M., & Logothetis, N. K. (2008). Neurophysiology of the BOLD fMRI signal in awake monkeys. *Current Biology*, *18*(9), 631–640. http://doi.org/10.1016/j.cub.2008.03.054

Goff, D. C., Romero, K., Paul, J., Mercedes Perez-Rodriguez, M., Crandall, D., & Potkin, S. G. (2016). Biomarkers for drug development in early psychosis: Current issues and promising directions. *European Neuropsychopharmacology*, *26*(6), 923–937. http://doi.org/10.1016/j.euroneuro.2016.01.009

Goldich, Y., Barkana, Y., Pras, E., Zadok, D., Hartstein, M., & Morad, Y. (2010). The Effects of Sleep Deprivation on Oculomotor Responses. *Current Eye Research*, *35*(12), 1135–1141. http://doi.org/10.3109/02713683.2010.507902

Gooding, D. C. (1999). Antisaccade task performance in questionnaire-identified schizotypes. *Schizophrenia Research*, *35*(2), 157–166. http://doi.org/10.1016/S0920-9964(98)00120-0

Gooding, D. C., & Basso, M. A. (2008). The tell-tale tasks: A review of saccadic research in psychiatric patient populations. *Brain and Cognition*, *68*(3), 371–390. http://doi.org/10.1016/j.bandc.2008.08.024

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. http://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. http://doi.org/10.1016/S0165-1781(00)00113-X

Gooding, D. C., Mohapatra, L., & Shea, H. B. (2004). Temporal stability of saccadic task performance in schizophrenia and bipolar patients. *Psychological Medicine*, *34*(5), 921–32. http://doi.org/10.1017/S003329170300165X

Gooding, D. C., Shea, H. B., & Matts, C. W. (2005). Saccadic performance in questionnaire-identified schizotypes over time. *Psychiatry Research*, *133*, 173–186. http://doi.org/10.1016/j.psychres.2003.12.029

Gooding, D. C., Tallent, K. a, & Matts, C. W. (2005). Clinical status of at-risk individuals 5 years later: Further validation of the psychometric high-risk strategy. *Journal of Abnormal Psychology*, *114*(1), 170–175. http://doi.org/10.1037/0021-843X.114.1.170

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

Gould, T. D., & Gottesman, I. I. (2006). Psychiatric endophenotypes and the development of valid animal models. *Genes, Brain and Behavior*, *5*(2), 113–119. http://doi.org/10.1111/j.1601-183X.2005.00186.x

Grace, P. M., Stanford, T., Gentgall, M., & Rolan, P. E. (2010). Utility of saccadic eye movement analysis as an objective biomarker to detect the sedative interaction between opioids and sleep deprivation in opioid-naive and opioid-tolerant populations. *Journal of Psychopharmacology*, *24*(11), 1631–1640. http://doi.org/10.1177/0269881109352704

Grant, P. (2015). Is schizotypy per se a suitable endophenotype of schizophrenia? - Do not forget to distinguish positive from negative facets. *Frontiers in Psychiatry*, *6*(OCT), 10–13. http://doi.org/10.3389/fpsyt.2015.00143

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*, 1–11. http://doi.org/10.3389/fnhum.2013.00001

Grant, P., Munk, A. J. L., Kuepper, Y., Wielpuetz, C., & Hennig, J. (2015). Additive genetic effects for schizotypy support a fully-dimensional model of psychosis-proneness. *Journal of Individual Differences*, *36*(2), 87–92. http://doi.org/10.1027/1614-0001/a000155

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry*, *153*(3), 321–330. http://doi.org/10.1111/j.1530-0277.2006.00335.x

Green, M. F. (2016). Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *The Journal of Clinical Psychiatry*, *77*, 8–11. http://doi.org/10.4088/JCP.14074su1c.02

Green, M. F., Butler, P. D., Chen, Y., Geyer, M. A., Silverstein, S., Wynn, J. K., … Zemon, V. (2009). Perception measurement in clinical trials of schizophrenia: Promising paradigms from CNTRICS. *Schizophrenia Bulletin*, *35*(1), 163–181. http://doi.org/10.1093/schbul/sbn156

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the “right stuff”? *Schizophrenia Bulletin*, *26*(1), 119–136. http://doi.org/10.1093/oxfordjournals.schbul.a033430

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: Implications for MATRICS. *Schizophrenia Research*, *72*(1), 41–51. http://doi.org/10.1016/j.schres.2004.09.009

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., … Marder, S. R. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological Psychiatry*, *56*(5), 301–307. http://doi.org/10.1016/j.biopsych.2004.06.023

Greenwood, T. A., Lazzeroni, L. C., Calkins, M. E., Freedman, R., Green, M. F., Gur, R. E., … Braff, D. L. (2016). Genetic assessment of additional endophenotypes from the Consortium on the Genetics of Schizophrenia Family Study. *Schizophrenia Research*, *170*(1), 30–40. http://doi.org/10.1016/j.schres.2015.11.008

Grootens, K. P., Van Luijtelaar, G., Buitelaar, J. K., Van der Laan, A., Hummelen, J. W., & Verkes, R. J. (2008). Inhibition errors in borderline personality disorder with psychotic-like symptoms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(1), 267–273. http://doi.org/10.1016/j.pnpbp.2007.08.020

Gross, G. M., Mellin, J., Silvia, P. J., Barrantes-Vidal, N., & Kwapil, T. R. (2014). Comparing the factor structure of the Wisconsin Schizotypy Scales and the Schizotypal Personality Questionnaire. *Personality Disorders: Theory, Research, and Treatment*, *5*(4), 397–405. http://doi.org/10.1037/per0000090

Gross, G. M., Silvia, P. J., Barrantes-Vidal, N., & Kwapil, T. R. (2015). The dimensional structure of short forms of the Wisconsin Schizotypy Scales. *Schizophrenia Research*, *166*(1–3), 80–85. http://doi.org/10.1016/j.schres.2015.05.016

Guloksuz, S., & Van Os, J. (2017). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine*, 1–16. http://doi.org/10.1017/S0033291717001775

Halberstadt, A. L., & Geyer, M. A. (2013). Serotonergic hallucinogens as translational models relevant to schizophrenia. *The International Journal of Neuropsychopharmacology*, *16*(10), 2165–80. http://doi.org/10.1017/S1461145713000722

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research*, *18*(10), 1279–1296. http://doi.org/10.1016/0042-6989(78)90218-3

Haraldsson, H. M., Ettinger, U., Magnusdottir, B. B., Sigmundsson, T., Sigurdsson, E., Ingason, A., & Petursson, H. (2009). COMT val158met genotype and smooth pursuit eye movements in schizophrenia. *Psychiatry Research*, *169*(2), 173–175. http://doi.org/10.1016/j.psychres.2008.10.003

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. http://doi.org/10.1007/s00406-008-0806-y

Harris, M. S. H., Reilly, J. L., Keshavan, M. S., & Sweeney, J. A. (2006). Longitudinal studies of antisaccades in antipsychotic-naive first-episode schizophrenia. *Psychological Medicine*, *36*(4), 485–494. http://doi.org/10.1017/S0033291705006756

Harris, M. S. H., Reilly, J. L., Thase, M. E., Keshavan, M. S., & Sweeney, J. A. (2009). Response suppression deficits in treatment-naïve first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. *Psychiatry Research*, *170*(2–3), 150–156. http://doi.org/10.1016/j.psychres.2008.10.031

Harrison, Y., & Horne, J. A. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *Journal of Sleep Research*, *7*(2), 95–100. http://doi.org/10.1046/j.1365-2869.1998.00104.x

Harrison, Y., & Horne, J. A. (2000). The impact of sleep deprivation on decision making: A review. *Journal of Experimental Psychology. Applied*, *6*(3), 236–249. http://doi.org/10.1037/1076-898X.6.3.236

Harrison, Y., Horne, J. A., & Rothwell, A. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults—a model for healthy aging? *Sleep*, *23*(8), 1–7. http://doi.org/10.1093/sleep/23.8.1f

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. http://doi.org/10.1016/j.schres.2013.04.039

Heeger, D. J., & Ress, D. (2002). What does fMRI tell us about neuronal activity? *Nature Reviews Neuroscience*, *3*(2), 142–151. http://doi.org/10.1038/nrn730

Heilbronner, U., Samara, M., Leucht, S., Falkai, P., & Schulze, T. G. (2016). The Longitudinal Course of Schizophrenia Across the Lifespan. *Harvard Review of Psychiatry*, *24*(2), 118–128. http://doi.org/10.1097/HRP.0000000000000092

Heinemann, L. G. (1966). Der mehrtägige Schlafentzug in der experimentellen Psychoseforschung: Psychopathologie und EEG. *Archiv Für Psychiatrie Und Nervenkrankheiten Vereinigt Mit Zeitschrift Für Die Gesamte Neurologie Und Psychiatrie*, *208*(2), 177–197. http://doi.org/10.1007/BF00343267

Heinrichs, R. W. (2004). Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? *Neuroscience and Biobehavioral Reviews*, *28*(4), 379–94. http://doi.org/10.1016/j.neubiorev.2004.06.003

Heron, J., Jones, I., Williams, J., Owen, M. J., Craddock, N., & Jones, L. A. (2003). Self-reported schizotypy and bipolar disorder: Demonstration of a lack of specificity of the Kings Schizotypy Questionnaire. *Schizophrenia Research*, *65*(2–3), 153–158. http://doi.org/10.1016/S0920-9964(03)00004-5

Herweg, N. A., Weber, B., Kasparbauer, A., Meyhöfer, I., Steffens, M., Smyrnis, N., & Ettinger, U. (2014). Functional magnetic resonance imaging of sensorimotor transformations in saccades and antisaccades. *NeuroImage*, *102*, 848–860. http://doi.org/10.1016/j.neuroimage.2014.08.033

Hill, S. K., Bishop, J. R., Palumbo, D., & Sweeney, J. A. (2010). Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Review of Neurotherapeutics*, *10*(1), 43–57. http://doi.org/10.1586/ern.09.143.Effect

Hill, S. K., Reilly, J. L., Harris, M. S. H., Khine, T., & Sweeney, J. A. (2008). Oculomotor and neuropsychological effects of antipsychotic treatment for schizophrenia. *Schizophrenia Bulletin*, *34*(3), 494–506. http://doi.org/10.1093/schbul/sbm112

Hill, S. K., Reilly, J. L., Keefe, R. S. E., Gold, J. M., Bishop, J. R., Gershon, E. S., … Sweeney, J. A. (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *American Journal of Psychiatry*, *170*(11), 1275–1284. http://doi.org/10.1176/appi.ajp.2013.12101298

Hirvonen, K., Puttonen, S., Gould, K., Korpela, J., Koefoed, V. F., & Müller, K. (2010). Improving the saccade peak velocity measurement for detecting fatigue. *Journal of Neuroscience Methods*, *187*(2), 199–206. http://doi.org/10.1016/j.jneumeth.2010.01.010

Hoff, A. L., Svetina, C., Shields, G., Stewart, J., & DeLisi, L. E. (2005). Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophrenia Research*, *78*(1), 27–34. http://doi.org/10.1016/j.schres.2005.05.010

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. http://doi.org/10.1016/j.schres.2004.10.005

Holmqvist, K., Nyström, M., Andersson, R., Dewhurst, R., Jarodzka, H., & Van de Weijer, J. (2011). *Eye tracking. A comprehensive guide to methods and measures.* Oxford University Press.

Holst, S. C., Müller, T., Valomon, A., Seebauer, B., Berger, W., & Landolt, H.-P. (2017). Functional polymorphisms in dopaminergic genes modulate neurobehavioral and neurophysiological consequences of sleep deprivation. *Scientific Reports*, *7*(April), 1–11. http://doi.org/10.1038/srep45982

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

Hong, E. L., Avila, M. T., Adami, H., Elliot, A., & Thaker, G. K. (2003). Components of the smooth pursuit function in deficit and nondeficit schizophrenia. *Schizophrenia Research*, *63*(1–2), 39–48. http://doi.org/10.1016/S0920-9964(02)00388-2

Hong, E. L., Tagamets, M., Avila, M. T., 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), 726–32. http://doi.org/10.1016/j.biopsych.2004.12.015

Horne, J. (2000). Images of lost sleep. *Nature*, *403*(6770), 605–606. http://doi.org/10.1038/35001174

Horne, J. A. (1993). Human sleep, sleep loss and behaviour. Implications for the prefrontal cortex and psychiatric disorder. *The British Journal of Psychiatry*, *162*(3), 413–419. http://doi.org/10.1192/bjp.162.3.413

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*(1), 1–55. http://doi.org/10.1080/10705519909540118

Hudgens-Haney, M. E., Ethridge, L. E., Knight, J. B., McDowell, J. E., Keedy, S. K., Pearlson, G. D., … Clementz, B. A. (2017). Intrinsic neural activity differences among psychotic illnesses. *Psychophysiology*, (March). http://doi.org/10.1111/psyp.12875

Huettel, S. A., Song, A. W., & McCarthy, G. (2008). *Functional magnetic resonance imaging* (2nd ed.). Sunderland: Sinauer Associates.

Hunt, A. R., & Kingstone, A. (2003). Covert and overt voluntary attention: Linked or independent? *Cognitive Brain Research*, *18*(1), 102–105. http://doi.org/10.1016/j.cogbrainres.2003.08.006

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

Hutton, S. B., Crawford, T. J., Gibbins, H., Cuthbert, I., Barnes, T. R., Kennard, C., & Joyce, E. M. (2001). Short and long term effects of antipsychotic medication on smooth pursuit eye tracking in schizophrenia. *Psychopharmacology*, *157*(3), 284–91. http://doi.org/10.1007/s002130100803

Hutton, S. B., Crawford, T. J., Puri, B. K., Duncan, L. J., Chapman, M., Kennard, C., … Joyce, E. M. (1998). Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. *Psychological Medicine*, *28*(3), 685–692. http://doi.org/10.1017/S0033291798006722

Hutton, S. B., & Ettinger, U. (2006). The antisaccade task as a research tool in psychopathology: A critical review. *Psychophysiology*, *43*(3), 302–313. http://doi.org/10.1111/j.1469-8986.2006.00403.x

Hutton, S. B., Huddy, V., Barnes, T. R. E., Robbins, T. W., Crawford, T. J., Kennard, C., & Joyce, E. M. (2004). The relationship between antisaccades, smooth pursuit, and executive dysfunction in first-episode schizophrenia. *Biological Psychiatry*, *56*(8), 553–559. http://doi.org/10.1016/j.biopsych.2004.07.002

Hutton, S. B., Joyce, E. M., Barnes, T. R. E., & Kennard, C. (2002). Saccadic distractibility in first episode schizophrenia. *Neuropsychologia*, *40*, 1729–1736.

Hutton, S., & Kennard, C. (1998). Oculomotor abnormalities in schizophrenia: A critical review. *Neurology*, *50*(3), 604–9. http://doi.org/10.1212/WNL.50.3.604

Ilg, U. J., & Thier, P. (2008). The neural basis of smooth pursuit eye movements in the rhesus monkey brain. *Brain and Cognition*, *68*(3), 229–40. http://doi.org/10.1016/j.bandc.2008.08.014

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. http://doi.org/10.1176/appi.ajp.2010.09091379

Insel, T. R., & Cuthbert, B. N. (2009). Endophenotypes: Bridging genomic complexity and disorder heterogeneity. *Biological Psychiatry*, *66*(11), 988–989. http://doi.org/10.1016/j.biopsych.2009.10.008

Ivleva, E. I., Moates, A. F., Hamm, J. P., Bernstein, I. H., O'Neill, H. B., Cole, D., … Tamminga, C. A. (2014). Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. *Schizophrenia Bulletin*, *40*(3), 642–652. http://doi.org/10.1093/schbul/sbt047

Jaafari, N., Rigalleau, F., Rachid, F., Delamillieure, P., Millet, B., Olié, J.-P. P., … Vibert, N. (2011). A critical review of the contribution of eye movement recordings to the neuropsychology of obsessive compulsive disorder. *Acta Psychiatrica Scandinavica*, *124*(2), 87–101. http://doi.org/10.1111/j.1600-0447.2011.01721.x

Jackson, M. L., Gunzelmann, G., Whitney, P., Hinson, J. M., Belenky, G., Rabat, A., & Van Dongen, H. P. A. (2013). Deconstructing and reconstructing cognitive performance in sleep deprivation. *Sleep Medicine Reviews*, *17*(3), 215–225. http://doi.org/10.1016/j.smrv.2012.06.007

Jamadar, S. D., Fielding, J., & Egan, G. F. (2013). Quantitative meta-analysis of fMRI and PET studies reveals consistent activation in fronto-striatal-parietal regions and cerebellum during antisaccades and prosaccades. *Frontiers in Psychology*, *4*(OCT), 1–15. http://doi.org/10.3389/fpsyg.2013.00749

Jann, M. W. (2014). Diagnosis and treatment of bipolar disorders in adults: A review of the evidence on pharmacologic treatments. *American Health & Drug Benefits*, *7*(9), 489–499.

Javitt, D. C., Zukin, S. R., Heresco-Levy, U., & Umbricht, D. (2012). Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophrenia Bulletin*, *38*(5), 958–966. http://doi.org/10.1093/schbul/sbs069

Johnston, K., & Everling, S. (2008). Neurophysiology and neuroanatomy of reflexive and voluntary saccades in non-human primates. *Brain and Cognition*, *68*(3), 271–283. http://doi.org/10.1016/j.bandc.2008.08.017

Jones, K., & Harrison, Y. (2001). Frontal lobe function, sleep loss and fragmented sleep. *Sleep Medicine Reviews*, *5*(6), 463–475. http://doi.org/10.1053/smrv.2001.0203

Just, M. A., & Carpenter, P. A. (1980). A theory of reading: From eye fixations to comprehension. *Psychological Review*, *87*(4), 329–354. http://doi.org/10.1037/0033-295X.87.4.329

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., & Killgore, W. D. S. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Medicine*, *8*(3), 215–221. http://doi.org/10.1016/j.sleep.2006.08.007

Kales, A., Tan, T. L., Kollar, E. J., Naitoh, P., Preston, T. A., & Malmstrom, E. J. (1970). Sleep patterns following 205 hours of sleep deprivation. *Psychosomatic Medicine*, *32*, 189–200.

Kallimani, D., Theleritis, C., Evdokimidis, I., Stefanis, N. C., Chatzimanolis, I., & Smyrnis, N. (2009). The effect of change in clinical state on eye movement dysfunction in schizophrenia. *European Psychiatry*, *24*(1), 17–26. http://doi.org/10.1016/j.eurpsy.2008.08.003

Kang, S. S., Dionisio, D. P., & Sponheim, S. R. (2011). Abnormal mechanisms of antisaccade generation in schizophrenia patients and unaffected biological relatives of schizophrenia patients. *Psychophysiology*, *48*(3), 350–361. http://doi.org/10.1111/j.1469-8986.2010.01074.x

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. http://doi.org/10.1016/j.neuroimage.2016.07.012

Kathmann, N., Hochrein, A., Uwer, R., & Bondy, B. (2003). Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. *The American Journal of Psychiatry*, *160*(4), 696–702. http://doi.org/10.1176/appi.ajp.160.4.696

Kathmann, N., Wagner, M., Rendtorff, N., Schöchlin, C., & Engel, R. R. (1995). Information processing during eye tracking as revealed by event-related potentials in schizophrenics, alcoholics, and healthy controls. *Schizophrenia Research*, *16*(2), 145–156. http://doi.org/10.1016/0920-9964(94)00066-H

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. http://doi.org/10.1037/0021-843X.100.4.526

Katsanis, J., Iacono, W. G., & Beiser, M. (1996). Eye-tracking performance and adaptive functioning over the short-term course of first-episode psychosis. *Psychiatry Research*, *64*(1), 19–26. http://doi.org/10.1016/0165-1781(96)02889-2

Katsanis, J., Kortenkamp, S., Iacono, W. G., & Grove, W. M. (1997). Antisaccade performance in patients with schizophrenia and affective disorder. *Journal of Abnormal Psychology*, *106*(3), 468–472. http://doi.org/http://dx.doi.org/10.1037/0021-843X.106.3.468

Kattoulas, E., Evdokimidis, I., Stefanis, N. C., Avramopoulos, D., Stefanis, C. N., & Smyrnis, N. (2011). Predictive smooth eye pursuit in a population of young men: II. Effects of schizotypy, anxiety and depression. *Experimental Brain Research*, *215*(3–4), 219–226. http://doi.org/10.1007/s00221-011-2888-4

Kattoulas, E., Smyrnis, N., Stefanis, N. C., Avramopoulos, D., Stefanis, C. N., & Evdokimidis, I. (2011). Predictive smooth eye pursuit in a population of young men: I. Effects of age, IQ, oculomotor and cognitive tasks. *Experimental Brain Research*, *215*(3–4), 207–218. http://doi.org/10.1007/s00221-011-2887-5

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. http://doi.org/10.1016/j.pscychresns.2006.01.003

Keefe, R. S. E., Buchanan, R. W., Marder, S. R., Schooler, N. R., Dugar, A., Zivkov, M., & Stewart, M. (2013). Clinical trials of potential cognitive-enhancing drugs in schizophrenia: What have we learned so far? *Schizophrenia Bulletin*, *39*(2), 417–435. http://doi.org/10.1093/schbul/sbr153

Keefe, R. S. E., Haig, G. M., Marder, S. R., Harvey, P. D., Dunayevich, E., Medalia, A., … Stern, R. G. (2015). Report on ISCTM consensus meeting on clinical assessment of response to treatment of cognitive impairment in schizophrenia. *Schizophrenia Bulletin*, *42*(1), sbv111. http://doi.org/10.1093/schbul/sbv111

Kelley, M. P., & Bakan, P. (1999). Eye tracking in normals: SPEM asymmetries and association with schizotypy. *International Journal of Neuroscience*, *98*(1–2), 27–81. http://doi.org/10.3109/00207459908994793

Kelly, P., Rennie, C., Gordon, E., Anderson, J., Howson, A., & Meares, R. (1990). Smooth pursuit eye tracking dysfunction and negative symptoms in schizophrenia. *Psychiatry Research*, *34*(1), 89–97. http://doi.org/10.1016/0165-1781(90)90060-I

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. http://doi.org/10.1016/0165-1781(91)90114-5

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., & Balkin, T. J. (2008). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Medicine*, *9*(5), 517–526. http://doi.org/10.1016/j.sleep.2007.07.003

Killgore, W. D. S., Richards, J. M., Killgore, D. B., Kamimori, G. H., & Balkin, T. J. (2007). The trait of Introversion–Extraversion predicts vulnerability to sleep deprivation. *Journal of Sleep Research*, *16*(4), 354–363. http://doi.org/10.1111/j.1365-2869.2007.00611.x

Klein, C., & Ettinger, U. (2008). A hundred years of eye movement research in psychiatry. *Brain and Cognition*, *68*(3), 215–8. http://doi.org/10.1016/j.bandc.2008.08.012

Klein, C. H., Brügner, G., Foerster, F., Müller, W., & Schweickhardt, A. (2000). The gap effect in pro-saccades and anti-saccades in psychometric schizotypes. *Biological Psychology*, *55*(1), 25–39. http://doi.org/10.1016/S0301-0511(00)00062-4

Klein, C., Heinks, T., Andresen, B., Berg, P., & Moritz, S. (2000). Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biological Psychiatry*, *47*(11), 978–990. http://doi.org/10.1016/S0006-3223(00)00234-1

Koethe, D., Hoyer, C., & Leweke, F. M. (2009). The endocannabinoid system as a target for modelling psychosis. *Psychopharmacology*, *206*(4), 551–561. http://doi.org/10.1007/s00213-009-1591-7

Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews*, *3*, 711–715. http://doi.org/10.1038/nrd1470

Kollar, E. J., Pasnau, R. O., Rubin, R. T., Naitoh, P., Slater, G. G., & Kales, A. (1969). Psychological, psychophysiological, and biochemical correlates of prolonged sleep deprivation. *American Journal of Psychiatry*, *126*(4), 488–497. http://doi.org/10.1176/ajp.126.4.488

Koranyi, E. K., & Lehmann, H. E. (1960). Experimental sleep deprivation in schizophrenic patients. *Archives of General Psychiatry*, *2*(5), 534–544. http://doi.org/10.1001/archpsyc.1960.03590110058007

Koslowsky, M., & Babkoff, H. (1992). Meta-analysis of the relationship between total sleep deprivation and performance. *Chronobiology International*, *9*(2), 132–6. http://doi.org/10.3109/07420529209064524

Köster, L.-S., Carbon, M., & Correll, C. U. (2014). Emerging drugs for schizophrenia: an update. *Expert Opinion on Emerging Drugs*, *19*(4), 511–31. http://doi.org/10.1517/14728214.2014.958148

Kowler, E. (2011). Eye movements: The past 25years. *Vision Research*, *51*(13), 1457–1483. http://doi.org/10.1016/j.visres.2010.12.014

Koychev, I., Barkus, E., Ettinger, U., Killcross, S., Roiser, J. P., Wilkinson, L., & Deakin, B. (2011). Evaluation of state and trait biomarkers in healthy volunteers for the development of novel drug treatments in schizophrenia. *Journal of Psychopharmacology*, *25*(9), 1207–1225. http://doi.org/10.1177/0269881111414450

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), 1–8. http://doi.org/10.1038/tp.2016.64

Koychev, I., McMullen, K., Lees, J., Dadhiwala, R., Grayson, L., Perry, C., … Barkus, E. (2012). A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study. *European Neuropsychopharmacology*, *22*(7), 469–481. http://doi.org/10.1016/j.euroneuro.2011.10.005

Krause, A. J., Simon, E. Ben, Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., & Walker, M. P. (2017). The sleep-deprived human brain. *Nature Reviews Neuroscience*, *18*(7), 404–418. http://doi.org/10.1038/nrn.2017.55

Krishna, N., O'Neill, H., Sánchez-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. http://doi.org/10.1016/j.schres.2014.05.035

Kuswanto, C., Chin, R., Sum, M. Y., Sengupta, S., Fagiolini, A., McIntyre, R. S., … Sim, K. (2016). Shared and divergent neurocognitive impairments in adult patients with schizophrenia and bipolar disorder: Whither the evidence? *Neuroscience & Biobehavioral Reviews*, *61*, 66–89. http://doi.org/10.1016/j.neubiorev.2015.12.002

Kwapil, T. R., & Barrantes-Vidal, N. (2015). Schizotypy: Looking back and moving forward. *Schizophrenia Bulletin*, *41*(2), S366–S373. http://doi.org/10.1093/schbul/sbu186

Kwapil, T. R., Barrantes-Vidal, N., & Silvia, P. J. (2008). The dimensional structure of the wisconsin schizotypy scales: Factor identification and construct validity. *Schizophrenia Bulletin*, *34*(3), 444–457. http://doi.org/10.1093/schbul/sbm098

Kwapil, T. R., & Chun, C. A. (2015). The psychometric assessment of schizotypy. In O. J. Mason & G. Claridge (Eds.), *Schizotypy. New dimensions.* (pp. 7–32). London and New York: Routledge.

Lai, C.-Y., Scarr, E., Udawela, M., Everall, I., Chen, W. J., & Dean, B. (2016). Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics. *World Journal of Psychiatry*, *6*(1), 102. http://doi.org/10.5498/wjp.v6.i1.102

Larrison, A. L., Babin, S. L., Xing, Y., Patel, S. S., Wassef, A. A., & Sereno, A. B. (2011). Effects of adjunct valproic acid on clinical symptoms and saccadic eye movements in schizophrenia. *Human Psychopharmacology: Clinical and Experimental*, *26*(7), 517–525. http://doi.org/10.1002/hup.1236

Larrison, A. L., Ferrante, C. F., Briand, K. A., & Sereno, A. B. (2000). Schizotypal traits, attention and eye movements. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *24*(3), 357–372. http://doi.org/10.1016/S0278-5846(99)00104-9

Laux, L., Glanzmann, P., Schaffner, P., & Spielberger, C. D. (1981). *Das State-Trait-Angstinventar*. Weinheim: Beltz.

Lee, J., Manousakis, J., Fielding, J., & Anderson, C. (2015). Alcohol and sleep restriction combined reduces vigilant attention, whereas sleep restriction alone enhances distractibility. *Sleep*, *38*(5), 765–75. http://doi.org/10.5665/sleep.4672

Lee, K. H., Williams, L. M., Loughland, C. M., Davidson, D. J., & Gordon, E. (2001). Syndromes of schizophrenia and smooth-pursuit eye movement dysfunction. *Psychiatry Research*, *101*(1), 11–21. http://doi.org/10.1016/S0165-1781(00)00242-0

Lees Roitman, S. E., Keefe, R. S. E., Harvey, P. D., Siever, L. J., & Mohs, R. C. (1997). Attentional and eye tracking deficits correlate with negative symptoms in schizophrenia. *Schizophrenia Research*, *26*(2–3), 139–146. http://doi.org/10.1016/S0920-9964(97)00044-3

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

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), 30–8. http://doi.org/10.1016/j.pscychresns.2011.06.011

Lencer, R., Malchow, C. P., Krecker, K., Nolte, A., Pinnow, M., Zimmerman v. Siefart, S., … Arolt, V. (1999). Smooth pursuit performance in families with multiple occurrence of schizophrenia and nonpsychotic families. *Biological Psychiatry*, *45*(6), 694–703. http://doi.org/10.1016/S0006-3223(98)00310-2

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), 1256–9. http://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), 1430–6. http://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), 217–23. http://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), 1146–54. http://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. http://doi.org/10.1016/j.schres.2015.09.032

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

Lencer, R., Trillenberg, P., Trillenberg-Krecker, K., Junghanns, K., Kordon, A., Brooks, A., … Arolt, V. (2004). Smooth pursuit deficits in schizophrenia, affective disorder and obsessive-compulsive disorder. *Psychological Medicine*, *34*(3), 451–460. http://doi.org/10.1017/S0033291703001314

Lenzenweger, M. F. (2006). Schizotypy: An organizing framework for schizophrenia research. *Current Directions in Psychological Science*, *15*(4), 162–166. http://doi.org/10.1111/j.1467-8721.2006.00428.x

Lenzenweger, M. F. (2010). *Schizotypy and schizophrenia. The view from experimental psychophathology.* New York and London: The Guilford Press.

Lenzenweger, M. F. (2015). Thinking clearly about schizotypy: Hewing to the schizophrenia liability core, considering interesting tangents, and avoiding conceptual quicksand. *Schizophrenia Bulletin*, *41*(2), S483–S491. http://doi.org/10.1093/schbul/sbu184

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. http://doi.org/10.1037/0021-843X.115.4.779

Leonard, C. J., Robinson, B. M., Kaiser, S. T., Hahn, B., McClenon, C., Harvey, A. N., … Gold, J. M. (2013). Testing sensory and cognitive explanations of the antisaccade deficit in schizophrenia. *Journal of Abnormal Psychology*, *122*(4), 1111–1120. http://doi.org/10.1037/a0034956

Levy, D. L., Holzman, P. S., Matthysse, S., & Mendell, N. R. (1993). Eye tracking dysfunction and schizophrenia: A critical perspective. *Schizophrenia Bulletin*, *19*(3), 461–536. http://doi.org/10.1093/schbul/19.3.461

Levy, D. L., Holzman, P. S., Matthysse, S., & Mendell, N. R. (1994). Eye tracking and schizophrenia: A selective review. *Schizophrenia Bulletin*, *20*(1), 47–62. http://doi.org/10.1093/schbul/20.1.47

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. http://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. In *Current Topics in Behavioral Neurosciences* (Vol. 4, pp. 311–347). Berlin Heidelberg: Springer. http://doi.org/10.1007/7854_2010_60

Lewandowski, K. E., Cohen, B. M., & Ngur, D. (2011). Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychological Medicine*, *41*(March 2010), 225–41. http://doi.org/10.1017/S0033291710001042

Liddle, P. F. (1987). The symptoms of chronic schizophrenia. A re-examination of the positive- negative dichotomy. *The British Journal of Psychiatry*, *151*(2), 145–151. http://doi.org/10.1192/bjp.151.2.145

Light, G. A., Swerdlow, N. R., Rissling, A. J., Radant, A., Sugar, C. A., Sprock, J., … Braff, D. L. (2012). Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. *PLoS ONE*, *7*(7), e39434. http://doi.org/10.1371/journal.pone.0039434

Lim, J., & Dinges, D. F. (2008). Sleep deprivation and vigilant attention. *Annals of the New York Academy of Sciences*, *1129*, 305–322. http://doi.org/10.1196/annals.1417.002

Lim, J., & Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychological Bulletin*, *136*(3), 375–389. http://doi.org/10.1037/a0018883

Linscott, R. J. (2013). The taxonicity of schizotypy: Does the same taxonic class structure emerge from analyses of different attributes of schizotypy and from fundamentally different statistical methods? *Psychiatry Research*, *210*(2), 414–421. http://doi.org/10.1016/j.psychres.2013.07.029

Linscott, R. J., & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(2013), 1133–1149. http://doi.org/10.1017/S0033291712001626

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. http://doi.org/10.1146/annurev.ne.10.030187.000525

Lisberger, S. G., & Westbrook, L. E. (1985). Properties of visual inputs that initiate horizontal smooth pursuit eye movements in monkeys. *The Journal of Neuroscience*, *5*(6), 1662–1673.

Litman, R. E., Hommer, D. W., Clem, T., Ornsteen, M. L., Ollo, C., & Pickar, D. (1991). Correlation of Wisconsin Card Sorting Test performance with eye tracking in schizophrenia. *American Journal of Psychiatry*, *148*(11), 1580–1582. http://doi.org/10.1176/ajp.148.11.1580

Litman, R. E., Hommer, D. W., Radant, A., Clem, T., & Pickar, D. (1994). Quantitative effects of typical and atypical neuroleptics on smooth pursuit eye tracking in schizophrenia. *Schizophrenia Research*, *12*(2), 107–20. http://doi.org/10.1016/0920-9964(94)90068-X

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *357*(1424), 1003–1037. http://doi.org/10.1098/rstb.2002.1114

Logothetis, N. K. (2007). The ins and outs of fMRI signals. *Nature Neuroscience*, *10*(10), 1230–1232. http://doi.org/10.1038/nn1007-1230

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

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–7. http://doi.org/10.1038/35084005

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annual Review of Physiology*, *66*(1), 735–769. http://doi.org/10.1146/annurev.physiol.66.082602.092845

Louchart-De La Chapelle, S., Nkam, I., Houy, E., Belmont, A., Ménard, J.-F., Roussignol, A. C., … Thibaut, F. (2005). A concordance study of three electrophysiological measures in schizophrenia. *American Journal of Psychiatry*, *162*(3), 466–474. http://doi.org/10.1176/appi.ajp.162.3.466

Luby, E. D., Grisell, J. L., Frohman, C. E., Lees, H., Cohen, B. D., & Gottlieb, J. S. (1962). Biochemical, psychological, and behavioral responses to sleep deprivation. *Annals of the New York Academy of Sciences*, *96*, 71–79. http://doi.org/10.1111/j.1749-6632.1962.tb50102.x

Malaspina, D., Coleman, E., Goetz, R. R., Harkavy-Friedman, J., Corcoran, C., Amador, X., … Gorman, J. M. (2002). Odor identification, eye tracking and deficit syndrome schizophrenia. *Biological Psychiatry*, *51*(10), 809–815. http://doi.org/10.1016/S0006-3223(01)01319-1

Mancuso, S. G., Morgan, V. A., Mitchell, P. B., Berk, M., Young, A., & Castle, D. J. (2015). A comparison of schizophrenia, schizoaffective disorder, and bipolar disorder: Results from the Second Australian national psychosis survey. *Journal of Affective Disorders*, *172*, 30–37. http://doi.org/10.1016/j.jad.2014.09.035

Manly, T., Lewis, G. H., Robertson, I. H., Watson, P. C., & Datta, A. K. (2002). Coffee in the cornflakes: Time-of-day as a modulator of executive response control. *Neuropsychologia*, *40*(1), 1–6. http://doi.org/10.1016/S0028-3932(01)00086-0

Manoach, D. S., Lee, A. K. C., Hämäläinen, M. S., Dyckman, K. A., Friedman, J. S., Vangel, M., … Barton, J. J. S. (2013). Anomalous use of context during task preparation in schizophrenia: A magnetoencephalography study. *Biological Psychiatry*, *73*(10), 967–975. http://doi.org/10.1016/j.biopsych.2012.12.018

Mao, P., Cui, D., Zhao, X. D., & Ma, Y. Y. (2015). Prefrontal dysfunction and a monkey model of schizophrenia. *Neuroscience Bulletin*, *31*(2), 235–241. http://doi.org/10.1007/s12264-014-1506-4

Marsden, C. A., King, M. V., & Fone, K. C. F. (2011). Influence of social isolation in the rat on serotonergic function and memory - Relevance to models of schizophrenia and the role of 5-HT6 receptors. *Neuropharmacology*, *61*(3), 400–407. http://doi.org/10.1016/j.neuropharm.2011.03.003

Martin, L. F., Hall, M.-H., Ross, R. G., Zerbe, G., Freedman, R., & Olincy, A. (2007). Physiology of schizophrenia, bipolar disorder, and schizoaffective disorder. *The American Journal of Psychiatry*, *164*(12), 1900–6. http://doi.org/10.1176/appi.ajp.2007.06010017

Maruff, P., Danckert, J., Pantelis, C., & Currie, J. (1998). Saccadic and attentional abnormalities in patients with schizophrenia. *Psychological Medicine*, *28*(5), 1091–1100. http://doi.org/10.1017/S0033291798007132

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), 203–11. http://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. http://doi.org/10.1016/0191-8869(94)00132-C

Mason, O. J. (2014). The duality of schizotypy: Is it both dimensional and categorical? *Frontiers in Psychiatry*, *5*(September), 134. http://doi.org/10.3389/fpsyt.2014.00134

Mason, O. J. (2015). The assessment of schizotypy and its clinical relevance. *Schizophrenia Bulletin*, *41*, 374–385. http://doi.org/10.1093/schbul/sbu194

Mason, O. J., Morgan, C. J. M., Stefanovic, A., & Curran, H. V. (2008). The Psychotomimetic States Inventory (PSI): Measuring psychotic-type experiences from ketamine and cannabis. *Schizophrenia Research*, *103*(1–3), 138–142. http://doi.org/10.1016/j.schres.2008.02.020

Mason, O., Linney, Y., & Claridge, G. (2005). Short scales for measuring schizotypy. *Schizophrenia Research*, *78*(2–3), 293–6. http://doi.org/10.1016/j.schres.2005.06.020

Massen, C. (2004). Parallel programming of exogenous and endogenous components in the antisaccade task. *The Quarterly Journal of Experimental Psychology Section A*, *57*(3), 475–498. http://doi.org/10.1080/02724980343000341

Mather, J. A., Neufeld, R. W., Merskey, H., & Russell, N. C. (1992). Disruption of saccade production during oculomotor tracking in schizophrenia and the use of its changes across target velocity as a discriminator of the disorder. *Psychiatry Research*, *43*(1), 93–109. http://doi.org/10.1016/0165-1781(92)90145-S

Mazhari, S., Price, G., Dragović, M., Waters, F. A., Clissa, P., & Jablensky, A. (2011). Revisiting the suitability of antisaccade performance as an endophenotype in schizophrenia. *Brain and Cognition*, *77*(2), 223–230. http://doi.org/10.1016/j.bandc.2011.08.006

McClelland, L. E., Pilcher, J. J., & Moore, D. D. (2010). Oculomotor measures as predictors of performance during sleep deprivation. *Aviation, Space, and Environmental Medicine*, *81*(9), 833–842. http://doi.org/10.3357/ASEM.2653.2010

McDowell, J. E., Brown, G. G., Paulus, M., Martinez, A., Stewart, S. E., Dubowitz, D. J., & Braff, D. L. (2002). Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biological Psychiatry*, *51*(3), 216–223. http://doi.org/10.1016/S0006-3223(01)01204-5

McDowell, J. E., & Clementz, B. A. (1997). The effect of fixation condition manipulations on antisaccade performance in schizophrenia: Studies of diagnostic specificity. *Experimental Brain Research*, *115*(2), 333–344. http://doi.org/10.1007/PL00005702

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. http://doi.org/10.1016/j.bandc.2008.08.016

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist*, *17*(12), 827–838. http://doi.org/10.1037/h0041029

Meehl, P. E. (1989). Schizotaxia revisited. *Archives of General Psychiatry*, *46*(10), 935. http://doi.org/10.1001/archpsyc.1989.01810100077015

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

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

Meyhöfer, I., Kumari, V., Hill, A., Petrovsky, N., & Ettinger, U. (2017). Sleep deprivation as an experimental model system for psychosis: Effects on smooth pursuit, prosaccades, and antisaccades. *Journal of Psychopharmacology*, *31*(4), 418–433. http://doi.org/10.1177/0269881116675511

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*, 1–15. http://doi.org/10.1111/psyp.12917

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

Millard, S. P., Shofer, J., Braff, D., Calkins, M., Cadenhead, K., Freedman, R., … Tsuang, D. W. (2016). Prioritizing schizophrenia endophenotypes for future genetic studies: An example using data from the COGS-1 family study. *Schizophrenia Research*, *174*(1–3), 1–9. http://doi.org/10.1016/j.schres.2016.04.011

Missal, M., & Heinen, S. J. (2004). Supplementary eye fields stimulation facilitates anticipatory pursuit. *Journal of Neurophysiology*, *92*(2), 1257–62. http://doi.org/10.1152/jn.01255.2003

Mitchell, J. P., Macrae, C. N., & Gilchrist, I. D. (2002). Working memory and the suppression of reflexive saccades. *Journal of Cognitive Neuroscience*, *14*(1), 95–103. http://doi.org/10.1162/089892902317205357

Monti, J. M., & Monti, D. (2004). Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Medicine Reviews*, *8*(2), 133–148. http://doi.org/10.1016/S1087-0792(02)00158-2

Morgan, V. A., Waterreus, A., Carr, V., Castle, D., Cohen, M., Harvey, C., … Jablensky, A. (2017). Responding to challenges for people with psychotic illness: Updated evidence from the Survey of High Impact Psychosis. *Australian & New Zealand Journal of Psychiatry*, *51*(2), 124–140. http://doi.org/10.1177/0004867416679738

Morita, K., Miura, K., Fujimoto, M., Yamamori, H., Yasuda, Y., Iwase, M., … Hashimoto, R. (2017). Eye movement as a biomarker of schizophrenia: Using an integrated eye movement score. *Psychiatry and Clinical Neurosciences*, *71*(2), 104–114. http://doi.org/10.1111/pcn.12460

Mukherjee, T., Battifarano, M., Simoncini, C., & Osborne, L. C. (2015). Shared sensory estimates for human motion perception and pursuit eye movements. *Journal of Neuroscience*, *35*(22), 8515–8530. http://doi.org/10.1523/JNEUROSCI.4320-14.2015

Müller, N., Riedel, M., Eggert, T., & Straube, A. (1999). Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part II. Saccadic latency, gain, and fixation suppression errors. *European Archives of Psychiatry and Clinical Neuroscience*, *249*(1), 7–14. http://doi.org/10.1007/s004060050059

Munoz, D. P., & Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nature Reviews*, *5*(3), 218–228. http://doi.org/10.1038/nrn1345

Müri, R. M., & Nyffeler, T. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain and Cognition*, *68*(3), 284–292. http://doi.org/10.1016/j.bandc.2008.08.018

Murray, R. M., Sham, P., Van Os, J., Zanelli, J., Cannon, M., & McDonald, C. (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research*, *71*(2–3), 405–416. http://doi.org/10.1016/j.schres.2004.03.002

Myles, J. B., Rossell, S. L., Phillipou, A., Thomas, E., & Gurvich, C. (2017). Insights to the schizophrenia continuum: A systematic review of saccadic eye movements in schizotypy and biological relatives of schizophrenia patients. *Neuroscience and Biobehavioral Reviews*, *72*, 278–300. http://doi.org/10.1016/j.neubiorev.2016.10.034

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), 483–92. http://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), 300–9. http://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), 1–8. http://doi.org/10.1371/journal.pone.0038494

Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Kömpf, 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), 1319–25. http://doi.org/10.1016/j.neuroimage.2005.08.050

Nakashima, Y., Momose, T., Sano, I., Katayama, S., Nakajima, T., Niwa, S. I., & Matsushita, M. (1994). Cortical control of saccade in normal and schizophrenic subjects: a PET study using a task-evoked rCBF paradigm. *Schizophrenia Research*, *12*(3), 259–264. http://doi.org/10.1016/0920-9964(94)90036-1

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 and Biobehavioral Reviews*, *37*(3), 317–327. http://doi.org/10.1016/j.neubiorev.2013.01.004

Nielsen, R. E., Levander, S., Kjaersdam Telléus, G., Jensen, S. O. W., Østergaard Christensen, T., & Leucht, S. (2015). Second-generation antipsychotic effect on cognition in patients with schizophrenia--a meta-analysis of randomized clinical trials. *Acta Psychiatrica Scandinavica*, *131*(3), 185–96. http://doi.org/10.1111/acps.12374

Nieman, D. H., Bour, L. J., Linszen, D. H., Goede, J., Koelman, J. H. T. M., Gersons, B. P. R., & De Visser, B. W. O. (2000). Neuropsychological and clinical correlates of antisaccade task performance in schizophrenia. *Neurology*, *54*(4), 866–871. http://doi.org/10.1212/WNL.54.4.866

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, & Behavioral Neuroscience*, *12*(2), 241–268. http://doi.org/10.3758/s13415-011-0083-5

Nieuwenhuis, S., Broerse, A., Nielen, M. M. A., & Jong, R. De. (2004). A goal activation approach to the study of executive function: An application to antisaccade tasks. *Brain and Cognition*, *56*(2 SPEC. ISS.), 198–214. http://doi.org/10.1016/j.bandc.2003.12.002

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), 992–7. http://doi.org/10.1016/j.biopsych.2009.11.029

Nkam, I., Thibaut, F., Denise, P., Van Der Elst, A., Ségard, L., Brazo, P., … Petit, M. (2001). Saccadic and smooth-pursuit eye movements in deficit and non-deficit schizophrenia. *Schizophrenia Research*, *48*, 145–153. http://doi.org/10.1016/S0920-9964(99)00165-6

Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., … Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *American Journal of Psychiatry*, *165*(2), 203–213. http://doi.org/10.1176/appi.ajp.2007.07010042

Nuechterlein, K. H., Subotnik, K. L., Green, M. F., Ventura, J., Asarnow, R. F., Gitlin, M. J., … Mintz, J. (2011). Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia Bulletin*, *37*(SUPPL. 2), 33–40. http://doi.org/10.1093/schbul/sbr084

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. http://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), 837–43. http://doi.org/10.1001/archpsyc.55.9.837

Ogawa, S. (2012). Finding the BOLD effect in brain images. *NeuroImage*, *62*(2), 608–609. http://doi.org/10.1016/j.neuroimage.2012.01.091

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*, *87*(24), 9868–9872. http://doi.org/10.1073/pnas.87.24.9868

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., & Jönsson, B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*(1), 155–162. http://doi.org/10.1111/j.1468-1331.2011.03590.x

Olincy, A., Johnson, L. 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. http://doi.org/10.1016/S0165-1781(03)00022-2

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. http://doi.org/10.1113/jphysiol.2007.139881

Palmer, B. W., Dawes, S. E., & Heaton, R. K. (2009). What do we know about neuropsychological aspects of schizophrenia? *Neuropsychology Review*, *19*(3), 365–84. http://doi.org/10.1007/s11065-009-9109-y

Patrick, G. T. W., & Gilbert, J. A. (1896). Studies from the psychological laboratory of the University of Iowa: On the effects of loss of sleep. *Psychological Review*, *3*(5), 496–483.

Pauling, L., & Coryell, C. D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences*, *22*(4), 210–216. http://doi.org/10.1073/pnas.22.4.210

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. http://doi.org/10.1001/archpsyc.64.1.19

Petrovsky, N., Ettinger, U., Hill, A., Frenzel, L., Meyhöfer, I., Wagner, M., … Kumari, V. (2014). Sleep deprivation disrupts prepulse inhibition and induces psychosis-like symptoms in healthy humans. *The Journal of Neuroscience*, *34*(27), 9134–9140. http://doi.org/10.1523/JNEUROSCI.0904-14.2014

Philip, P., Taillard, J., Sagaspe, P., Valtat, C., Sanchez-Ortuno, M., Moore, N., … Bioulac, B. (2004). Age, performance and sleep deprivation. *Journal of Sleep Research*, *13*(2), 105–110. http://doi.org/10.1111/j.1365-2869.2004.00399.x

Phillips, B. A. (2005). Sleep loss and performance in residents and nonphysicians: A metaanalytic examination. *Sleep*, *28*(11), 1392–1402. http://doi.org/10.1093/sleep/28.11.1392

Pilcher, J. J., Band, D., Odle-Dusseau, H. N., & Muth, E. R. (2007). Human performance under sustained operations and 'acute sleep deprivation conditions: Toward a model of controlled attention. *Aviation Space and Environmental Medicine*, *78*(5 II), 15–24.

Pilcher, J. J., & Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep*, *19*(4), 318–26. http://doi.org/10.1093/sleep/19.4.318

Poletti, B., Carelli, L., Solca, F., Lafronza, A., Pedroli, E., Faini, A., … Silani, V. (2017). An eye-tracker controlled cognitive battery: overcoming verbal-motor limitations in ALS. *Journal of Neurology*, *264*(6), 1136–1145. http://doi.org/10.1007/s00415-017-8506-z

Polli, F. E., Barton, J. J. S., Thakkar, K. N., Greve, D. N., Goff, D. C., Rauch, S. L., & Manoach, D. S. (2008). Reduced error-related activation in two anterior cingulate circuits is related to impaired performance in schizophrenia. *Brain*, *131*(4), 971–986. http://doi.org/10.1093/brain/awm307

Porcu, S., Ferrara, M., Urbani, L., Bellatreccia, A., & Casagrande, M. (1998). Smooth pursuit and saccadic eye movements as possible indicators of nighttime sleepiness. *Physiology & Behavior*, *65*(3), 437–443. http://doi.org/10.1016/S0031-9384(98)00181-4

Pratt, J., Winchester, C., Dawson, N., & Morris, B. (2012). Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap. *Nature Reviews. Drug Discovery*, *11*(7), 560–79. http://doi.org/10.1038/nrd3649

Price, G. W., Michie, P. T., Johnston, J., Innes-Brown, H., Kent, A., Clissa, P., & Jablensky, A. V. (2006). A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian Family Study of Schizophrenia. *Biological Psychiatry*, *60*(1), 1–10. http://doi.org/10.1016/j.biopsych.2005.09.010

Pynn, L. K., & DeSouza, J. F. X. (2013). The function of efference copy signals: Implications for symptoms of schizophrenia. *Vision Research*, *76*, 124–133. http://doi.org/10.1016/j.visres.2012.10.019

Quigley, N., Green, J. F., Morgan, D., Idzikowski, C., & King, D. J. (2000). The effect of sleep deprivation on memory and psychomotor function in healthy volunteers. *Hum Psychopharmacol*, *15*(3), 171–177. http://doi.org/10.1002/(SICI)1099-1077(200004)15:3<171::AID-HUP155>3.0.CO;2-D

Rabinowitz, J., Levine, S. Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C. G., & Kapur, S. (2012). Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. *Schizophrenia Research*, *137*(1–3), 147–150. http://doi.org/10.1016/j.schres.2012.01.015

Radant, A. D., Dobie, D. J., Calkins, M. E., Olincy, A., Braff, D. L., Cadenhead, K. S., … Tsuang, D. W. (2010). Antisaccade performance in schizophrenia patients, their first-degree biological relatives, and community comparison subjects: data from the COGS study. *Psychophysiology*, *47*(5), 846–56. http://doi.org/10.1111/j.1469-8986.2010.01004.x

Radant, A. D., & Hommer, D. W. (1992). A quantitative analysis of saccades and smooth pursuit during visual pursuit tracking. A comparison of schizophrenics with normals and substance abusing controls. *Schizophrenia Research*, *6*(3), 225–235. http://doi.org/10.1016/0920-9964(92)90005-P

Radant, A. D., Millard, S. P., Braff, D. L., Calkins, M. E., Dobie, D. J., Freedman, R., … Tsuang, D. W. (2015). Robust differences in antisaccade performance exist between COGS schizophrenia cases and controls regardless of recruitment strategies. *Schizophrenia Research*, *163*(1–3), 47–52. http://doi.org/10.1016/j.schres.2014.12.016

Rado, S. (1953). Dynamics and classification of disordered behavior. *American Journal of Psychiatry*, *110*, 406–416.

Raemaekers, M., Jansma, J. M., Cahn, W., Van der Geest, J. N., Van der Linden, J. A., Kahn, R. S., & Ramsey, N. F. (2002). Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Archives of General Psychiatry*, *59*(4), 313–320. http://doi.org/10.1001/archpsyc.59.4.313

Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin*, *17*(4), 555–64. http://doi.org/10.1093/schbul/17.4.555

Raine, A., & Benishay, D. (1995). The SPQ-B: A Brief Screening Instrument for Schizotypal Personality Disorder. *Journal of Personality Disorders*, *9*(4), 346–355. http://doi.org/10.1521/pedi.1995.9.4.346

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. http://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. http://doi.org/10.1113/jphysiol.1961.sp006811

Ratcliff, R., & Van Dongen, H. P. A. (2009). Sleep deprivation affects multiple distinct cognitive processes. *Psychonomic Bulletin & Review*, *16*(4), 742–751. http://doi.org/10.3758/PBR.16.4.742

Rawlings, D., Williams, B., Haslam, N., & Claridge, G. (2008a). Is schizotypy taxonic? Response to. *Personality and Individual Differences*, *44*(8), 1663–1672. http://doi.org/10.1016/j.paid.2008.01.021

Rawlings, D., Williams, B., Haslam, N., & Claridge, G. (2008b). Taxometric analysis supports a dimensional latent structure for schizotypy. *Personality and Individual Differences*, *44*(8), 1640–1651. http://doi.org/10.1016/j.paid.2007.06.005

Reeve, S., Emsley, R., Sheaves, B., & Freeman, D. (2017). Disrupting Sleep: The Effects of Sleep Loss on Psychotic Experiences Tested in an Experimental Study With Mediation Analysis. *Schizophrenia Bulletin*, *42*, 96–115. http://doi.org/10.1093/schbul/sbx103

Reichenberg, A., & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological Bulletin*, *133*(5), 833–858. http://doi.org/10.1037/0033-2909.134.3.382

Reichenberg, A., Harvey, P. D., Bowie, C. R., Mojtabai, R., Rabinowitz, J., Heaton, R. K., & Bromet, E. (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia Bulletin*, *35*(5), 1022–1029. http://doi.org/10.1093/schbul/sbn044

Reilly, J. L., Frankovich, K., Hill, S., Gershon, E. S., Keefe, R. S. E., Keshavan, M. S., … Sweeney, J. A. (2014). Elevated antisaccade error rate as an intermediate phenotype for psychosis across diagnostic categories. *Schizophrenia Bulletin*, *40*(5), 1011–21. http://doi.org/10.1093/schbul/sbt132

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

Reilly, J. L., & Sweeney, J. A. (2014). Generalized and specific neurocognitive deficits in psychotic disorders: Utility for evaluating pharmacological treatment effects and as intermediate phenotypes for gene discovery. *Schizophrenia Bulletin*, *40*(3), 516–522. http://doi.org/10.1093/schbul/sbu013

Remington, G., Foussias, G., Fervaha, G., Agid, O., Takeuchi, H., Lee, J., & Hahn, M. (2016). Treating negative symptoms in schizophrenia: an update. *Current Treatment Options in Psychiatry*, *3*(2), 133–150. http://doi.org/10.1007/s40501-016-0075-8

Reuter, B., Herzog, E., Endrass, T., & Kathmann, N. (2006). Brain potentials indicate poor preparation for action in schizophrenia. *Psychophysiology*, *43*(6), 604–611. http://doi.org/10.1111/j.1469-8986.2006.00454.x

Reuter, B., & Kathmann, N. (2004). Using saccade tasks as a tool to analyze executive dysfunctions in schizophrenia. *Acta Psychologica*, *115*(2–3), 255–269. http://doi.org/10.1016/j.actpsy.2003.12.009

Reuter, B., & Kathmann, N. (2007). Störungen der Handlungskontrolle im Kontext neuropsychologischer Befunde bei Schizophrenie. *Fortschritte Der Neurologie · Psychiatrie*, *75*(10), 607–616. http://doi.org/10.1055/s-2007-959203

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), 603–18. http://doi.org/10.1093/oxfordjournals.schbul.a033481

Rinaldi, R., & Lefebvre, L. (2016). Goal-directed behaviors in patients with schizophrenia: Concept relevance and updated model. *Psychiatry and Clinical Neurosciences*, *70*(9), 394–404. http://doi.org/10.1111/pcn.12401

Robinson, D. A. (1965). The mechanics of human smooth pursuit eye movement. *The Journal of Physiology*, *180*(3), 569–591. http://doi.org/10.1113/jphysiol.1965.sp007718

Robinson, D. A., Gordon, J. L., & Gordon, S. E. (1986). A model of the smooth pursuit eye movement system. *Biological Cybernetics*, *55*(1), 43–57. http://doi.org/10.1007/BF00363977

Rodrigues-Amorim, D., Rivera-Baltanás, T., López, M., Spuch, C., Olivares, J. M., & Agís-Balboa, R. C. (2017). Schizophrenia: A review of potential biomarkers. *Journal of Psychiatric Research*, *93*, 37–49. http://doi.org/10.1016/j.jpsychires.2017.05.009

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), 107–15. http://doi.org/10.1093/cercor/12.2.107

Rösler, L., Rolfs, M., Van der Stigchel, S., Neggers, S. F. W., Cahn, W., Kahn, R. S., & Thakkar, K. N. (2015). Failure to use corollary discharge to remap visual target locations is associated with psychotic symptom severity in schizophrenia. *Journal of Neurophysiology*, *114*(2), 1129–1136. http://doi.org/10.1152/jn.00155.2015

Ross, D. E., Thaker, G. K., Buchanan, R. W., Kirkpatrick, B., Lahti, A. C., Medoff, D., … Tien, A. (1997). Eye tracking disorder in schizophrenia is characterized by specific ocular motor defects and is associated with the deficit syndrome. *Biological Psychiatry*, *42*(9), 781–96. http://doi.org/10.1016/S0006-3223(96)00492-1

Ross, D. E., Thaker, G. K., Buchanan, R. W., Lahti, A. C., Medoff, D., Bartko, J. J., … Hartley, J. (1996). Association of abnormal smooth pursuit eye movements with the deficit syndrome in schizophrenic patients. *American Journal of Psychiatry*, *153*(9), 1158–1165. http://doi.org/10.1176/ajp.153.9.1158

Ross, D. E., Thaker, G. K., Holcomb, H. H., Cascella, N. G., Medoff, D. R., & Tamminga, C. A. (1995). Abnormal smooth pursuit eye movements in schizophrenic patients are associated with cerebral glucose metabolism in oculomotor regions. *Psychiatry Research*, *58*(1), 53–67. http://doi.org/10.1016/0165-1781(95)02724-B

Ross, J. J. (1965). Neurological findings after prolonged sleep deprivation. *Archives of Neurology*, *12*(4), 399–403. http://doi.org/10.1001/archneur.1965.00460280069006

Ross, R. G., Olincy, A., Harris, J. G., Radant, A., Adler, L. E., Compagnon, N., & Freedman, R. (1999). The effects of age on a smooth pursuit tracking task in adults with schizophrenia and normal subjects. *Biological Psychiatry*, *46*(3), 383–91. http://doi.org/10.1016/S0006-3223(98)00369-2

Ross, R. G., Olincy, A., Harris, J. G., Radant, A., Adler, L. E., & Freedman, R. (1998). Anticipatory saccades during smooth pursuit eye movements and familial transmission of schizophrenia. *Biological Psychiatry*, *44*(8), 690–697. http://doi.org/10.1016/S0006-3223(98)00052-3

Ross, R. G., Olincy, A., Harris, J. G., Sullivan, B., & Radant, A. (2000). Smooth pursuit eye movements in schizophrenia and attentional dysfunction: Adults with schizophrenia, ADHD, and a normal comparison group. *Biological Psychiatry*, *48*(3), 197–203. http://doi.org/10.1016/S0006-3223(00)00825-8

Ross, R. G., Olincy, A., Mikulich, S. K., Radant, A. D., Harris, J. G., Waldo, M., … Freedman, R. (2002). Admixture analysis of smooth pursuit eye movements in probands with schizophrenia and their relatives suggests gain and leading saccades are potential endophenotypes. *Psychophysiology*, *39*(6), 809–819. http://doi.org/10.1111/1469-8986.3960809

Ross, R. G., Olincy, A., & Radant, A. (1999). Amplitude criteria and anticipatory saccades during smooth pursuit eye movements in schizophrenia. *Psychophysiology*, *36*(4), 464–468. http://doi.org/10.1111/1469-8986.3640464

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), 325–33. http://doi.org/10.1017/S0048577201991784

Rossi, A., & Daneluzzo, E. (2002). Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. *Schizophrenia Research*, *54*(1–2), 67–75. http://doi.org/10.1016/S0920-9964(01)00353-X

Rössler, W., Ajdacic-Gross, V., Müller, M., Rodgers, S., Haker, H., & Hengartner, M. P. (2015). Assessing sub-clinical psychosis phenotypes in the general population — A multidimensional approach. *Schizophrenia Research*, *161*(2–3), 194–201. http://doi.org/10.1016/j.schres.2014.11.033

Rothschild, A. J. (2013). Challenges in the treatment of major depressive disorder with psychotic features. *Schizophrenia Bulletin*, *39*(4), 787–796. http://doi.org/10.1093/schbul/sbt046

Rowland, L. M., Thomas, M. L., Thorne, D. R., Sing, H. C., Krichmar, J. L., Davis, H. Q., … Belenky, G. (2005). Oculomotor responses during partial and total sleep deprivation. *Aviation, Space, and Environmental Medicine*, *76*(7), 104–113.

Rund, B. R., Barder, H. E., Evensen, J., Haahr, U., Hegelstad, W. T. V., Joa, I., … Friis, S. (2016). Neurocognition and duration of psychosis: A 10-year follow-up of first-episode patients. *Schizophrenia Bulletin*, *42*(1), 87–95. http://doi.org/10.1093/schbul/sbv083

Rupp, T. L., Killgore, W. D. S., & Balkin, T. J. (2010). Socializing by day may affect performance by night: Vulnerability to sleep deprivation is differentially mediated by social exposure in extraverts vs introverts. *Sleep*, *33*(11), 1475–1485. http://doi.org/10.1093/sleep/33.5.1475

Russo, M., Thomas, M., Thorne, D., Sing, H., Redmond, D., Rowland, L., … Balkin, T. (2003). Oculomotor impairment during chronic partial sleep deprivation. *Clinical Neurophysiology*, *114*(4), 723–736. http://doi.org/10.1016/S1388-2457(03)00008-7

Rybakowski, J. K., & Borkowska, A. (2002). Eye movement and neuropsychological studies in first-degree relatives of schizophrenic patients. *Schizophrenia Research*, *54*(1–2), 105–110. http://doi.org/10.1016/S0920-9964(01)00357-7

Safer, D. J. (1970a). The concomitant effects of mild sleep loss and an anticholinergic drug. *Psychopharmacologia*, *17*(5), 425–433. http://doi.org/10.1007/BF00403813

Safer, D. J. (1970b). The effect of LSD on sleep-deprived men. *Psychopharmacologia*, *17*(5), 414–424. http://doi.org/10.1007/BF00403812

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42–50. http://doi.org/10.1016/j.schres.2013.07.009

Schermelleh-Engel, K., Keith, N., Moosbrugger, H., & Hodapp, V. (2004). Decomposing person and occasion-specific effects: An extension of latent state-trait (LST) theory to hierarchical LST models. *Psychological Methods*, *9*(2), 198–219. http://doi.org/10.1037/1082-989X.9.2.198

Schlenker, R., & Cohen, R. (1995). Smooth-pursuit eye-movement dysfunction and motor control in schizophrenia: a follow-up study. *European Archives of Psychiatry and Clinical Neuroscience*, *245*(2), 125–6.

Schlenker, R., Cohen, R., Berg, P., Hubman, W., Mohr, F., Watzl, H., & Werther, P. (1994). Smooth-pursuit eye movement dysfunction in schizophrenia: the role of attention and general psychomotor dysfunctions. *European Archives of Psychiatry and Clinical Neuroscience*, *244*(3), 153–60.

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), 331–45. http://doi.org/10.1007/s00213-013-2973-4

Schmid, A., Rees, G., Frith, C., & Barnes, G. (2001). An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport*, *12*(7), 1409–14.

Schmitt, A., Martins-de-Souza, D., Akbarian, S., Cassoli, J. S., Ehrenreich, H., Fischer, A., … Falkai, P. (2016). Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia, part III: Molecular mechanisms. *The World Journal of Biological Psychiatry*, 1–27. http://doi.org/10.1080/15622975.2016.1224929

Schmitt, A., Rujescu, D., Gawlik, M., Hasan, A., Hashimoto, K., Iceta, S., … Falkai, P. (2016). Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part II: Cognition, neuroimaging and genetics. *The World Journal of Biological Psychiatry*, *17*(6), 406–428. http://doi.org/10.1080/15622975.2016.1183043

Schneider, W. X. (1995). VAM: A neuro-cognitive model for visual attention control of segmentation, object recognition, and space-based motor action. *Visual Cognition*, *2*(2–3), 331–376. http://doi.org/10.1080/13506289508401737

Schulze, K., MacCabe, J. H., Rabe-Hesketh, S., Crawford, T., Marshall, N., Zanelli, J., … McDonald, C. (2006). The relationship between eye movement and brain structural abnormalities in patients with schizophrenia and their unaffected relatives. *Journal of Psychiatric Research*, *40*(7), 589–598. http://doi.org/10.1016/j.jpsychires.2005.05.003

Scott, J. P. R., McNaughton, L. R., & Polman, R. C. J. (2006). Effects of sleep deprivation and exercise on cognitive, motor performance and mood. *Physiology & Behavior*, *87*(2), 396–408. http://doi.org/10.1016/j.physbeh.2005.11.009

Seidman, L. J., Shapiro, D. I., Stone, W. S., Woodberry, K. A., Ronzio, A., Cornblatt, B. A., … Woods, S. W. (2016). Association of neurocognition with transition to psychosis. *JAMA Psychiatry*, *73*(12), 1239. http://doi.org/10.1001/jamapsychiatry.2016.2479

Shallo-Hoffmann, J., Perersen, J., & Muhlendyck, H. (1989). How Normal ore " Normal " Square Wave Jerks ? *Investigative Ophthalmology & Visual Science*, *30*(5), 5–7.

Sharpe, J. a. (2008). Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. *Brain and Cognition*, *68*(3), 241–54. http://doi.org/10.1016/j.bandc.2008.08.015

Siddi, S., Petretto, D. R., & Preti, A. (2017). Neuropsychological correlates of schizotypy: a systematic review and meta-analysis of cross-sectional studies. *Cognitive Neuropsychiatry*, *22*(3), 186–212. http://doi.org/10.1080/13546805.2017.1299702

Siever, L. J. (1982). Smooth Pursuit Eye Tracking Impairment. Relation to other "markers" of schizophrenia and psychologic correlates. *Archives of General Psychiatry*, *39*(9), 1001. http://doi.org/10.1001/archpsyc.1982.04290090011003

Siever, L. J., Coursey, R. D., Alterman, I. S., Zahn, T., Brody, L., Bernad, P., … Murphy, D. L. (1989). Clinical, psychophysiological, and neurological characteristics of volunteers with impaired smooth pursuit eye movements. *Biological Psychiatry*, *26*(1), 35–51. http://doi.org/10.1016/0006-3223(89)90006-1

Simons, R. F., & Katkin, W. (1985). Smooth pursuit eye movements in subjects reporting physical anhedonia and perceptual aberrations. *Psychiatry Research*, *14*(4), 275–89. http://doi.org/10.1016/0165-1781(85)90096-4

Smulders, F. T., Kenemans, J. L., Jonkman, L. M., & Kok, A. (1997). The effects of sleep loss on task performance and the electroencephalogram in young and elderly subjects. *Biol Psychol*, *45*(1–3), 217–239. http://doi.org/10.1016/S0301-0511(96)05229-5

Smyrnis, N. (2008). Metric issues in the study of eye movements in psychiatry. *Brain and Cognition*, *68*(3), 341–58. http://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*, 397–408. http://doi.org/10.1007/s00221-006-0797-8

Smyrnis, N., Evdokimidis, I., Stefanis, N. C., Avramopoulos, D., Constantinidis, T. S., Stavropoulos, A., & Stefanis, C. N. (2003). Antisaccade performance of 1,273 men: effects of schizotypy, anxiety, and depression. *Journal of Abnormal Psychology*, *112*(3), 403–414. http://doi.org/10.1037/0021-843X.112.3.403

Sommer, I. E. C., Slotema, C. W., Daskalakis, Z. J., Derks, E. M., Blom, J. D., & Van Der Gaag, M. (2012). The treatment of hallucinations in schizophrenia spectrum disorders. *Schizophrenia Bulletin*, *38*(4), 704–714. http://doi.org/10.1093/schbul/sbs034

Spengler, D., Trillenberg, P., Sprenger, A., Nagel, M., Kordon, A., Junghanns, K., … Lencer, R. (2006). Evidence from increased anticipation of predictive saccades for a dysfunction of fronto-striatal circuits in obsessive-compulsive disorder. *Psychiatry Research*, *143*(1), 77–88. http://doi.org/10.1016/j.psychres.2005.08.020

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

Sperry, R. W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of Comparative and Physiological Psychology*, *43*(6), 482–489. http://doi.org/10.1037/h0055479

Sponheim, S. R., Iacono, W. G., Thuras, P. D., Nugent, S. M., & Beiser, M. (2003). Sensitivity and specificity of select biological indices in characterizing psychotic patients and their relatives. *Schizophrenia Research*, *63*(1–2), 27–38. http://doi.org/10.1016/S0920-9964(02)00385-7

Sprenger, A., Trillenberg, P., Nagel, M., Sweeney, J. A., & Lencer, R. (2013). Enhanced top-down control during pursuit eye tracking in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(3), 223–231. http://doi.org/10.1007/s00406-012-0332-9

Steeds, H., Carhart-Harris, R. L., & Stone, J. M. (2015). Drug models of schizophrenia. *Therapeutic Advances in Psychopharmacology*, *5*(1), 43–58. http://doi.org/10.1177/2045125314557797

Stefanis, N. C., Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Ntzoufras, I., & Stefanis, C. N. (2004). Factorial composition of self-rated schizotypal traits among young males undergoing military training. *Schizophrenia Bulletin*, *30*(2), 335–350. http://doi.org/10.1093/oxfordjournals.schbul.a007083

Stefanis, N. C., Trikalinos, T. A., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Ntzani, E. E., … Stefanis, C. N. (2007). Impact of schizophrenia candidate genes on schizotypy and cognitive endophenotypes at the population level. *Biological Psychiatry*, *62*(7), 784–92. http://doi.org/10.1016/j.biopsych.2006.11.015

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. http://doi.org/10.1002/hbm.23294

Steyer, R., Ferring, D., & Schmitt, J. (1992). States and traits in psychological assessment. *European Journal of Psychological Assessment*, *8*(2), 79–98.

Steyer, R., Mayer, A., Geiser, C., & Cole, D. A. (2015). A theory of states and traits—Revised. *Annual Review of Clinical Psychology*, *11*(1), 71–98. http://doi.org/10.1146/annurev-clinpsy-032813-153719

Steyer, R., Schmitt, M., & Eid, M. (1999). Latent state-trait theory and research in personality and individual differences. *European Journal of Personality*, *13*(5), 389–408. http://doi.org/10.1002/(sici)1099-0984(199909/10)13:5<389::aid-per361>3.3.co;2-1

Steyer, R., & Schmitt, M. J. (1990). The effects of aggregation across and within occasions on consistency, specificity and reliability. *Methodika*, *4*, 58–94.

Stöber, G., Ben-Shachar, D., Cardon, M., Falkai, P., Fonteh, A. N., Gawlik, M., … Riederer, P. (2009). Schizophrenia: From the brain to peripheral markers. A consensus paper of the WFSBP task force on biological markers. *The World Journal of Biological Psychiatry*, *10*(2), 127–155. http://doi.org/10.1080/15622970902898980

Stuve, T. A., Friedman, L., Jesberger, J. A., Gilmore, G. C., Strauss, M. E., & Meltzer, H. Y. (1997). The relationship between smooth pursuit performance, motion perception and sustained visual attention in patients with schizophrenia and normal controls. *Psychological Medicine*, *27*(1), 143–152. http://doi.org/10.1017/S0033291796004230

Sweeney, J. A., Clementz, B. A., Escobar, M. D., Li, S., Pauler, D. K., & Haas, G. L. (1993). Mixture analysis of pursuit eye-tracking dysfunction in schizophrenia. *Biological Psychiatry*, *34*(5), 331–340. http://doi.org/10.1016/0006-3223(93)90090-Z

Sweeney, J. A., Clementz, B. A., Haas, G. L., Escobar, M. D., Drake, K., & Frances, A. J. (1994). Eye tracking dysfunction in schizophrenia: characterization of component eye movement abnormalities, diagnostic specificity, and the role of attention. *Journal of Abnormal Psychology*, *103*(2), 222–30. http://doi.org/10.1037/0021-843X.103.2.222

Sweeney, J. A., Haas, G. L., Li, S., & Weiden, P. J. (1994). Selective effects of antipsychotic medications on eye-tracking performance in schizophrenia. *Psychiatry Research*, *54*(2), 185–198. http://doi.org/10.1016/0165-1781(94)90006-X

Sweeney, J. A., Luna, B., Haas, G. L., Keshavan, M. S., Mann, J. J., & Thase, M. E. (1999). Pursuit tracking impairments in schizophrenia and mood disorders: Step-ramp studies with unmedicated patients. *Biological Psychiatry*, *46*(5), 671–680. http://doi.org/10.1016/S0006-3223(99)00132-8

Sweeney, J. A., Luna, B., Srinivasagam, N. M., Keshavan, M. S., Schooler, N. R., Haas, G. L., & Carl, J. R. (1998). Eye tracking abnormalities in schizophrenia: evidence for dysfunction in the frontal eye fields. *Biological Psychiatry*, *44*(8), 698–708. http://doi.org/10.1016/S0006-3223(98)00035-3

Takahashi, H., Iwase, M., Canuet, L., Yasuda, Y., Ohi, K., Fukumoto, M., … Takeda, M. (2010). Relationship between prepulse inhibition of acoustic startle response and schizotypy in healthy Japanese subjects. *Psychophysiology*, *47*(5), 831–837. http://doi.org/10.1111/j.1469-8986.2010.01000.x

Talanow, T., Kasparbauer, A.-M., Steffens, M., Meyhöfer, I., Weber, B., Smyrnis, N., & Ettinger, U. (2016). Facing competition: Neural mechanisms underlying parallel programming of antisaccades and prosaccades. *Brain and Cognition*, *107*, 37–47. http://doi.org/10.1016/j.bandc.2016.05.006

Tamminga, C. A., Ivleva, E. I., Keshavan, M. S., Pearlson, G. D., Clementz, B. A., Witte, B., … Sweeney, J. A. (2013). Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *American Journal of Psychiatry*, *170*(11), 1263–1274. http://doi.org/10.1176/appi.ajp.2013.12101339

Tanaka, M., & Lisberger, S. G. (2001). Regulation of the gain of visually guided smooth-pursuit eye movements by frontal cortex. *Nature*, *409*(6817), 191–4. http://doi.org/10.1038/35051582

Tandon, R. (1999). Moving beyond findings: concepts and model-building in schizophrenia. *Journal of Psychiatric Research*, *33*(6), 467–471. http://doi.org/10.1016/S0022-3956(99)00036-9

Tatler, B. W., & Hutton, S. B. (2007). Trial by trial effects in the antisaccade task. *Experimental Brain Research*, *179*(3), 387–396. http://doi.org/10.1007/s00221-006-0799-6

Taylor, D. J., & McFatter, R. M. (2003). Cognitive performance after sleep deprivation: does personality make a difference? *Personality and Individual Differences*, *34*(7), 1179–1193. http://doi.org/10.1016/S0191-8869(02)00108-3

Tendolkar, I., Ruhrmann, S., Brockhaus-Dumke, A., Pauli, M., Mueller, R., Pukrop, R., & Klosterkötter, J. (2005). Neural correlates of visuo-spatial attention during an antisaccade task in schizophrenia: an ERP study. *International Journal of Neuroscience*, *115*(5), 681–698. http://doi.org/10.1080/00207450590887475

Thaker, G. K. (2000). Defining the schizophrenia phenotype. *Current Psychiatry Reports*, *2*(5), 398–403. http://doi.org/10.1007/s11920-000-0022-6

Thaker, G. K. (2008). Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophrenia Bulletin*, *34*(4), 760–773. http://doi.org/10.1093/schbul/sbn049

Thaker, G. K., Cassady, S., Adami, H., Moran, M., & Ross, D. E. (1996). Eye movements in Spectrum Personality Disorders: Comparison of community subjects and relatives of schizophrenic patients. *American Journal of Psychiatry*, *153*(3), 362–368.

Thaker, G. K., Moran, M., Adami, H., & Cassady, S. (1993). Psychosis proneness scales in schizophrenia spectrum personality disorders: Familial vs. nonfamilial samples. *Psychiatry Research*, *46*, 47–57.

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. http://doi.org/10.1016/S0165-1781(99)00084-0

Thaker, G. K., Ross, D. E., Cassady, S. L., Adami, H. M., Medoff, D. R., & Sherr, J. (2000). Saccadic eye movement abnormalities in relatives of patients with schizophrenia. *Schizophrenia Research*, *45*(3), 235–244. http://doi.org/10.1016/S0920-9964(99)00193-0

Thibaut, F., Boutros, N. N., Jarema, M., Oranje, B., Hasan, A., Daskalakis, Z. J., … Falkai, P. (2015). Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. *The World Journal of Biological Psychiatry*, *16*(5), 280–290. http://doi.org/10.3109/15622975.2015.1050061

Thomas, M. L., Sing, H. C., Belenky, G., Holcomb, H. H., Mayberg, H. S., Dannals, R. F., … Redmond, D. P. (2003). Neural basis of alertness and cognitive performance impairments during sleepiness II. Effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. *Thalamus and Related Systems*, *2*(3), 199. http://doi.org/10.1017/S1472928803000207

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., … Redmond, D. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research*, *9*(4), 335–352. http://doi.org/10.1046/j.1365-2869.2000.00225.x

Tomasik, J., Rahmoune, H., Guest, P. C., & Bahn, S. (2016). Neuroimmune biomarkers in schizophrenia. *Schizophrenia Research*, *176*(1), 3–13. http://doi.org/10.1016/j.schres.2014.07.025

Tong, J., Maruta, J., Heaton, K. J., Maule, A. L., & Ghajar, J. (2014). Adaptation of visual tracking synchronization after one night of sleep deprivation. *Experimental Brain Research*, *232*(1), 121–131. http://doi.org/10.1007/s00221-013-3725-8

Tregellas, J. R., 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. *American Journal of Psychiatry*, *161*(2), 315–321. http://doi.org/10.1176/appi.ajp.161.2.315

Trillenberg, P., Heide, W., Junghanns, K., Blankenburg, M., Arolt, V., & Kömpf, D. (1998). Target anticipation and impairment of smooth pursuit eye movements in schizophrenia. *Experimental Brain Research*, *120*(3), 316–324. http://doi.org/10.1007/s002210050405

Trillenberg, P., Lencer, R., & Heide, W. (2004). Eye movements and psychiatric disease. *Current Opinion in Neurology*, *17*(1), 43–7.

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. http://doi.org/10.1007/s00406-016-0671-z

Trotta, A., Murray, R. M., & MacCabe, J. H. (2015). Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. *Psychological Medicine*, *45*(2), 381–394. http://doi.org/10.1017/S0033291714001512

Tseng, K. Y., Chambers, R. A., & Lipska, B. K. (2009). The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. *Behavioural Brain Research*, *204*(2), 295–305. http://doi.org/10.1016/j.bbr.2008.11.039

Tu, P. C., Yang, T. H., Kuo, W. J., Hsieh, J. C., & Su, T. P. (2006). Neural correlates of antisaccade deficits in schizophrenia, an fMRI study. *Journal of Psychiatric Research*, *40*(7), 606–612. http://doi.org/10.1016/j.jpsychires.2006.05.012

Tucker, A. M., Stern, Y., Basner, R. C., & Rakitin, B. C. (2011). The prefrontal model revisited: Double dissociations between young sleep deprived and elderly subjects on cognitive components of performance. *Sleep*, *34*(8), 1039–1050. http://doi.org/10.5665/SLEEP.1158

Van Den Buuse, M. (2010). Modeling the positive symptoms of schizophrenia in genetically modified mice: Pharmacology and methodology aspects. *Schizophrenia Bulletin*, *36*(2), 246–270. http://doi.org/10.1093/schbul/sbp132

Van Dongen, H. P. A., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep*, *27*(3), 423–433.

Van Kampen, D., & Deijen, J. B. (2009). SPEM dysfunction and general schizotypy as measured by the SSQ: a controlled study. *BMC Neurology*, *9*(27), 1–7. http://doi.org/10.1186/1471-2377-9-27

Van Os, J. (2016). "Schizophrenia" does not exist. *Bmj*, *375*(February), i375. http://doi.org/10.1136/bmj.i375

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), 179–95. http://doi.org/10.1017/S0033291708003814

Van Steveninck, A. L., Van Berckel, B. N. M., Schoemaker, R. C., Breimer, D. D., Van Gerven, J. M. A., & Cohen, A. F. (1999). The sensitivity of pharmacodynamic tests for the central nervous system effects of drugs on the effects of sleep deprivation. *Journal of Psychopharmacology*, *13*(1), 10–17. http://doi.org/10.1177/026988119901300102

Venables, P. H., & Raine, A. (2015). The stability of schizotypy across time and instruments. *Psychiatry Research*, *228*(3), 585–90. http://doi.org/10.1016/j.psychres.2015.05.047

Vingerhoets, W. A. M., Bloemen, O. J. N., Bakker, G., & Van Amelsvoort, T. A. M. J. (2013). Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: What's the evidence? *Frontiers in Psychiatry*, *4*, 1–22. http://doi.org/10.3389/fpsyt.2013.00157

Vollema, M. G., & Van den Bosch, R. J. (1995). The multidimensionality of schizotypy. *Schizophrenia Bulletin*, *21*(1), 19–31. http://doi.org/10.1093/schbul/21.1.19

Vollenweider, F. X., Barro, M., Csomor, P. A., & Feldon, J. (2006). Clozapine enhances prepulse inhibition in healthy humans with low but not with high prepulse inhibition levels. *Biological Psychiatry*, *60*(6), 597–603. http://doi.org/10.1016/j.biopsych.2006.03.058

Von Holst, E., & Mittelstaedt, H. (1950). Das Reafferenzprinzip - Wechselwirkungen zwischen Zentralnervensystem und Peripherie. *Die Naturwissenschaften*, *37*(20), 464–476. http://doi.org/10.1007/BF00622503

Wachowicz, B., Beldzik, E., Domagalik, A., Fafrowicz, M., Gawlowska, M., Janik, J., … Marek, T. (2015). Different types of errors in saccadic task are sensitive to either time of day or chronic sleep restriction. *PLoS ONE*, *10*(5), 1–11. http://doi.org/10.1371/journal.pone.0126502

Walter, E. E., Fernandez, F., Snelling, M., & Barkus, E. (2016). Genetic consideration of schizotypal traits: A review. *Frontiers in Psychology*, *7*(NOV). http://doi.org/10.3389/fpsyg.2016.01769

Wan, L., Thomas, Z., Pisipati, S., Jarvis, S. P., & Boutros, N. N. (2017). Inhibitory deficits in prepulse inhibition, sensory gating, and antisaccade eye movement in schizotypy. *International Journal of Psychophysiology*, *114*, 47–54. http://doi.org/10.1016/j.ijpsycho.2017.02.003

Webb, W. B. (1985). A further analysis of age and sleep deprivation effects. *Psychophysiology*, *22*(2), 156–161. http://doi.org/10.1111/j.1469-8986.1985.tb01579.x

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. http://doi.org/10.1155/2013/510402

Wilkinson, R. T. (1961). Interaction of lack of sleep with knowledge of results, repeated testing, and individual differences. *Journal of Experimental Psychology*, *62*(3), 263–271. http://doi.org/10.1037/h0048787

Williams, H. L., Lubin, A., & Goodnow, J. J. (1959). Impaired performance with acute sleep loss. *Psychological Monographs: General and Applied*, *73*(14), 1–26. http://doi.org/10.1037/h0093749

Wilson, S., & Argyropoulos, S. (2012). Sleep in schizophrenia: time for closer attention. *The British Journal of Psychiatry*, *200*(4), 273–274. http://doi.org/10.1192/bjp.bp.111.104091

Winterstein, B. P., Silvia, P. J., Kwapil, T. R., Kaufman, J. C., Reiter-Palmon, R., & Wigert, B. (2011). Brief assessment of schizotypy: Developing short forms of the Wisconsin Schizotypy Scales. *Personality and Individual Differences*, *51*(8), 920–924. http://doi.org/10.1016/j.paid.2011.07.027

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. http://doi.org/10.1016/j.bandc.2012.09.010

Wuthrich, V., & Bates, T. C. (2005). Reliability and validity of two Likert versions of the Schizotypal Personality Questionnaire (SPQ). *Personality and Individual Differences*, *38*(7), 1543–1548. http://doi.org/10.1016/j.paid.2004.09.017

Wyatt, H. J., & Pola, J. (1987). Smooth eye movements with step-ramp stimuli: The influence of attention and stimulus extent. *Vision Research*, *27*(9), 1565–1580. http://doi.org/10.1016/0042-6989(87)90165-9

Xiang, Y., Weng, Y., Leung, C., Tang, W., Lai, K. Y. C., & Ungvari, G. S. (2009). Prevalence and correlates of insomnia and its impact on quality of life in Chinese schizophrenia patients. *Sleep*, *32*, 105–109. http://doi.org/10.5665/sleep/32.1.105

Yasui, S., & Young, L. (1975). Perceived visual motion as effective stimulus to pursuit eye movement system. *Science*, *190*(4217), 906–908. http://doi.org/10.1126/science.1188373

Yee, C. M., Nuechterlein, K. H., & Dawson, M. E. (1998). A longitudinal analysis of eye tracking dysfunction and attention in recent-onset schizophrenia. *Psychophysiology*, *35*(4), 443–51. http://doi.org/10.1111/1469-8986.3540443

Young, J. W., & Geyer, M. (2015). Developing treatments for cognitive deficits in schizophrenia: The challenge of translation. *Journal of Psychopharmacology*, *29*(2), 178–196. http://doi.org/10.1177/0269881114555252

Young, L. R., & Sheena, D. (1975). Eye-movement measurement techniques. *American Psychologist*, *30*, 315–330.

Yu, J., Bernardo, A. B. I., & Zaroff, C. M. (2016). Chinese version of the Schizotypal Personality Questionnaire: Factor structure replication and invariance across sex. *Asia-Pacific Psychiatry*, *8*(3), 226–237. http://doi.org/10.1111/appy.12215

Zhou, X., Wu, T., Yu, J., & Lei, X. (2017). Sleep deprivation makes the young brain resemble the elderly brain: A large-scale brain networks study. *Brain Connectivity*, *7*(1), 58–68. http://doi.org/10.1089/brain.2016.0452

Zils, E., Sprenger, A., Heide, W., Born, J., & Gais, S. (2005). Differential effects of sleep deprivation on saccadic eye movements. *Sleep*, *28*(9), 1109–1115.

IX APPENDIX A [List of figures and tables]

Figures

Tables

X APPENDIX B [List of abbreviations]

AS	Antisaccade
BUS	Back-up Saccade [SPEM Saccade Type]
CUS	Catch-up Saccade [SPEM Saccade Type]
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	Functional Magnetic Resonance Imaging
LST	Latent State-Trait [Theory]
O-LIFE	Oxford Liverpool Inventory of Feelings and Experiences
PS	Prosaccade
PSI	Psychotomimetic States Inventory
PPI	Prepulse Inhibition
SPEM	Smooth Pursuit Eye Movements
SPQ	Schizotypal Personality Questionnaire
SEM	Structural Equation Modeling
SWJ	Square Wave Jerk [SPEM Saccade Type]
VCPCR	Video-Based Combined Pupil and Corneal Reflection [Eye Movement Measurement Methodology]

XI APPENDIX C [Publications included in the thesis]

The present thesis is based on four original publications. Additionally, three further relevant original publications and one manuscript are included in the thesis. To avoid violations of copyright, the articles were removed from the appendix section. The articles can be found online using the following references or in hardcopies of the present thesis at the Universitäts- und Landesbibliothek Bonn.

Relevant publications for the present thesis
Meyhöfer, I., Bertsch, K., Esser, M., & Ettinger, U. (2015). Variance in saccadic eye movements reflects stable traits. *Psychophysiology, 53*, 566–578. http://doi.org/10.1111/psyp.12592
Meyhöfer, I., Steffens, M., Kasparbauer, A., Grant, P., Weber, B., & Ettinger, U. (2015). Neural mechanisms of smooth pursuit eye movements in schizotypy. *Human Brain Mapping, 36*, 340–353. http://doi.org/10.1002/hbm.22632
Meyhöfer, I., Kumari, V., Hill, A., Petrovsky, N., & Ettinger, U. (2016). Sleep deprivation as an experimental model system for psychosis: Effects on smooth pursuit, prosaccades, and antisaccades. *Journal of Psychopharmacology, 31*(4), 418-433. http://doi.org/10.1177/0269881116675511
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,* 1-15. http://doi.org/10.1111/psyp.12917
Further relevant publications
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), 1–16. http://doi.org/10.3389/fpsyt.2014.00018
Steffens, M., Becker, B., Neumann, C., Kasparbauer, A. M., **Meyhöfer, I.**, Weber, B., Mehta, M.A., Hurlemann, R, & Ettinger, U. (2016). Effects of ketamine on brain function during smooth pursuit eye movements. *Human Brain Mapping, 37*(11), 4047–4060. http://doi.org/10.1002/hbm.23294
Petrovsky, N., Ettinger, U., Hill, A., Frenzel, L., **Meyhöfer, I.**, Wagner, M., Backhaus, J., & Kumari, V. (2014). Sleep deprivation disrupts prepulse inhibition and induces psychosis-like symptoms in healthy humans. *The Journal of Neuroscience, 34*(27), 9134–9140. http://doi.org/10.1523/JNEUROSCI.0904-14.2014
Meyhöfer, I., Ettinger, U., Faiola, E., Petrovsky, N., & Kumari, V. (to be submitted). The effects of schizotypy and sleep deprivation on prepulse inhibition.