NEURAL MECHANISMS AND TRAINABILITY OF INHIBITORY CONTROL

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Tobias Preißler (geb. Talanow)

aus

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Zusammensetzung der Prüfungskommission:

Prof. Dr. Rainer Banse (Vorsitzender)

Prof. Dr. Ulrich Ettinger (Betreuer und Gutachter)

Prof. Dr. Henning Gibbons (Gutachter)

Prof. Dr. Bernd Weber (weiteres prüfungsberechtigtes Mitglied)

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"Start by doing what's necessary,

then do what's possible,

and suddenly you are doing the impossible."

-Attributed to Saint Francis of Assisi (1181/1182 - 1226)

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2. Abstract

Response inhibition is a facet of mental functions, termed executive functions, by which humans control their behavior in consideration of environmental conditions. Response inhibition allows to control automatic and impulsive reactions in favor of more appropriate, voluntary and goal-directed responses. It is a behavioral mechanism that is crucially involved in accomplishing many everyday tasks. Its deficits play an important role in psychopathology. The model system of saccadic eye movements is a well-established framework to study response inhibition in psychology and cognitive neuroscience. However, the precise nature of the response inhibition mechanism and the potential of inhibition abilities to be subject to training and transfer remain not fully understood to date despite intensive research. Thus, this dissertation comprises three peer-reviewed research projects that aimed to contribute to a better understanding of the response inhibition component and how it shapes our behavior.

An initial study reported evidence in favor of the competitive integrative nature of opposing response decision signals in the antisaccade task. The results matched a metaphorical account of a horse-race towards a response threshold. It implies that response inhibition does not require a distinct stop or inhibition signal, but an accumulation mechanism.

A second study investigated brain activations during the planning (proactive) and response (reactive) phase in two saccadic response inhibition tasks by altering the certainty of the task-set. Task-set certainty likely biased task-set and stimulus encoding as well as processes underlying response selection, that resulted in more successful inhibition. Foreknowledge of the task-set distinctly altered proactive and reactive brain signals. The results indicated an important role of a brain region in supramarginal gyrus/inferior parietal lobe in planning and facilitation of saccadic response inhibition.

A third study assessed training and transfer effects of response inhibition abilities in the light of Miyake and Friedman's *Unity and Diversity Model* of executive functions. A transfer of inhibition gains to updating, shifting and response planning abilities was expected according to the model. Response inhibition abilities were indeed subject to training. However, training gains were limited to the trained inhibition task and did not transfer to other untrained facets of executive functions. Further research in samples that deviate from an optimal level of inhibition abilities might be a promising next step to exhibit long-term training and transfer effects in inhibition.

Overall, this dissertation highlights fundamental principles of planning and facilitation underlying reflex control and decision making. It challenges the assumption of performance transfer in cognitive training.

3. Zusammenfassung

Exekutive Funktionen sind geistige Funktionen, mit welchen Menschen unter Berücksichtigung ihrer Umwelt ihr Verhalten steuern und regulieren. Dazu zählt der Verhaltensmechanismus der Inhibition, welcher es ermöglicht automatische und impulsive Reaktionen zu Gunsten willentlich geplanter und zielgerichteter Antwortreaktionen zu hemmen. Eine Fehlfunktion dieser alltagsrelevanten Fähigkeit spielt oft eine wichtige Rolle in der Pathologie psychischer Störungen. Als gängige Methode zur Erforschung von Inhibition nutzen die Psychologie und die kognitiven Neurowissenschaften Analysen sakkadischer Augenbewegungen. Trotz intensiver Forschung ist die Funktionsweise des inhibitorischen Verhaltensmechanismus noch nicht gänzlich erfasst. Auch die Wirksamkeit von Impulskontrolltraining sowie dessen Effekte auf andere exekutive Funktionsbereiche sind noch unklar. Diese Dissertation umfasst drei publizierte Forschungsprojekte als Beitrag zu einem besseren Verständnis von Inhibition und dessen Bedeutung für unser Verhalten.

Das erste Projekt verdeutlichte, dass in der Antisakkaden-Aufgabe kortikale Signale gegensätzlicher Verhaltensentscheidungen miteinander um das Erreichen einer Reaktionsschwelle konkurrieren, vergleichbar mit einem Pferderennen. Dies impliziert, dass zur Kontrolle impulsiver Verhaltensentscheidungen kein eigenständiges Stopp- oder Inhibitionssignal erforderlich ist, sondern ein geschwindigkeitsabhängiger Akkumulationsmechanismus.

Das zweite Projekt untersuchte Gehirnaktivität während der Planungs- (proaktiv) und Reaktionsphase (reaktiv) zweier Inhibitionsaufgaben, in denen die Vorhersehbarkeit der Aufgabenanforderung (task-set) variiert wurde. Vorhersehbare Aufgabenanforderungen ergaben eine verbesserte Inhibitionsleistung. Dies ist vermutlich auf ihren Einfluss auf die Aufgaben- und Zielreizenkodierung sowie auf Prozesse, die der Antwortauswahl zugrunde liegen, zurückzuführen. Vorwissen über die Anforderungen beeinflusste proaktive und reaktive Gehirnsignale. Eine wichtige Rolle bei der Planung und Umsetzung sakkadischer inhibitorischer Kontrolle spielte eine Gehirnregion im Gyrus supramarginalis/inferioren Parietallappen.

Das dritte Projekt analysierte Trainings- und Transfereffekte der Inhibition im Kontext von Miyake und Friedmans *Unity and Diversity-Modell* der exekutiven Funktionen. Das Training verbesserte zwar die Impulskontrolle in der Trainingsaufgabe, hatte entgegen der Erwartungen jedoch keinen Effekt auf Parameter des Arbeitsgedächtnisses, der geistigen Flexibilität und der Antwortplanung. Um nachhaltige Trainings- und Transfereffekte von Inhibition nachzuweisen, wäre weitere Forschung an Stichproben mit Abweichungen von einem optimalen Funktionsniveau der Impulskontrolle ein vielversprechender Ansatz.

Zusammengefasst veranschaulicht die vorliegende Dissertation Grundlagen der Planung und Umsetzung von Reflexkontrolle und Entscheidungsfindung. Sie hinterfragt kritisch die Annahme des Leistungstransfers von kognitivem Training.

4. Inhibition

Every time humans try to resist temptations and impulses and think before they act an effortful mental process or mechanism termed *inhibition* is at play. Inhibition is part of a broader set of mental processes referred to as *executive functions* (Diamond, 2013).

4.1 Taxonomies of Inhibition

The French philosopher René Descartes vividly illustrates that humans often find themselves in situations in which they have a choice between seemingly conflicting courses of action: *"… if anger makes the hand rise in order to strike, the will can ordinarily restrain it ..."* (Descartes 1989, p. 44, in Bari & Robbins, 2013). Here, the intervening force that guides the actor's behavior is a process or mechanism that is understood in psychology as the concept of *inhibition*. The American Psychological Association's (APA) Dictionary of Psychology provides a comprehensive understanding of *inhibition* as *"the process of restraining one's impulses or behavior, either consciously or unconsciously ..."* (APA, 2018). This dissertation focuses on inhibition as a key facet of EFs and response selection. In this context, inhibition refers to *"the suppression of covert responses in order to prevent incorrect responses"* (APA, 2018).

From a historical perspective, the concepts of *inhibition* and *interference control* have been a topic of intensive research for over 120 years now (Bari & Robbins, 2013; Dempster, 1995). Although its origin is in early theories on learning and forgetting, inhibition and interference control are now thought to be critically relevant dimensions of cognition in a variety of psychological processes including attention, perception, working memory, cognitive development, and age-related declines in cognitive abilities (Dempster, 1995; Friedman & Miyake, 2004). Further, deficits of inhibition-related processes are thought to play a key role in clinically relevant disorders, such as attention deficit hyperactivity disorder (ADHD) (Barkley, 1999; Casey et al., 1991; Quay, 1997), schizophrenia (Kaladjian, Jeanningros, Azorin, Anton, & Mazzola-Pomietto, 2011; Parwani et al., 2000), autism (Mosconi et al., 2009; Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009), and obsessive-compulsive disorder (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2007). The concept of inhibition is subject to a wide variety of research papers (Aron, 2007) and several textbooks (Dempster & Brainerd, 1995; MacLeod, 2007). However, the mechanisms underlying inhibition remain not fully understood till this day.

We apply inhibitory control in everyday life more often than we may think: at the office, sometimes we find ourselves doing things that distract us from work, such as checking our mobile phones, surfing on the internet or chatting with colleagues. Good inhibitors have the ability to stay focused on their work and postpone distracting activities. Furthermore, when bitten by a mosquito, it is reasonable that we want to scratch ourselves to relieve the itch. Good inhibitors are able to control

the urge to scratch and stand the itch, but bad inhibitors cannot resist the relieving temptation to scratch. Also, poor inhibitors may show a tendency to interrupt conversations and may answer questions impulsively without thinking them through (Bari & Robbins, 2013).

Different neural, cognitive and physical-response concepts of inhibition have been developed in research (MacLeod, 2007). This dissertation seeks to provide insights into neural underpinnings and trainability of behavioral inhibition in response selection in the light of a physical-response concept of inhibition. This concept postulates the widely accepted view that actions can be initiated and then cancelled (Logan & Cowan, 1984; MacLeod, 2007).

The following section outlines and integrates relevant taxonomies of inhibition that exist in the psychological sciences. This dissertation builds on Miyake & Friedman's view on inhibition. Nevertheless, it should be stressed at this point that other likewise valuable taxonomies of inhibition exist in the literature.

4.1.1 Miyake & Friedman

Research by the group around Miyake and Friedman suggests a three-part distinction of the concept of inhibition. Statistical techniques, such as latent-variable-analysis, revealed three related yet separable key facets of inhibitory control. These concepts of inhibition are (a) *prepotent response inhibition*, (b) *resistance to distractor interference*, and (c) *resistance to proactive interference* (Friedman & Miyake, 2004; Miyake et al., 2000).

Prepotent response inhibition defines the ability to deliberately suppress dominant, automatic or reflexive responses in favor of voluntary motor acts (Everling & Fischer, 1998; Friedman & Miyake, 2004; Miyake et al., 2000). *Resistance to distractor interference* means overcoming or resolving interference from information in the external environment that is irrelevant to a current task (Friedman & Miyake, 2004). *Resistance to proactive interference* refers to the ability to resist memory intrusions from information that was previously relevant to the task but has since become irrelevant (Friedman & Miyake, 2004). *Resistance to proactive interference* is conceptually different from *resistance to distractor interference* because in the former task-relevant interfering information precedes the target information, and in the later task-irrelevant distractor information is presented simultaneously to the target information (Friedman & Miyake, 2004).

Prepotent response inhibition has proven to be a reasonably reliable construct (split half $r > .70$, intra-class correlation = .86) (Congdon et al., 2012; Friedman & Miyake, 2004; Miyake et al., 2000) with temporally stable performance parameters. Its degree of reliability varies between behavioral response inhibition tasks (Table 1). However, the construct of resistance to distractor interference is

moderately reliable (split half *r* = .59 - .76), while descriptive statistics by Friedman & Miyake (2004) show that resistance to proactive interference is a rather unreliable construct (Cronbach's alpha < .53).

Overall, proven stable inhibition measures encourage the assumption that inhibition related functions reflect stable individual differences (Wöstmann et al., 2013).

Table 1

Reliability of Response Inhibition Parameters

	Prepotent response inhibition			Resistance to distractor interference	Resistance to proactive interference
	Antisaccade errors (in %)	Stop signal RT (in ms)	Stroop effect (in ms)		
Split half reliability[a]	.87	.72	.80	.59 - .76	
Split half reliability[b]	.77	.92	.72		
Cronbach's alpha retest[c]	.94	.93	.97		< .53
Intra-class correlation[d]		.86			

Note. RT = reaction time. [a]Miyake et al. (2000). [b]Friedman & Miyake (2004). [c]Wöstmann et al. (2013). [d]Congdon et al. (2012).

4.1.2 Harnishfeger

Harnishfeger and Bjorklund (1993) proposed a resource model of effective cognitive processing that highlights the interaction of sufficient inhibitory processes and limited working memory resources. Sufficient inhibitory mechanisms keep irrelevant information from entering working-memory space according to the authors' proposal. This way, less irrelevant information occupies mental space, which leaves more mental resources for task-relevant information processing. Vice versa, more working-memory space is blocked by task irrelevant information processing in the case of insufficient inhibition. According to this view, good inhibitors do not necessarily possess more mental resources, but instead more efficient mechanisms to screen irrelevant information out of working memory.

Harnishfeger's approach to cognitive processing derived from research on the cognitive development of children (Harnishfeger & Bjorklund, 1993) as well as on the observation that young children's poor memory performance was partly related to irrelevant information they remembered (Harnishfeger & Pope, 1996). It is a central aspect of a child's cognitive development to be able to keep irrelevant information out of working memory via sufficient inhibition. Accordingly, inhibitory mechanisms become more efficient during early development (Harnishfeger & Bjorklund, 1993; Harnishfeger, 1995). Throughout their cognitive development, children become more capable to guide their motor behavior, to focus attention in competition of distraction and to monitor and control their thoughts and behavior, as inhibitory mechanisms become more effective over time

(Bjorklund & Harnishfeger, 1990). Here, more effective means that more frequently irrelevant information is sufficiently kept from entering working-memory space.

4.1.3 Nigg

Nigg (2000) proposed an overarching taxonomy of inhibitory processes in developmental psychopathology. His framework roughly classifies inhibition in relation to higher order cognition into executive, motivational and automatic inhibitory key concepts. The author distinguishes eight kinds of inhibition within this organization and provides tasks, measurements and underlying neural systems of each sub-domain of inhibition (Table 2). The framework outlines and integrates the cognitive, personality centered and neural perspective on each sub-process of inhibition respectively. The degree of overlap between sub-processes of inhibition is to date unclear.

It is particularly noteworthy for this dissertation that Nigg's research explicitly separated inhibition in the context of oculomotor control from other classes and processes of executive inhibition. This distinction acknowledges the existence of a distinct cortical network underlying mechanisms of oculomotor control. Nigg's theory addressed another distinct inhibitory mechanism in relation to oculomotor control termed *Inhibition of return* (IOR). IOR is a form of inhibition on attentional processes and refers to the phenomenon where responses generated to targets at previously attended locations are delayed (Ro, Pratt, & Rafal, 2000). Nigg's classification used a detailed breakdown of inhibition mechanisms to nicely illustrate the heterogeneity and complexity of inhibitory control.

Table 2

Taxonomy of Inhibition Constructs According to Nigg (2000)

	Inhibition class & process	Cognitive level	Neural level
Executive inhibition effects	Interference control: prevent interference due to resource or stimulus competition	Stroop task; flanker task; dual task interference; priming tasks	Anterior cingulate → dorsolateral prefrontal / premotor cortex → basal ganglia
	Cognitive inhibition: suppress irrelevant elements of thought to protect working memory/attention	Directed ignoring; ratings of intrusive thoughts; negative priming	Anterior cingulate → prefrontal cortex → association cortex
	Behavioral inhibition: suppress prepotent response	Stop task; go/no-go task; suppress attentional orienting	Lateral and orbital prefrontal cortex → premotor cortex
	Oculomotor inhibtion: effortfully suppress reflexive saccade	Antisaccade task; oculomotor tasks	Frontal eye fields / orbitofrontal cortex
Motivational inhibition effects	Response to punishment cues or learned social context domains	Inhibit primary response: modified go/no-go (Newman, Patterson, & Kosson, 1987); inhibit competing response; emotional Stroop task	Septal-hippocampal formation → cingulate cortex → motor systems
	Response to novelty		Amygdaloid system
Automatic inhibition of attention	Suppress recently inspected stimuli for attention and oculomotor saccade	Attentional and oculomotor inhibition of return	Superior colliculus → midbrain or oculomotor pathway
	Suppress information at unattended locations while attending elsewhere	Covert attentional orienting; neglect	Posterior association cortex & subcortical pathways

Note. Classification of key concepts of inhibition. Please note that oculomotor control is classified as a distinct process subserving executive inhibition. Adapted from Nigg (2000).

4.1.4 Hasher's Classification

Lynn Hasher's theoretical framework on inhibition derived from a developmental psychological perspective and aims to contribute to the understanding which cognitive mechanisms change over the course of the age span and which remain stable (Hasher, Lustig, & Zacks, 2007; Lustig, Hasher, & Zacks, 2007). The author proposed that inhibition involves three subordinate functions that operate in concert and possibly independently: (a) controlling relevant information to enter the focus of attention early in the processing stream (*access*), (b) deleting irrelevant information from the focus of attention and from working memory (*deletion*), and (c) suppressing or restraining strong but in a situation inappropriate responses (*restraint*). These executive control processes serve to narrow or constrain the content of consciousness to be goal relevant for best performance (Hasher et al., 2007). Differences in the subordinate functions of *access*, *deletion* and *restraint* may underlie intra-individual or inter-individual differences as well as group-level differences in mental processing speed and working memory, for example (Lustig et al., 2007).

In accordance with this model, deficits in *access* control enable distractors to influence the processing of target stimuli. Research supports the idea that the ability to activate goal relevant information is largely preserved throughout the lifespan (Lustig et al., 2007). The same authors also report evidence in favor of the view that poorer performance in older adults results from specific deficits in inhibition. According to Hasher's classification, differences in working memory between groups of different ages do not result from differences in the mental working space but from differences in the *deletion* function, to keep goal-irrelevant information from occupying working memory capacities. Good inhibitors as compared to poor inhibitors use their working memory space more effectively and fill it with more goal-related information. In like manner, age differences in *restraint* abilities exist in low-level and high-level tasks (Lustig et al., 2007).

4.1.5 Taxonomies of Inhibition: No Consensus Yet

Despite the history of intensive research on inhibition, there is not yet a consensus or a common understanding of the inhibition function. It is debated whether inhibition relates to a single process (Hasher & Zacks, 1988; Kane, Bleckley, Conway, & Engle, 2001) or multiple processes to control distracting information in favor of goal-relevant thought and behavior. However, in the current discussion on inhibition, there is a strong tendency for theorists to recognize that inhibition involves a set of subordinate functions (Friedman & Miyake, 2004; Hasher et al., 2007; Nigg, 2000). Groups that acknowledged multiple processes underlying inhibition, however, differ regarding the exact taxonomy of these subordinate functions as shown by the outline presented above. But some degree of overlap in the understanding of subordinate inhibition processes exists despite the authors' different terminology, for example when comparing Friedman and Miyake's (2004) process of *prepotent response inhibition* to Hasher et al.'s (2007) *restraint* function. Further, some theorists have even challenged the view that inhibition may exist at all. Instead, they have proposed that variability in performance originally ascribed to inhibition differences actually relates to the failure to activate relevant information (Lustig et al., 2007) and to conflict resolution resulting from memory retrieval (MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). According to the later view, good relative to bad inhibitors are more successful in keeping irrelevant and distracting information from entering working memory space leaving more working memory capacity to activate and process goal-relevant information (Harnishfeger & Bjorklund, 1993; Harnishfeger & Pope, 1996). Furthermore, Friedman and Miyake (2004), Hasher et al. (2007) and Nigg (2000) suggested that inhibition differences may be independent from differences in the quality of the inhibition mechanism per se. Instead, the authors argued that differences in inhibition performance are the result of differences in mental resources where good inhibitors have more mental resources ascribed to an inhibition function than bad inhibitors.

Initially, one might have assumed that a simple regulatory mechanism mediates the somewhat self-evident ability to resist temptations and impulses. The different understanding of the psychological concept of inhibition presented in this section draws a more complex image of the inhibition mechanism. These different perspectives stimulate the scientific discourse and illustrate the need for further research in this area.

4.2 Executive Functions

The psychological concept of *executive functions* (EFs), also called *cognitive control,* subsumes a set of effortful top-down mental processes, including inhibition, that modulate cognitive sub-systems to regulate thoughts and behavior (Diamond, 2013; Jurado & Rosselli, 2007; Miyake & Friedman, 2012; Miyake et al., 2000). EFs are thinking skills that aid reasoning, planning and problem solving (Blair, 2017; Diamond, 2013). They are of particular purpose when neither automatic or reflexive behavior nor intuition are useful to achieve a behavioral goal (Diamond, 2013). EFs help to strategically organize our behavior when we are faced with distraction and several possibilities for action.

EFs comprise three different cognitive abilities: they enable us to update, monitor and dynamically manipulate information in working memory (*Updating*) (Diamond, 2013; Miyake et al., 2000; Neil & Jones, 1990). They allow us to shift our focus of attention between multiple tasks or mental sets (*Shifting*) (Monsell, 1996, 2003). They qualify us to deliberately inhibit highly automatic thoughts and responses to stimulation and to control interference (*Inhibition*) (Diamond, 2013; Miyake et al., 2000).

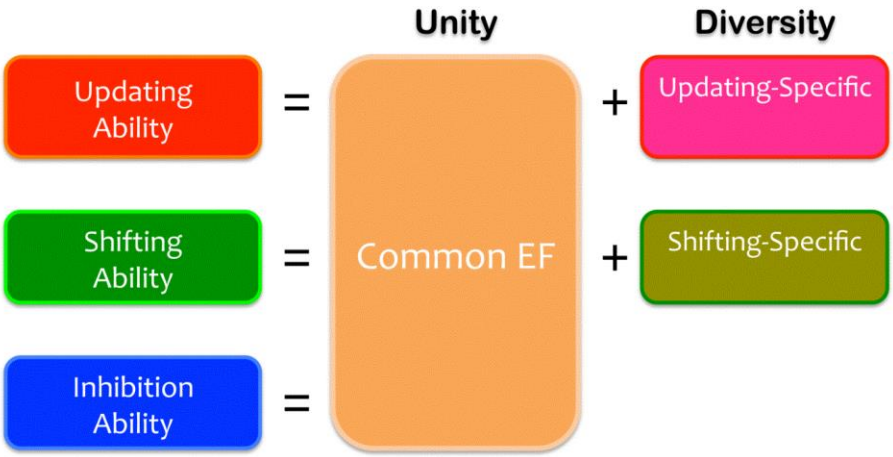
This dissertation refers to the concept of EFs according to the *Unity and Diversity Model* (Friedman & Miyake, 2017; Miyake & Friedman, 2012) (Figure 1). This model states that any expression of core EFs (i.e., Updating, Shifting, Inhibition) are determined by (a) processes common to all facets of core EFs (i.e., formally expressed by the shared variance of a *Common EF* factor) and (b) facet-specific processes (i.e., formally expressed by variance independent of *Common EF*). Moderate (*Unity*) but not perfect (*Diversity*) correlations between core EFs empirically support this view (Friedman & Miyake, 2017; Miyake & Friedman, 2012). The *Common EF* factor is thought to classify processes mainly related to the active maintenance of task goals, to task management and to goal representations which may bias goal-directed lower level mental processes. Valuable candidates for processes explicitly coded by the updating- and shifting specific factors are mechanisms, such as gating of information and working memory retrieval and the ease of transition to new representations in prefrontal cortex (PFC), respectively. No inhibition specific factor exists in the Unity and Diversity Model, suggesting that inhibition abilities are fully accounted for by processes common to all core EFs (Friedman, Miyake, Robinson, & Hewitt, 2011). This assumption is empirically

supported by an almost perfect correlation between inhibition and *Common EF* (Friedman & Miyake, 2017; Friedman et al., 2008, 2011).

EFs are crucially involved in everyday aspects of life, such as mental health (Burgess, Alderman, Evans, Emslie, & Wilson, 1998) and physical health (Allom, Mullan, & Hagger, 2016; Moffitt et al., 2011), education and public safety (see Diamond, 2013 for a summary) and other factors (Moffitt et al., 2011).

Figure 1

The Unity and Diversity Model of Executive Functions



Note. The unity and diversity of three facets of executive functions (EFs): updating, shifting and inhibition. Each facet of EFs is composed of what is common to all EFs (Common EF) and what is specific to them (e.g., updating-specific). The model does not include an inhibition-specific diversity component because research by the group around Miyake and Friedman has shown the absence of inhibition-specific variance once *Unity* (Common EF) is accounted for. Adapted from Miyake & Friedman (2012).

4.3 Research Methods to Study Inhibition

Our understanding of inhibitory control is heavily impacted by developments in the field of neuroscience and knowledge about cerebral structures and functions of the human brain. Clever behavioral and neuroscientific approaches as well as sophisticated statistical techniques provide powerful tools to gain deeper insight into the mechanisms underlying inhibitory control. In addition to a behavioral study, this dissertation thus includes two comprehensive functional magnetic resonance imaging (fMRI) studies that investigated the neuronal mechanisms underlying inhibition in addition to behavioral findings.

4.3.1 Manual Motor Functions

An individual's inhibition ability is measured by psychologists in tasks that instruct the execution or control of motor acts. For example, many popular behavioral experiments instruct subjects to provide stimulus-driven responses by means of button presses. In some trials these tasks instruct subjects to execute a motor act in response to a stimulus; in other trials a cue signals to suppress any stimulus driven motor reaction (inhibition trial). Control processes related to inhibition become visible on the behavioral level through longer *response latencies* (i.e., the interval from instruction onset to response onset) and increased *response error rates* (i.e., the execution of a motor act upon instruction to refrain from responding or the execution of a motor act that deviates from the instruction) in inhibition trials relative to non-inhibition trials. Frequently employed prepotent motor response inhibition paradigms are the stop signal task[1] (Logan, 1994), the Stroop task[2] (Stroop, 1935) and the antisaccade task (Hallett, 1978), that is described in more detail in section 4.4.4 *Prosaccades and Antisaccades*. To contrast the assessment of prepotent motor response inhibition to other facets of inhibition, it should be mentioned that the Eriksen flanker task (Eriksen & Eriksen, 1974) assesses the resistance to distractor interference, and for example a Brown-Peterson-like procedure (Friedman & Miyake, 2004; Kane & Engle, 2000) measures resistance to proactive interference.

4.3.2 Oculometry/Eye-Tracking

Eye-Tracking is a technique that accurately assesses a person's eye movements. Oculomotor recordings provide a solid theoretical basis and an easy to implement experimental approach to study inhibitory control. It is widely accepted that changes in gaze position are the result of complex cognitive control and decision-making processes (Glimcher, 2003; Hutton, 2008; Orquin & Mueller Loose, 2013) (for details please refer to section 4.4.2 *Why Humans Make Saccades*).

Video-Based Eye-Tracking. To assess changes in gaze position, a variety of eye-tracking systems are used in modern behavioral research (Duchowski, 2007; Holmqvist et al., 2011). One of them is *video-based eye-tracking*, that is employed in the research projects included in this dissertation. The table mounted EyeLink 1000 eye-tracker system (SR Research, http://www.sr-research.com /EL_1000.html) was used to record eye movements in the laboratory, and an equivalent fMRI suitable eye-tracking system was used in the scanner setting. Please refer to Holmqvist et al. (2011),

[1] The stop signal task instructs a subject to respond to a target stimulus as quickly and accurate as possible. In a certain proportion of trials, e.g., an auditory signal randomly occurs after target onset signaling to withhold the response to the target stimulus. The latency of the stop process (stop-signal reaction time) is an important marker of cognitive control processes involved in stopping.

[2] The Stroop task demonstrates interference in reaction times. For example, naming the color of a word stimulus takes longer and is more prone to errors if the meaning of the word and its ink color mismatch, e.g., the word "green" is printed in red ink.

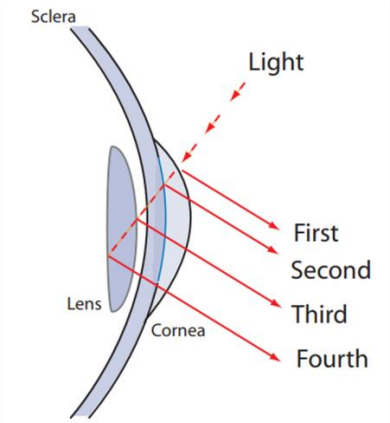
Duchowski (2007) as well as Klein and Ettinger (2019) for a comprehensive introduction to a variety of eye-tracking methodologies and eye-tracking measures. Furthermore, please see Duchowski (2007), Hammoud (2008) or Hansen & Ji (2010) for technical details of video-based eye-tracking.

In short, video-based eye-tracking is a state-of-the-art, non-invasive method to precisely measure a person's point of gaze from an image of the eye, i.e., where a person looks, by tracking the reflection of light from the pupil and the cornea. To do so, an infrared light source shines into a subject's eye. A video camera or other optical sensor tracks the resulting *corneal reflection* (1st Purkinje reflection) (Figure 2) and the center of the pupil (Figure 3) over time. The corneal reflection is the brightest reflection but the infrared light is also reflected further back by the sclera and the lens (Figure 2). The position data of the corneal reflection and the pupil are then used to detect changes in the eye's position, because the position of the corneal reflection changes as the eyes move. Finally, geometrical calculations and a calibration procedure map the position of the pupil's and cornea reflection's geometric centers in x- and y-coordinates on a stimulus (Holmqvist et al., 2011). Modern eye-tracking systems have a sampling frequency of a few Hertz (Hz) up to more than 1000Hz, which translates into one recording cycle of gaze data per millisecond (ms). Hence, the higher the recording frequency, the more precisely one can measure events of the eye.

User-friendly software solutions, such as EyeLink's *Data Viewer* (http://www.sr-research.com /accessories_EL1000_dv.html) are used for viewing, filtering and processing gaze data. The software is further used to detect events of interest in the data stream, such as rapid changes in gaze position and to extract a variety of relevant parameters for statistical data analysis.

Figure 2

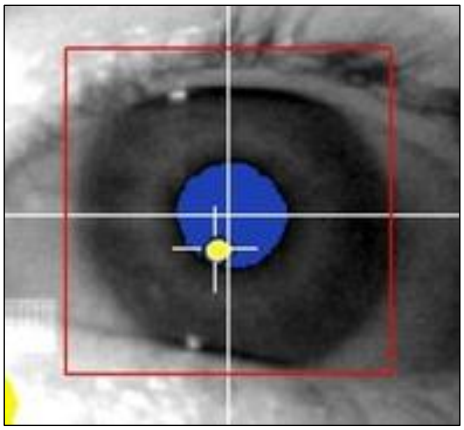
The Four Purkinje Reflections Resulting from Incoming Light



Note. Schematic illustration of a sagital cut through the human eye. The four Purkinje reflections (solid arrows, First to Fourth) result from incoming light (dashed arrows). Adapted from Hansen & Ji (2010).

Figure 3

The Pupil and The Cornea Reflection



Note. The correctly identified pupil (blue circle) and *corneal reflection* (yellow circle) of a subject's left eye. Cross hairs illustrate the pupil's and corneal reflection's geometric center respectively. Eye-tracking device: EyeLink 1000, SR Research. Source: private photograph.

Oculomotor Markers of Inhibition. Popular metrics of rapid changes in gaze position are their direction, amplitude, velocity, acceleration, accuracy and precision among other factors. Please refer to Holmqvist et al. (2011) for a comprehensive summary of oculomotor measures. Studies on oculomotor markers of inhibitory control frequently report response latencies of (a) initial and/or (b) subsequent eye movement responses, (c) fixation rates, (d) directional errors and (e) their correction.

The *latency* of an initial gaze response is defined as the time interval between the onset of a target stimulus and the onset of an oculomotor response. Response latencies resemble decision times. Their underlying decision process is sensitive to a vast variety of task-dependent mental influences (Hutton, 2008). Evidently, the volitional initiation of an eye movement is the result of a variety of different mental processes. In the antisaccade task (Antoniades et al., 2013; Hallett, 1978), for example, increased response latencies in *look away*-trials relative to *look at*-trials suggest time consuming cognitive processes mostly underlying inhibition and saccade programming. Smaller response latencies resemble more efficient underlying mental control processes.

Holding the eye in a stable position is termed *fixation*. Periods in which the eyes are held relatively stable are not incidental pauses until the next eye movement is triggered. The eyes are not stationary during fixation but move slightly by means of microsaccades, drift or tremor in order to hold a visual target on or near the fovea (Martinez-Conde, Macknik, Troncoso, & Hubel, 2009;

Martinez-Conde, Otero-Millan, & Macknik, 2013). Fixation is an active, effortful and dynamic process that involves many brain structures. They play a vital role in the control of eye movements, such as the superior colliculi and medio-posterior cerebellum (Krauzlis, Goffart, & Hafed, 2017).

Response errors, such as (a) an unintentional break of fixation or (b) an eye movement that does not match the task instruction are further markers of inhibitory control. For example, subjects frequently fail to refrain from initiating an eye movement when a stop signal follows a target stimulus moments later. Such saccade errors are interpreted as markers of cognitive demand in tasks including the antisaccade task (Hallett, 1978; Smyrnis et al., 2002), the go/no-go task (Montagnini & Chelazzi, 2009) and the countermanding task (Stuphorn & Schall, 2006), also termed stop signal task. The higher the error rate, the more often the saccade systems fails to inhibit the motor program of a visually triggered saccade towards a target, thus failing to meet task demands.

Corrective eye movements after a response error provide further insights into cognitive control mechanisms and into the architecture of saccade programming processes (Cohen & Ross, 1978; Haller et al., 2008; Tian et al., 2013). In the analysis of eye movement errors, metrics, such as latency (Fischer, Gezeck, & Hartnegg, 2000; Smyrnis et al., 2002), amplitude (Versino, Beltrami, Uggetti, & Cosi, 2000) or frequency (Burkhart Fischer et al., 2000) of corrective eye movements are of particular interest. Surprisingly, frequently involuntary eye movement errors and their correction remain unrecognized by the subject (Mokler & Fischer, 1999). Failures in gaze control likely occur due to deficits in fixation abilities or deficits in voluntary control of eye movements, or both (Fischer et al., 2000).

4.3.3 Brain Imaging

Functional Magnetic Resonance Imaging (fMRI). The non-invasive technique of Magnetic Resonance Imaging (MRI) was developed to create images of the human soft body tissue without using ionizing radiation, such as required for X-ray images (Savoy, 2001). Functional MRI is an adaptation of MRI. fMRI is a non-invasive method in cognitive neuroscience to visualize functionally active brain regions. The key difference between the output of MRI and fMRI is that the former produces structural images of tissue, and the later detects hemodynamic changes induced by neural activity (Savoy, 2001).

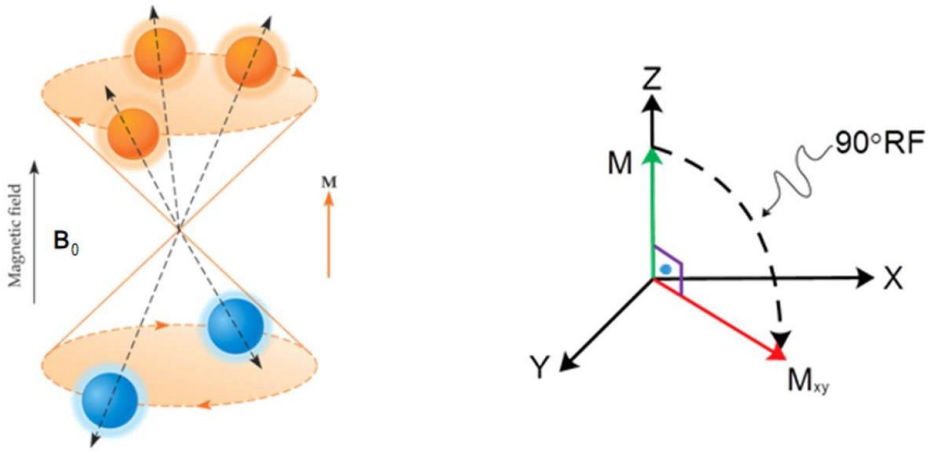
General Physical Principles. The general physical principles of MRI and fMRI have been documented in several text books (Faro & Mohamed, 2006; Huettel, Song, & McCarthy, 2004; Matthews & Jezzard, 2007; Toga & Mazziotta, 2002; Weishaupt, Köchli, & Marincek, 2006) and

research articles (Amaro & Barker, 2006; Buxton, 2013; Glover, 2011; Heeger & Ress, 2002; Logothetis & Wandell, 2004; Savoy, 2001). In short, MRI relies on the magnetic properties of hydrogen atoms of water molecules in the body to produce images. When placed in the strong static permanent magnetic field of an MRI scanner, the majority of otherwise randomly oriented, wobbly spinning (*processing*) protons align parallel to the primary magnet field of a scanner, resulting in a net magnetic vector (longitudinal magnetization) (Figure 4a). The rate at which a proton spins when placed in a magnetic field is termed the *Larmor frequency* (Weishaupt et al., 2006). Radio frequency (RF) pulses with a frequency matching the Larmor frequency, create a second magnetic field perpendicular to the main magnetic field of the scanner (Figure 4b) and disturb the proton alignment causing some protons to (a) flip to a higher energy state and (b) to process in phase, that is in coherence. As a result, longitudinal magnetization decreases, and the net magnetization vector shifts towards a right angle to the primary magnetic field, called *transverse magnetization*. Magnetic gradients along the x-, y-, and z-axis systematically create secondary magnetic fields, that selectively address protons within a slice of tissue or location in three-dimensional space to allow spatial encoding and to create volumetric images (Huettel et al., 2004). Protons emit characteristic RF waves, that are detected by RF coils, when released from displacement and resuming a low energy state in the primary magnetic field, a process called *relaxation*. The resulting increase in longitudinal magnetization over time is termed *T1 relaxation*. Also, protons that processed in phase lose coherences (*dephase*) due to energy transfer between spins (*spin-spin relaxation*), resulting in a decay of transverse magnetization over time called *T2 relaxation*. Additional time-independent inhomogeneities in the scanner's magnetic field contribute to dephasing, referred to as *T2* relaxation*. *T1* and *T2** relaxation times vary depending on tissue composition and structure allowing a classification of tissue types, such as fat, cerebrospinal fluid and grey matter. A computer system then processes the released RF signals and translates them into images (Buxton, 2013; Glover, 2011; Huettel et al., 2004).

Figure 4

Net Magnetization and Transverse Magnetization

a. b.



Note. Schematic illustration of net magnetization (a) and transverse magnetization (b) in MRI physics. (a) The strong primary magnetic field of the fMRI causes most protons to align their axis along the magnetic field lines (B_0) to a parallel state (orange protons). They process in phase with a lower energy level. Some protons align to an antiparallel state with a higher energy level (blue protons). The net magnetization (M) derives from the difference between the number of protons spinning in the parallel state and the number of protons spinning in the antiparallel state. For simplification purposes the figure does not show the protons spinning around their axis. (b) Radio frequency (RF) pulses are supplied while tissues are exposed to the strong magnet of the scanner. The RF pulse causes the net magnetic field (M_z shown in green) to tilt away from the main magnetic field (B_o) into the transverse xy-plane (M_{xy} shown in red). Adapted from Huettel et al. (2014) and Adair et al. (2019).

The BOLD Signal. fMRI uses contrasts between different states of activity to detect differences in magnetic properties of brain regions. It is sensitive to regional increases in oxygenated cerebral blood flow related to neural activations (neurovascular coupling) and uses endogenous hemoglobin for an indirect marker of brain activity (Goebel, 2007; Logothetis & Wandell, 2004).

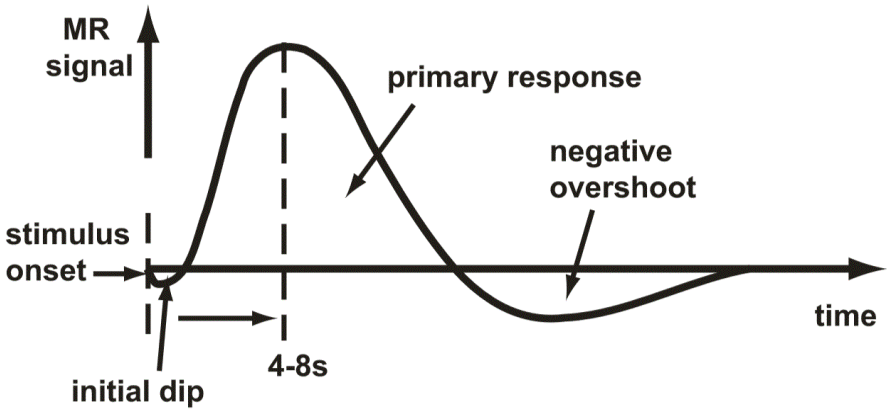
Brain activity that is driven by responses to stimuli or modulations in background brain activity requires the metabolization of glucoses and oxygen (Arthurs & Boniface, 2002; Buxton, 2013; Kornak, Hall, & Haggard, 2011; Matthews & Jezzard, 2007). Upon neural activity, initial oxygen extraction increases the concentration of deoxygenated relative to oxygenated blood, which translates into a slight decrease in the scanner's MR signal (initial dip) until fresh oxygen-containing blood flows in (Figure 5). With a delay of 4 to 8 seconds, the rate and volume of cerebral blood flow to an active brain region rapidly increases, delivering more oxygenated hemoglobin than local oxygen consumption (haemodynamic response). This results in a greater ratio of oxygenated to deoxygenated hemoglobin. At the same time, less oxygen carried by the blood is removed when passing through the capillary bed, and the venous blood is thus more oxygenated (Buxton, 2013).

This smaller oxygen extraction fraction and a corresponding increase in local cerebral blood flow result in an increased oxy-hemoglobin concentration in the blood during brain activity. The smaller oxygen extraction fraction translates into a local increase in the MR signal measured in fMRI termed the venous *blood-oxygenation level dependent* (BOLD) *response* (Arthurs & Boniface, 2002; Bandettini, 2014; Buxton, 2013). After over-compensation with oxygenated blood, the haemodynamic response falls below its initial level (negative overshoot) and returns to baseline after up to 40 seconds (Poser, van Mierlo, & Norris, 2011; Yacoub, Ugurbil, & Harel, 2006). fMRI relies on different magnetic properties of oxygenated and deoxygenated hemoglobin. A higher proportion of paramagnetic oxygenated hemoglobin relative to diamagnetic deoxygenated hemoglobin in the venous blood promotes little distortion to the scanner's magnetic field. More precisely, higher levels of oxygenated hemoglobin slow de-phasing of hydrogen protons after RF pulses, resulting in a flatter *T2**-relaxation curve and a stronger corresponding magnetic resonance BOLD signal relative to baseline. In un-stimulated tissue, higher levels of deoxygenated to oxygenated hemoglobin cause inhomogeneities in the magnetic field, shorten *T2**-relaxation times and decrease the BOLD signal (Heeger & Ress, 2002; Kornak et al., 2011; Matthews & Jezzard, 2007).

The BOLD signal provides a delayed, indirect measurement of brain activity (Figure 6). However, research has suggested a fairly direct relationship between neural activity and the BOLD signal (Arthurs & Boniface, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis & Wandell, 2004; Logothetis, 2003). The BOLD signal measured by fMRI likely reflects the synchronized synaptic input to populations of neurons and intracortical processing in a given area rather than spiking output activity of neurons (Eckstrom, 2010; Logothetis et al., 2001; Logothetis & Wandell, 2004; Logothetis, 2003), although diverging opinions exist (Eckstrom, 2010; Heeger & Ress, 2002). According to a different view, the BOLD signal may resemble changes in the excitation-inhibition balance of glutamatergic and GABAergic cells (Logothetis, 2008). However, these ideas of what the BOLD signal represents might be an over-simplification (Arthurs & Boniface, 2002; Logothetis, 2008). The fMRI BOLD response is influenced by many physiological, biophysical and experimental parameters (Arthurs & Boniface, 2002; Heeger & Ress, 2002; Logothetis & Wandell, 2004; Matthews & Jezzard, 2007). Therefore, a thorough planning of the experimental task, the study design (Henson, 2007) and the data analysis is necessary to separate the signal of interest from noise (Amaro & Barker, 2006).

Figure 5

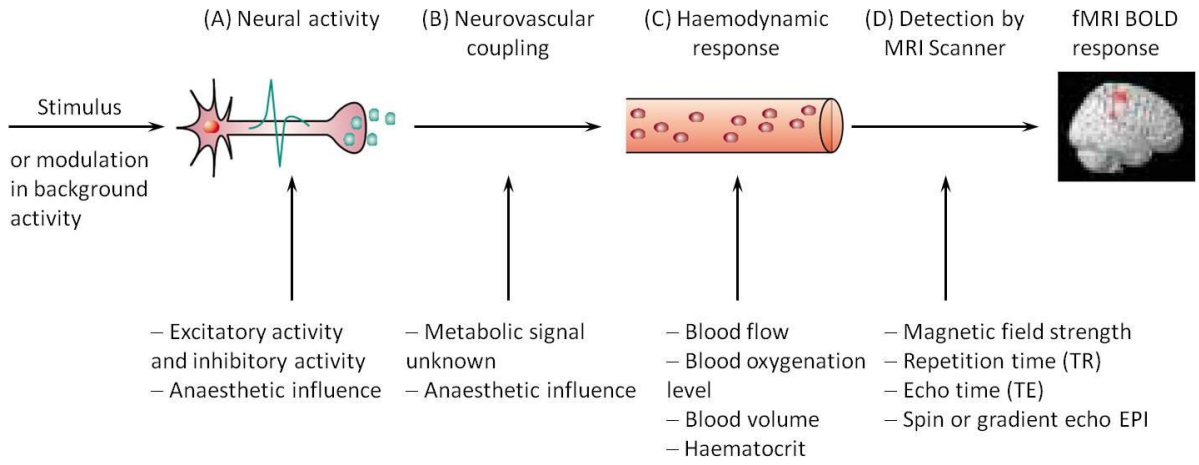
The MR BOLD Signal



Note. Schematic illustration of the blood-oxygenation level dependent (BOLD) magnetic resonance (MR) signal over time following the onset of a stimulus. Adapted from Kornak et al. (2011).

Figure 6

BOLD fMRI as an Indirect Measure of Neural Activity



Note. Constituents of the fMRI BOLD response. The complex connection between an fMRI BOLD response to stimulation or modulation in background activity is dermined by (A) the neural activity to the stimulus or background activity, (B) its relationship to triggering a haemodynamic response (neurovascular coupling), (C) the haemodynamic response itself, and (D) properties of the MRI scanner to detect the haemodynamic response. Adapted from Arthurs & Boniface (2002).

Data Preprocessing and Data Analysis. Several textbooks (Friston, 2007; Huettel et al., 2004; Jezzard, Matthews, & Smith, 2001) and research papers (Friston, 2005; Mumford & Nichols, 2006; Smith, 2004) have documented fMRI data processing and analysis. Publication I and publication II of this dissertation used the *Statistical Parametric Mapping* software package (The FIL Methods Group; http://www.fil.ion.ucl.ac.uk/spm/) for brain image analysis. Therefore, the following section outlines

the methodology of Statistical Parametric Mapping, and summarizes common steps in fMRI image analysis.

Statistical Parametric Mapping (SPM). SPM refers to the *"construction of spatially extended statistical processes to test hypotheses about regionally specific effects"* (Friston, 2005). In their textbook, Friston and colleagues (2007) defined Statistical Parametric Maps (SPMs) as *"fields with values* [one for each volume element called voxel in a volume of interest] *that are, under the null hypothesis, distributed according to a known probability density function such as the Student's t- or F-distribution"*. Any statistical test is used to analyze each voxel. The resulting statistical parameters are then assembled into an image. SPMs are thresholded in height and spatial extent. The probability to reach or exceed a peak in the SPMs by chance over a search area is represented by *p*-values. The *p*-values further allow inferences about the number of activated regions, the number of activated voxels comprising a particular region and about each peak within an activation cluster (Friston, 2007).

Preprocessing. Several mathematical procedures are required to prepare the fMRI data for statistical analysis and to increase the functional signal-to-noise ratio while minimizing the influence of unwanted artifact related variance. For example, sources of artifacts are head motion, physiological oscillations such as the heartbeat, inhomogeneities in the static magnetic field, and potential differences in the timing of image acquisition (Huettel et al., 2004). Following data quality assurance testing, common pre-processing steps are slice time correction, data realignment or motion correction, distortion correction, co-registration and/or normalization as well as temporal and spatial filtering (Strother, 2006; Weber, Mangus, & Huskey, 2015).

Most functional scanning sequences do not acquire every slice of a volume of interest simultaneously but sequentially with 24 slices or more every 1.5 to 3 seconds (Huettel et al., 2004). Slices are often acquired in interleaved sequences, i.e., all odd number slices prior to all even number slices, to minimize the influences of excitation pulsed on adjacent slices. Alternatively, slices are acquired in ascending or descending sequences. If slices are acquired sequentially, *slice time correction* takes into account timing differences between scans of a volume of interest that essentially represent activations of one given time point. Slice time correction employs temporal interpolation that uses data from nearby time points to estimate the magnetic resonance (MR) signal amplitude at onset of the RF pulse at repetition time (TR). Slice time correction is an important preprocessing step, because timing is crucial in many fMRI studies, especially in event related task designs.

A crucial confound in fMRI time series analysis are movements of the subject, in particular head motion. It may lead to data loss at the edges of image volumes, may induce noisy signal intensity changes over time, and may violate the assumption that each voxel represents a unique part of the brain. When motion occurs between slices, a portion of a slice may miss an excitation MR-pulse, and slice time correction may be impaired. *Motion correction* aims to adjust the time series of images in a way that the brain is in the same position in every image (Huettel et al., 2004). Spatial processing involves image *realignment* to adjust for movement-related effects. To do so, a rigid body spatial transformation estimates six movement parameters along the x, y and z-axis (three translational and three rotational) to minimize the sum of squared differences between a scan and a reference scan. These estimates can be integrated as predictor variables in the subsequent analysis. Differences between a time series of images from the same subject are not desired. Further, *unwarping* procedures correct geometric distortions, i.e., artifact related changes in the position *and* shape of a volume over time. Geometric distortions are caused by inhomogeneities in the main magnetic field of the scanner and are particularly severe in regions where there is an air-tissue interface (Ashburner et al., 2013). Unwarping distorted images is a necessary step to ensure that image realignment will sufficiently bring them into a common space.

A following pre-processing step is *co-registration*, a process that links the subject's high-resolution anatomical images (*T1* weighted) to the subject's functional images (*T2* weighted) of lower resolution. Co-registration aims to map low resolution functional information into high resolution anatomical space to enable better anatomical localization of activity within a subject. To do so, the procedure uses a rigid body transformation or sometimes more complex algorithms to minimize head motion related differences between anatomical and functional images and to compensate for image distortions.

A process termed *spatial normalization* subsequently corrects for the subject's variable morphology by transforming each subject's brain so that it matches all other brains in the sample in size and shape. These spatial transformations realign and map the raw fMRI data into a standard anatomical space (e.g., a stereotaxic space). They essentially allow to combine intra-subject, inter-subject and inter-task image volumes and to assign responses to a cortical area under the assumption that data from a certain voxel derive from the same part of the brain (Friston, 2004). *Segmentation*, a process that separates a subject's anatomical image into grey matter, white matter and cerebrospinal fluid images, can be used as an alternative to spatial normalization. Segmentation produces normalization parameters that can be used to write volumes registered with the anatomical image in stereotaxic space.

Temporal filters can remove data variance attributed to noise sources, such as task frequency, physiology or scanner drift, with the aim to improve the functional signal-to-noise ratio. *Spatial filters* smooth functional images, a process often referred to as *blurring*, to minimize remaining differences between scans. Spatial smoothing averages data over adjacent voxels of spatially corrected fMRI data, which reduces the false-positive rate. Filters of the same frequency as the signal of interest maximize the signal-to-noise ratio (Strother, 2006).

1st Level Analysis. Several mathematical approaches exist to determine which voxels of a brain volume are activated by a stimulus within a subject, ranging from simple correlation analysis to advanced modelling (Friston, 2005). To characterize the relationship between experimental manipulations and observed data, fMRI commonly builds on the univariate *General Linear Model* (GLM):

$$y(t) = x(t) * \beta + c + \varepsilon(t)$$

GLM expresses an observed response variable *y(t)* in terms of a linear combination of explanatory variables in a design matrix *x(t)*, where each column of the design matrix has an unknown parameter estimate β indicating its relative contribution to the signal response, plus a constant *c* and an error term *ε(t)*. In terms of fMRI, *y(t)* represents the measured MR-signal and *c* is the signal's baseline intensity, for example. The design matrix "*encodes and quantifies ... knowledge about how the expected* [MR-]*signal was produced*" (Friston, 2007). Each row of the design matrix represents a separate scan, whereas each column, termed *regressor*, represents a cause of the data, either an experimental effect or a confound. Regressors are convolved with a haemodynamic response function to imitate the brain's neurophysiological response to the stimulation. A good fit between the model and the observed data means that the data were probably caused by the stimulation or causes included in the GLM. "*Effects of interest* [for example, activation differences between experimental conditions or between an experimental condition and baseline] *are specified by a vector of* [regressors'] *contrast weights that give a weighted sum of parameter estimates termed contrast*" (Friston, 2007). Statistical inferences about parameter estimates are made using Student's *t*-statistics or *F*-statistics under the null hypothesis (H_0) that the β values of two regressors respectively two or more regressors do not differ significantly.

2nd Level Analysis. Subject's first level contrasts are transferred to a group-level random effects analysis to test results across different scanning sessions and/or across groups of subjects. Student's *t*-statistics test whether (a) activations of one experimental condition significantly differ from zero (one sample t-test), whether (b) activations of two experimental conditions obtained within the same

group of subjects differ significantly (paired t-test), or (c) whether activations of one experimental condition obtained in two different groups of subjects differ significantly (two sample t-test). *F*-statistics test within group effects and between group effects as well as their interaction across a number of different contrasts. Importantly, in fMRI analysis, a respective test statistic is applied for each voxel included in the analysis. Consequently, the false positive error rate (Type I error) inflates due to multiple comparisons. Different methods exist to control the false positive rate for multiple comparisons of resulting statistical activation maps, such as *Bonferroni correction, Family-wise-error* (FWE) *correction* or *Gaussian random field theory* (GRFT). These methods adjust the Type I error probability to .05 at the global level. Voxels that survive a corrected statistical threshold display significant mean stimulation related MR-signal changes strongly linked to brain activity (Friston, 2007) (Figure 6).

To accurately classify activated brain regions according to their position in standard anatomical space, several brain atlases, such as the *PickAtlas* (Maldjian, Laurienti, Kraft, & Burdette, 2003) and the *SPM Anatomy toolbox* (Eickhoff et al., 2005, 2007) are available.

4.4 Saccades: A Model System of Inhibitory Control

Humans perceive a sharp, stable visual image of their surrounding environment, although their eyes rapidly move about three times per second as they change focus from one point to another within the visual field (Findlay & Gilchrist, 2003; Rayner, 1998). This economical behavioral mechanism ensures detailed visual encoding of the environment.

4.4.1 Definition

Saccades are fast, jerky, ballistic movements of the eye followed by a time when the eye is relatively stationary (Gilchrist, 2011). Detailed characteristics of saccades have been documented in several textbooks (Findlay & Gilchrist, 2003; Holmqvist et al., 2011; Klein & Ettinger, 2019; Liversedge, Gilchrist, & Everling, 2011).

4.4.2 Why Humans Make Saccades

Saccades are a metabolically economical mechanism that point the eye's fovea to a region of interest in the visual field (Liversedge et al., 2011). For anatomical details of the human eye please refer to Figure 7 in this dissertation and to Willoughby et al. (2010) as well as Hughes (2007). The *fovea centralis* is an area, that spans less than 2° of the visual field located at the central part of the human retina (Figure 7a). The fovea has a high density of color sensitive photoreceptors, termed *cones*, that are important for detailed color vision during daylight. In contrast, peripheral areas of the

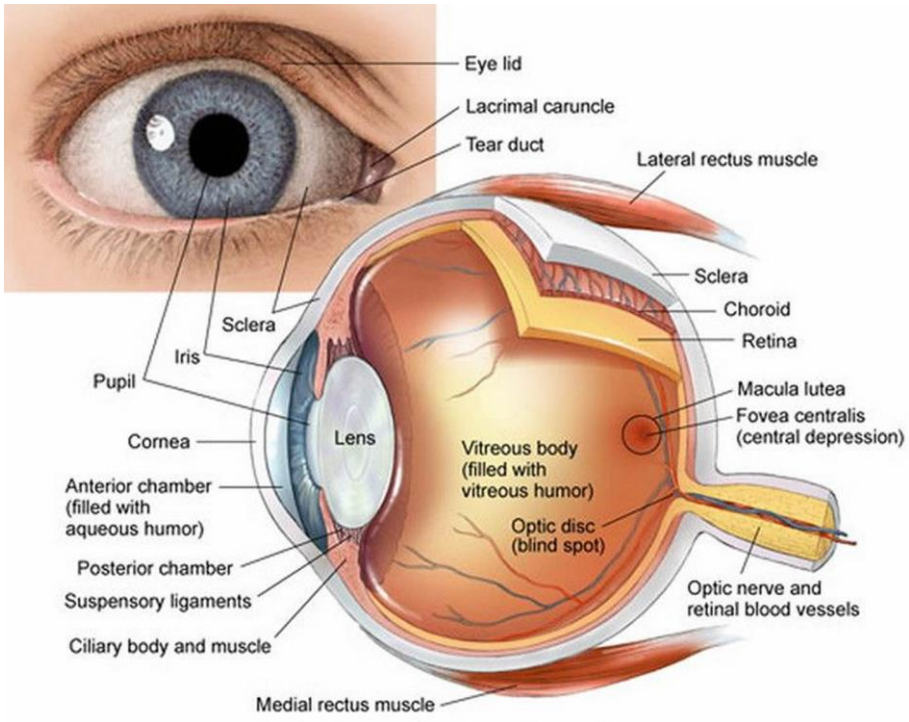
retina have a large density of *rods*, photoreceptors that are sensitive to light and support vision under dim light conditions (Baars & Gage, 2010; Holmqvist et al., 2011). Hence, saccades compensate for dramatically poorer peripheral vision. Also, foveal vision strongly determines proper visual stimulus recognition. Six extraocular muscles (Figure 7b) move the relatively light and mobile eyeball in a way that minimizes the movement duration and maximizes the number of foveal fixations on points of interest in the visual field (Liversedge et al., 2011). In this way saccadic eye movements minimize moments of decreased visual accuracy and also compensate for metabolically costly head movements. The characteristics of the fovea in interaction with the saccade frequency provide an optimal mechanism for the visual system to encode visual input. Peter E. Hallett (1978) concluded in his original research on the human saccade system: "*The saccade system is optimized for foveation*". The author also addressed the efficient interaction of two complementary mechanisms in saccade generation: a fast mechanism yields a first rough approximation of the saccade goal. A second co-activated but slower mechanism generates a more precise estimation of the saccade goal that can be used to rapidly initiate a second saccade to account for response offset or response errors.

In sum, saccades play a critical role in a variety of human behavior, for example, when obtaining information about the visual environment, searching for a specific visual target, when reading texts and when orienting to a salient event in the visual field (Findlay & Walker, 1999).

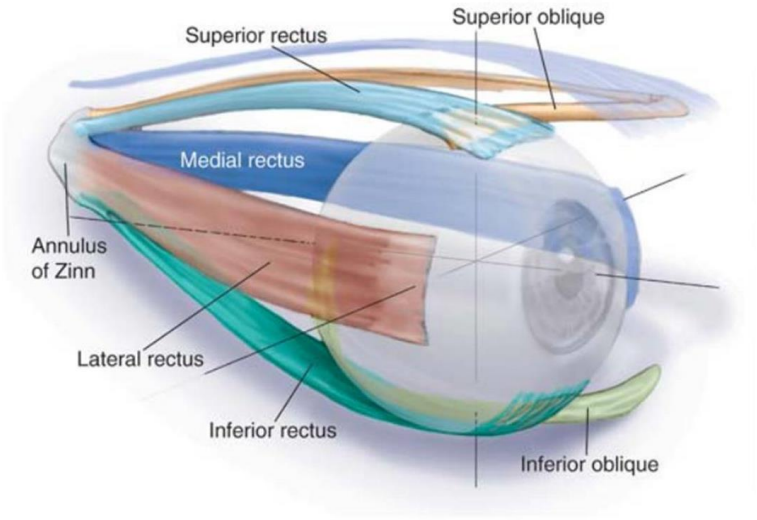
Figure 7

The Structure and Extraocular Muscles of The Human Eye

a.



b.



Note. Schematic drawings of the structure of the right human eye viewed from above (a) and the extraocular muscles involved in movements of the right human eye (b). Adapted from https://healthjade.com/human-eye/ last, accessed January 27th, 2019 and Hughes (2007).

4.4.3 Why Saccades Are Relevant for Psychologists

An old and rather philosophical quote by the English pediatrician and author Thomas Phaer (c. 1510-1560) states: "*The eyes … are the wyndowes of the mynde, for both ioye & anger … are seene … through them*" (Simpson & Speake, 2008). In modern slightly adapted terms: "*The eyes are the window to the soul*" (Simpson & Speake, 2008). This saying implies that the eyes tell something about a person her words might not, which is true from a psychological perspective: indeed, an individual's gaze provides insights into processes underlying thought and behavior (Hutton, 2008).

Saccades are closely related to a wide range of cognitive processes including attention, working memory, learning and decision making, that in turn influence the saccades' characteristics (Hutton, 2008). This is clearly shown by the fact that it takes around 60ms for a retinal neural signal to be transmitted through the brain to trigger a saccade (Carpenter, 1981). However, the time it takes for a reflex-like saccade to be initiated in the laboratory is much longer, around 200ms (Smyrnis et al., 2002) and even longer in some real-world settings (Malcolm & Shomstein, 2015). A bundle of cognitive processes, such as deciding where to look or whether to look at all, take place during this extra time (Hutton, 2008). Apart from this, saccades represent an ontogenetically highly automated and phylogenetically old attentional function of the human brain (New, Cosmides, & Tooby, 2007). They are a metabolically economical behavioral system that has prevailed throughout evolution to ensure proper visual encoding of the environment as well as rapid behavioral adaptation to changes in the environment. Saccades involve a direct sensory transformation of retinal information into an appropriate motor signal (Munoz & Everling, 2004). The time it takes to initiate a saccade, termed *saccade latency*, varies randomly between trials such as all reaction times. It gives insight into underlying decision processes because decision times are directly linked to reaction times (Antoniades et al., 2013; Hutton, 2008; Noorani & Carpenter, 2016). Saccade generation is the result of signals related to basic stimulus properties (*bottom up*) and one's own current goals and intentions (*top down*). For a summary of factors that determine saccade latencies refer to Sumner (2011).

From an admittedly detailed psychological perspective, real-world vision involves among other things (a) resolving the competition between two or more competing stimuli in the visual field, (b) a complex evaluation and stimulus interpretation to decide which stimulus is worth looking at or whether to look at all and (c) suppression of simple stimulus-response transformation processes in the colliculus brain region to withhold inadequate early eye movement responses in favor of deliberate decision making and looking (Hutton, 2008).

In sum, eye movements or eye fixations are the result of some complex decision processes. They can be used to investigate neurocognitive mechanisms central to the healthy brain (Eckstein, Guerra-Carrillo, Miller Singley, & Bunge, 2017; Popa et al., 2015) and to psychopathological disorders (Hutton & Ettinger, 2006) that represent information processing deficits (Hutton, 2008). Evidently, eye movements are (a) internally generated in the absence of external stimulation, (b) triggered by external stimulation, or (c) withheld, even though externally stimulated (Ludwig, 2011).

4.4.4 Prosaccades and Antisaccades

In psychological research, a series of saccadic eye movements are distinguished and classified according to their characteristics and underlying cognitive mechanisms. Saccadic eye movements can be classified as *mostly reflexive* visually-guided saccades triggered by a sudden onset target and *mostly volitional* endogenously guided saccades triggered and influenced by factors, such as expectations or learned rules (Hutton, 2008). Visually-guided saccades towards a stimulus are often referred to as *prosaccades.* Some authors claim that prosaccades reflect a *visual grasp reflex,* which is a difficult to control reflexive orienting response towards a visual stimulus (Hutchinson et al., 2014; Munoz & Everling, 2004; Theeuwes, Kramer, Hahn, & Irwin, 1998), although other research questions this view (Hutton, 2008). The prosaccade task instructs subjects to follow their prepotent response tendency to perform a rapid shift in gaze position towards a sudden onset peripheral target after a random period of central fixation.

Latencies of endogenously guided saccades usually exceed latencies of exogenous visually-guided prosaccades (Irving, Tajik-Parvinchi, Lillakas, González, & Steinbach, 2009; Smyrnis et al., 2002). These prolonged latencies likely reflect additional cognitive processes related to stimulus response mapping according to an external cue.

The Antisaccade Task: A Tool to Access Executive Control. The antisaccade task (Hallett, 1978) is a variant of the standard prosaccade task. The antisaccade task (Hallett, 1978) instructs subjects to volitionally inhibit their prepotent response tendency to perform a saccade towards a sudden onset peripheral target. Instead, the antisaccade task requires subjects to perform a shift in gaze position towards the mirror target location. This type of response is referred to as an *antisaccade* (Antoniades et al., 2013). In everyday terms: do not look, but look away.

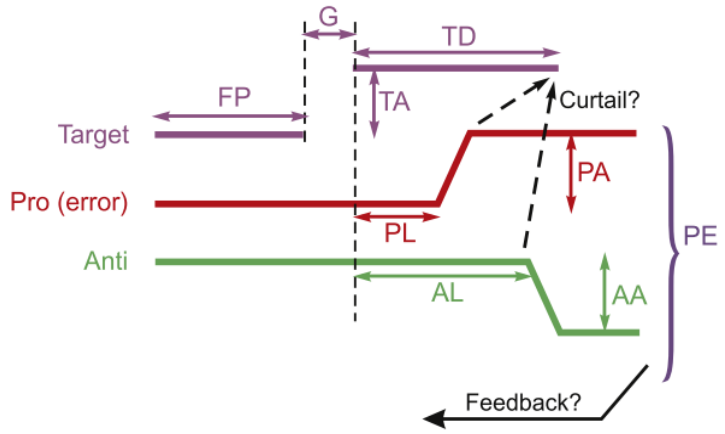
In contrast to tasks that demand prosaccades, the antisaccade task addresses top-down control processes mainly underlying prepotent response inhibition and saccade programming (i.e., predominantly inversion of the saccade target vector) (Herweg et al., 2014; Moon et al., 2007; Zhang & Barash, 2004).

Common antisaccade performance parameters include (a) the *antisaccade latency* defined as the time interval between target onset and beginning of the initial antisaccade eye movement and (b) *the directional error rate*, defined as the proportion of initial eye movements directionally incompatible to the trial instruction (Figure 8). Other informative metrics are the peak velocity, the amplitude or the landing position of correct or erroneous antisaccades. Latencies of correct antisaccades typically exceed latencies of correct prosaccades by around 100ms or more (Hutton, 2008; Irving et al., 2009; Smyrnis, Evdokimidis, Stefanis, Avramopoulos, & Constantinidis, 2003), reflecting time consuming top-down processes. Even healthy volunteers frequently fail to control the powerful urge to perform a prosaccade in a significant number of trials. Typical antisaccade error rates range around 20% in healthy samples (Hutton, 2008; Smyrnis et al., 2002) but may vary substantially within samples (Smyrnis et al., 2003) and between samples of different age (Harsay, Buitenweg, Wijnen, Guerreiro, & Ridderinkshof, 2010) or mental health (Everling & Fischer, 1998; Radant et al., 2010). Erroneous initial prosaccades are often followed by a rapid correction in gaze direction in antisaccade trials (Lee, Abegg, Rodriguez, Koehn, & Barton, 2010; Tatler & Hutton, 2007). Different explanations for antisaccade errors have been discussed in the literature (reviewed by Hutton, 2008), including deficits in inhibition (Barton, Pandita, Thakkar, Goff, & Manoach, 2008; Everling & Fischer, 1998), deficits in canceling the prepotent prosaccade motor program (Schachar et al., 2007), a failure to activate the antisaccade task goal (Reuter, Jäger, Bottlender, & Kathmann, 2007) or slowing in the antisaccade programming (Massen, 2004; Talanow et al., 2016). Overall, antisaccade performance is mediated by working memory (Crawford, Parker, Solis-Trapala, & Mayes, 2011; Taylor & Hutton, 2007), visual spatial attention (Kristjánsson, Chen, & Nakayama, 2001), and practice/learning effects (Dyckman & McDowell, 2005), among other factors including incentives (Duka & Lupp, 1997) and task instruction (Taylor & Hutton, 2007).

A comprehensive summary of informative statistical eye movement measures applicable to research in the antisaccade task and further gaze measures of position, numerosity, latency and distance can be found in several textbooks (Duchowski, 2007; Holmqvist et al., 2011; Klein & Ettinger, 2019).

Figure 8

Schematic Representation of an Antisaccade Trial



Note. Schematic illustration of an antisaccade trial over time and its performance parameters. Here, subjects fixate a target that moves to the left in a step-like manner after a short offset period (purple line). An error prosaccade response (red line) and a correct antisaccade response (green line) are shown. FP = foreperiod; G = gap duration; TA/TD = target amplitude and duration; PL/AL = pro- and antisaccade latency; PA/AA = pro- and antisaccade amplitude; PE = proportion of error (prosaccade) responses. Task designs may limit the target onset duration as well as the time window in which a response can be given. The task may provide response related feedback at the end of a trial. Adapted from Antoniades et al. (2013).

4.4.5 Saccade Task Designs

When planning research in the model system of saccades, it should be noted that task features as well as the task protocol affect cognitive processes addressed in the prosaccade and antisaccade task (for a summary refer to Smyrnis, 2008). A common experimental manipulation in saccade tasks concerns the temporal relationship between the offset of a central fixation stimulus and the onset of the peripheral target stimulus (Figure 9): following a random period of central fixation, the peripheral target appears either shortly after (gap design) or simultaneously (step design) to the offset of the central fixation stimulus. In another task variant, the central fixation stimulus remains visible throughout a trial while the peripheral target is presented (overlap design). Typically, prosaccade latencies and antisaccade latencies are reduced in gap designs (*gap effect*; Saslow, 1967) as compared to overlap designs (Crevits & Vandierendonck, 2005; Fischer, Gezeck, & Hartnegg, 1997; Fischer & Weber, 1997). Please refer to Hutton (2008) for an interpretation of mechanisms underlying the gap effect.

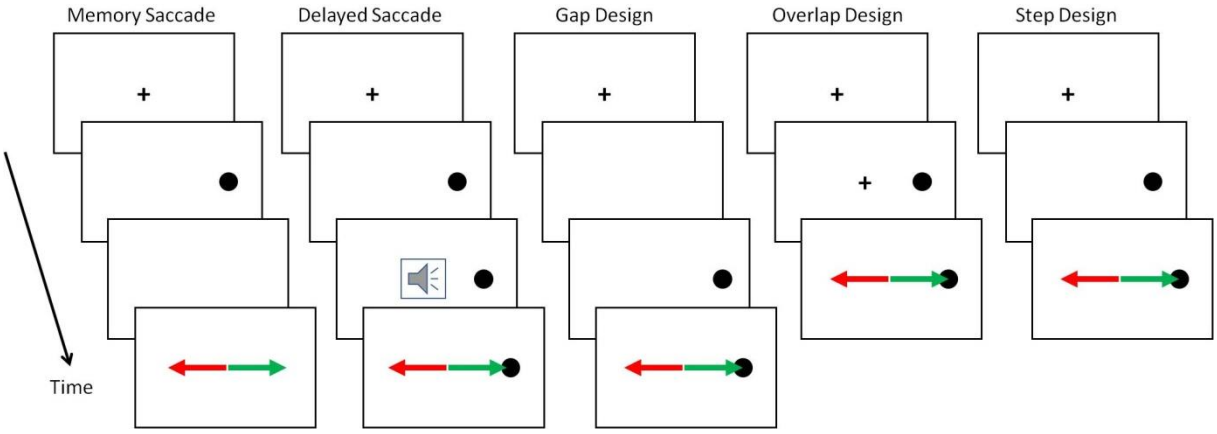
Some variants of the prosaccade and antisaccade task instruct subjects to delay their response until a go signal, for example an auditory signal, is presented (Ettinger et al., 2008). So called *delayed prosaccades* and *delayed antisaccades* demand the inhibition of a response upon target onset, provide time to allow sufficient response preparation and may not require demanding vector

transformation (Hutton, 2008). A commonly used variant of the delayed-saccade task cues saccade initiation after the onset of a briefly shown target stimulus. So called *memory-guided saccades* demand a great amount of working memory to hold the target location active in mind (Landgraf, Amado, Bourdel, Leonardi, & Krebs, 2008). Memory-guided saccades address sustained activity in the human posterior parietal cortex (PPC) (Schluppeck, Glimcher, & Heeger, 2005), intraparietal sulcus (IPS) (Brown, Goltz, Vilis, Ford, & Everling, 2006) and parietal cortical areas equivalent to the monkey's lateral intraparietal area (LIP) that plays a crucial role in processing sensory information for memory saccade generation (Li et al., 1999). Findings on memory-guided saccade latencies are somewhat inconsistent and latencies may depend on task conditions (Felßberg & Dombrowe, 2018): some studies reported longer latencies for memory-guided saccades than non-delayed visually-guided saccades (Felßberg & Dombrowe, 2018; Landgraf et al., 2008). Other research found the opposite effect, i.e., faster memory saccades than non-delayed saccades (Massendari, Lisi, Collins, & Cavanagh, 2018). Error rates of memory-guided saccades and visually-guided saccades do not differ significantly (Brown et al., 2004), but memory saccades are found to be spatially less accurate than visually-guided saccades (Hutton, 2008; Landgraf et al., 2008).

In all mentioned task design variants, prosaccade and antisaccade trials are either presented in blocked (Zeligman & Zivotofsky, 2017) or interleaved sequences (Ethridge, Brahmbhatt, Gao, McDowell, & Clementz, 2009). Further, saccade trials may vary in trial-type probability (Massen, 2004; Pierce & McDowell, 2016) or target-location probability (Jóhannesson, Haraldsson, & Kristjánsson, 2013). All these manipulations may affect task performance measures. Recommendations on the design of antisaccade tasks and informative outcome measures are summarized in an internationally standardized antisaccade protocol (Antoniades et al., 2013).

Figure 9

Prosaccade and Antisaccade Task Variants



Note. Schematic illustration of a variety of prosaccade and antisaccade task designs. Prosaccade trials (green arrows) and antisaccade trials (red arrows) are either presented in a block-wise manner of the same type of saccade within an experimental block, in mixed task designs with randomized interleaved order of prosaccade and antisaccade trials or in predefined sequences of trials. The trial order, onset durations, gap periods and inter-stimulus-intervals are subject to individual preferences in accordance with the goal of the research. Adapted from Hutton (2008).

4.4.6 Objectivity, Reliability and Validity

Important and fundamental features of sound eye-tracking research are unbiased, stable and truthful gaze parameters as measurements of behavior and its underlying cognition. Highly standardized eye-tracking procedures and data analysis algorithms as well as the internationally standardized antisaccade protocol (Antoniades et al., 2013) serve as the foundation for objective gaze research in the context of the antisaccade task.

In principle, oculomotor measures are reliably stable performance indicators with good test-retest reliabilities and high internal consistencies for a variety of parameters in healthy subjects (Ettinger et al., 2003; Klein & Fischer, 2005a; Raemaekers, Vink, van den Heuvel, Kahn, & Ramsey, 2006; Smyrnis, 2008; Wöstmann et al., 2013). With regards to the antisaccade task, antisaccade latencies (Ettinger et al., 2003; Roy-Byrne, Radant, Wingerson, & Cowley, 1995; Wöstmann et al., 2013), antisaccade error rates (Ettinger et al., 2003; Wöstmann et al., 2013; for an exception see Roy-Byrne et al., 1995) and other parameters (Versino et al., 1993) have shown good test-retest reliability in the laboratory setting. However, the *gain* – defined as the ratio of eye velocity over target velocity – seems to be an unreliable performance indicator in the antisaccade task (Ettinger et al., 2003). Prosaccade and antisaccade latencies as well as antisaccade error rates and other parameters have good to excellent reliability in terms of internal consistency (Klein & Fischer, 2005b). Furthermore, antisaccade and prosaccade measurements reflect stable trait components and are largely unaffected by situational factors (Meyhöfer, Bertsch, Esser, & Ettinger, 2016). In the fMRI scanner setting, antisaccade

latencies and error rates have been reliable performance indicators, too (Raemaekers et al., 2007). Raemaekers and colleagues (2007) showed highly reliable prosaccade and antisaccade fMRI activation maps at the group-level, but the reliability of the antisaccade versus prosaccade contrast, a marker of cognitive control, was only moderate.

In sum, prosaccades and antisaccades are valid markers of cognitive control given their objective measurement and reliable performance measures. To be noted, prosaccades and antisaccades are subject to some degree of variability due to task repetition (Ettinger et al., 2003; Talanow & Ettinger, 2018) and practice (Dyckman & McDowell, 2005).

4.4.7 Neural Correlates of Prepotent Response Inhibition in The Antisaccade Task

The neural underpinnings of saccadic eye movements have been subject to a growing body of research (Brown et al., 2006; Ettinger et al., 2008a; Munoz & Everling, 2004). Saccadic eye movements reliably activate an oculomotor control network enclosing brain regions of the frontal eye fields (FEFs), the supplementary eye fields (SEFs) (Schlag-Rey, Amador, Sanchez, & Schlag, 1997), the IPS, visual areas and also some subcortical areas (McDowell, Dyckman, Austin, & Clementz, 2008) (see Figure 10). Antisaccades commonly activate this basic saccade circuitry to a stronger extent (Jamadar, Fielding, & Egan, 2013) excluding visual cortex (McDowell et al., 2008) and/or recruit additional frontal and subcortical areas. Indeed, functional neuroimaging in humans has revealed a fronto-subcortical-parietal network strongly linked to the generation and voluntary control of saccadic eye movements in the antisaccade paradigm (Everling & Fischer, 1998; Hutton & Ettinger, 2006; Jamadar et al., 2013; McDowell et al., 2008). This finding is consistent with evidence from positron emission tomography (PET) (Jamadar et al., 2013; Sweeney et al., 1996), electroencephalography (EEG) (Everling & Fischer, 1998; McDowell et al., 2005) and animal single cell recordings (Munoz & Everling, 2004).

Additional regions sensitive to antisaccades are the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), the basal ganglia, the thalamus, the caudate nucleus (CN) and putamen as well as the anterior cingulate cortex (ACC) and the cerebellum (Jamadar et al., 2013; Munoz & Everling, 2004).

The FEF likely mediates saccade preparation and perceptual decision-making preceding saccade generation. This view derived from the observation that activity in the FEF negatively correlates with saccadic reaction times (Cieslik, Seidler, Laird, Fox, & Eickhoff, 2016; Connolly, Goodale, Goltz, Munoz, & Jason, 2005; Everling & Munoz, 2000). Furthermore, stronger FEF activity prior to antisaccade generation may suggest heightened inhibitory processes (McDowell et al., 2008). Medial and lateral FEF may serve different functions: the medial FEF might be more specifically involved in

volitional antisaccades and the lateral FEF in volitional antisaccades and visually-guided reflex-like prosaccades (Jamadar et al., 2013; McDowell et al., 2008).

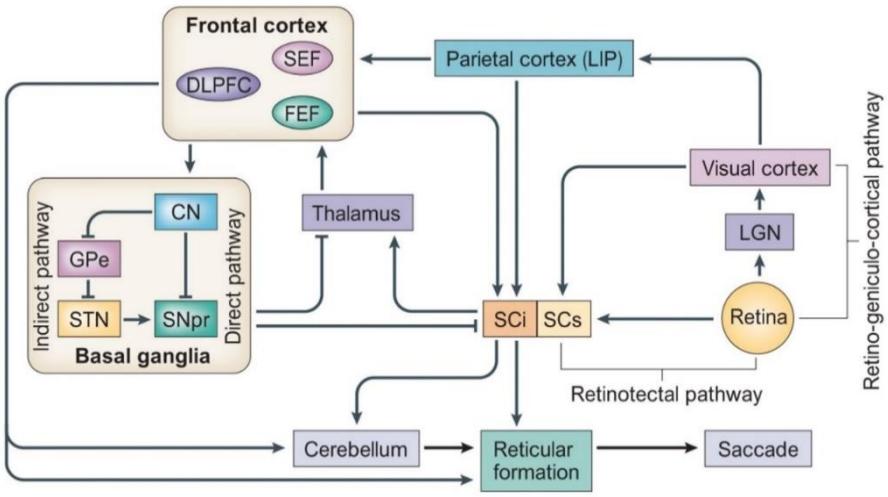
The SEF is the oculomotor extension of the supplementary motor area (SMA) (Schall, Stuphorn, & Brown, 2002). SEF has shown increased activity associated with movement generation during prosaccades (McDowell et al., 2008). However, SEF also plays a crucial role in antisaccade preparation, likely due to its inhibitory signals to suppress prosaccade preparation signals in antisaccade trials.

The human parietal cortex is involved in spatial processing (Corbetta, Kincade, Ollinger, McAvoy, & Gordon, 2000; Nobre, Gitelman, Dias, & Mesulam, 2000). It is widely accepted that the role of the IPS in antisaccades is linked to processes of saccade vector inversion, i.e., the translation of the visual target location to its mirrored image location (Brown, Vilis, & Everling, 2008; Herweg et al., 2014; Jamadar et al., 2013). An alternative view suggests an inhibitory role of the inferior parietal cortex (IPC) in antisaccade generation (Ettinger et al., 2008). The cortical eye fields and IPS exert a regulatory influence on the superior colliculus (SC), a structure crucially linked to the transformation of visual input signals into motor commands due to its retinotopic organization via a hyperdirect pathway (Gandhi & Katnani, 2011). The SC yields its influence via a direct (CN; substantia nigra pars reticulata, SNpr) and an indirect (CN; external globus pallidus, GPe; subthalamic nucleus, STN) basal ganglia pathway (Isoda & Hikosaka, 2011; Munoz & Everling, 2004) (Figure 10). Signals are further mediated by thalamus, cerebellum and premotor circuits in the reticular formation before the saccade is initiated. Additional activations in antisaccades relative to prosaccades may be related to performance monitoring and conflict detection (ACC) (Ford, Goltz, Brown, & Everling, 2005) or to biasing signals and general inhibition of unwanted prosaccade responses (right VLPFC, right DLPFC) (Ettinger et al., 2008).

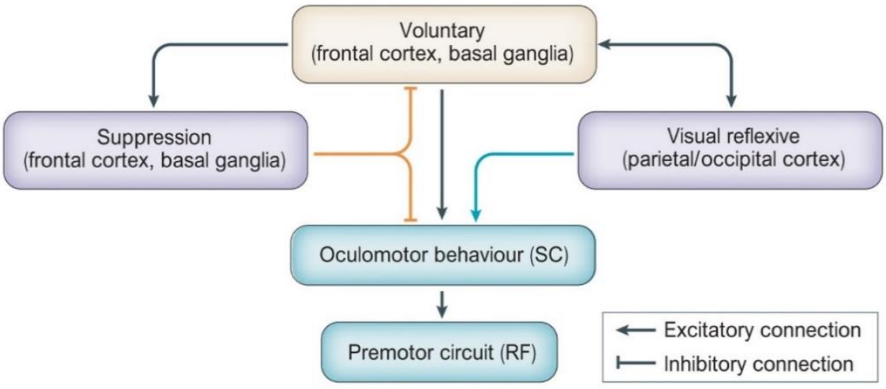
Figure 10

The Neural Circuitry of Saccadic Eye Movement Control

a.



b.



Note. Schematic illustration of neural network components and their neural pathways (a) as well as their functional role (b) in control of reflex-like and voluntary eye movements. Arrows display excitatory connections. One-way connections resemble inhibitory connections. DLPFC = dorsolateral prefrontal cortex; SEF = supplementary eye fields; FEF = frontal eye fields; CN = caudate nucleus; GPe = external segment of the globus pallidus; STN = subthalamic nucleus; SNpr = substantia nigra pars reticulata; SCi = inferior segment of the superior colliculus; SCs = superior segment of the superior colliculus; LGN = lateral geniculate nucleus. Adapted from Munoz and Everling (2004).

5. Evidence Integration Models of Saccadic Inhibition in The Antisaccade Task

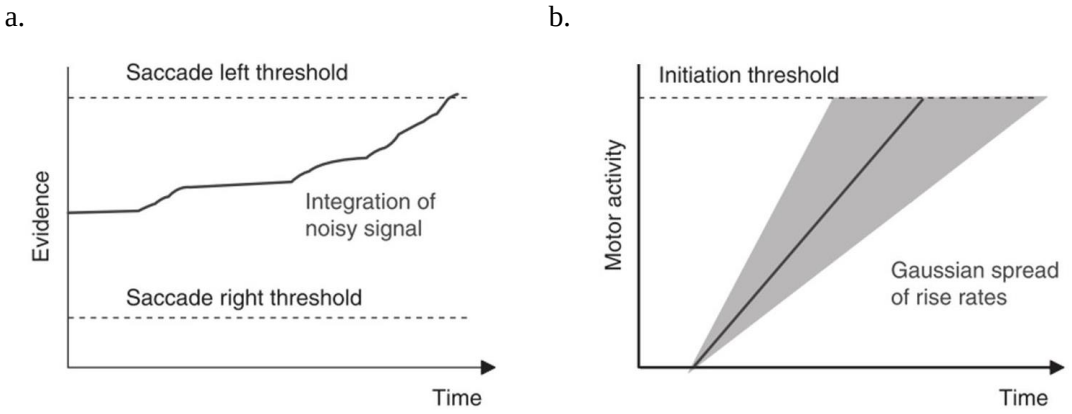
The following section outlines relevant research on functional models that provide a structured representation of the processes involved in saccadic decision-making. It introduces *evidence integration models* in the context of visually-guided saccade tasks to lay the theoretical foundation for a first fMRI project that was published during the course of this dissertation.

Evidence integration models are based on the principle that activity in a decision unit or a motor unit steadily rises, i.e., accumulates, from a baseline level towards a threshold. With respect to saccadic eye movements, a saccade is initiated when saccade related activity within the saccade system reaches an execution threshold (Ludwig, 2011; Sumner, 2011). Theoretical accounts on saccade programming in the antisaccade task have been twofold: early accounts postulated linear saccade programming in the antisaccade task, which requires active stopping of one saccade program to allow another (Hallett & Adams, 1980; Hallett, 1978). More recent accounts suggested parallel saccade programming that does not require an explicit stopping mechanism (Henderson & Ferreira, 1990; Massen, 2004; McPeek, Skavenski, & Nakayama, 2000; Mokler & Fischer, 1999; Morrison, 1984; Theeuwes et al., 1998).

Accumulator models on saccade generation differ not only in the assumption of sequential or parallel saccade programming, but also in their underlying assumptions about how the programming process proceeds. Some accumulator models have assumed a temporally dynamic noisy signal and define a relative stopping criterion in the form of a particular amount of net evidence in favor of one alternative over another (Usher & McClelland, 2001; Vickers, 1970). For example, so called *diffusion decision models* (Figure 11a) build on the idea of a noisy binary decision process that accumulates information from a starting point towards one of two response criteria (Ratcliff & Mckoon, 2008; Smith & Ratcliff, 2004). In the context of the antisaccade task, that means from onset of a visual peripheral stimulus towards a criterion for either a leftward or a rightward saccade. The rate of stochastic accumulation of information, termed *drift rate*, depends on the quality of information extracted from the stimulus. The drift rate is rather noisy and follows a random walk within a trial (Sumner, 2011). On the other hand, *ballistic* accumulator models (Figure 11b) have not assumed any temporal dynamic noise (Brown & Heathcote, 2008; Brown & Heathcote, 2005; Carpenter & Williams, 1995). Both types of accumulator models, noisy and ballistic, have in common that they define an *absolute stopping rule*: a decision process stops when one decision signal reaches a threshold criterion (Ludwig, 2011).

Figure 11

Diffusion Decision Models and Ballistic Accumulation Models in Saccade Generation



Note. Schematic illustrations of the decision process underlying saccade generation. Variability in saccade latencies derives from variability in stochastic accumulation within a trial (a; diffusion model) (see Ratcliff & Mckoon, 2008) or from an accumulation rate that follows a Gaussian distribution to a threshold level (b; ballistic accumulation model) (see Carpenter, 1981). Adapted from Sumner (2011).

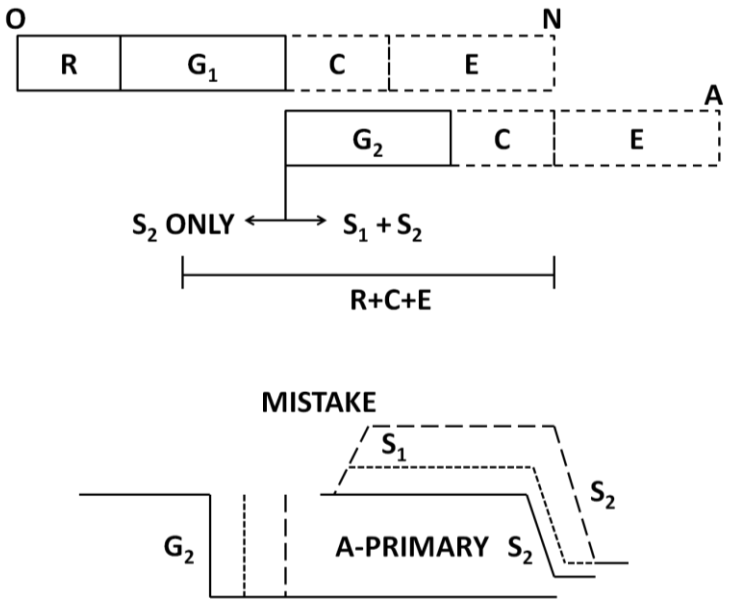
5.1 Linear Saccade Programming

Initially, models of saccade decision making in the antisaccade task have suggested a linear saccade programming sequence of a primary prosaccade followed by a subsequent antisaccade (Hallett & Adams, 1980; Hallett, 1978). This view implies the assumption that a prosaccade signal is canceled first before a voluntary antisaccade is generated. Hallett (1978) exemplified the idea of linear saccade programming by relating the antisaccade task to a two-step experiment where "*the subject eliminates his reflex to the first step* [the prosaccade] *and then creates an equal and opposite step to which he reflexly responds* [the antisaccade]". Consequently, such linear process models require some sort of stopping or inhibition mechanism. Hallett (1978) reasoned that the initial prosaccade goal is *degraded* or *substituted* in antisaccade trials around 130ms to 150ms before the antisaccade is initiated.

Hallett and Adams (1980) further elaborated the view of a sequential saccade programming process. The authors postulate that a retinal signal automatically triggers a reflex-like prosaccade. In their model, a *goal redefinition* process not described in detail, is required to cancel the initial prosaccade signal (Figure 12). The same goal-redefinition process provides the saccade goal for the following internally generated (anti)saccade. According to this view, erroneous initial prosaccades resulted from insufficient processes of goal-redefinition (Guitton, Buchtel, & Douglas, 1985; Hallett & Adams, 1980).

Figure 12

Sequential Saccade Programming in The Antisaccade Task



Note. Schematic drawing of the timing for the antisaccade task. In the upper figure, the upper row resembles programming of a primary prosaccade (N) triggered by the onset of a stimulus (O) over time. Underlying programming steps are processing of the retinal stimulus (R), primary saccade goal definition (G_1) as well as computational (C) and efferent delays (E) that follow saccade goal definition. An antisaccade (A), respectively second saccade (S_2), depends on a process of saccade goal redefinition (G_2). In the lower figure, G_2 interrupts programming of the initial saccade (S_1) in favor of S_2 as illustrated by the gap. According to this view, prosaccade programming and antisaccade programming are sequential processes. The outcome is an antisaccade (A-Primary) in case G_2 begins before G_1 is finished. An error prosaccade (Mistake) results in case G_1 finishes prior to G_2. Adapted from Hallett and Adams (1980).

5.2 Parallel Saccade Programming

5.2.1 General Introduction

A more recent strand of research suggests that opposing prosaccade and antisaccade decisions are generated at least partially in parallel, i.e., simultaneously, in the antisaccade task. The reason for refining the model assumption on saccadic decision making was that current behavioral findings in saccades are not compatible with the theoretical view of sequential saccade programming.

Point of reference are extremely short correction times of error saccades of around or less than 100ms (Godijn & Theeuwes, 2002; McPeek et al., 2000; Theeuwes et al., 1998), respectively short inter-saccadic intervals (ISIs) of erroneous prosaccades and corrective antisaccades in the antisaccade task (Amador, Schlag-Rey, & Schlag, 1998; Ettinger et al., 2005; Mokler & Fischer, 1999; Tatler & Hutton, 2007). ISIs can show latencies much shorter than would be expected if the corrective antisaccade were a response to the error prosaccade (Mokler & Fischer, 1999; Tatler & Hutton, 2007) and sometimes ISIs are as low as 0ms (Mokler & Fischer, 1999).

Further support for the parallel programming hypothesis comes from a negative correlation between prosaccade latencies and antisaccade error rates and vice versa (Massen, 2004; Talanow et al., 2016). This finding can be interpreted as evidence of a competitive race between the prosaccade and antisaccade decision signal towards an execution threshold. The faster decision signal (indicated by shorter latencies) is more likely to reach the execution threshold first (indicated by higher error rates of the opposing decision). The parallel programming account assumes that antisaccade errors arise as a consequence of insufficient response activation, whereas in sequential programming saccade errors are a result of insufficient inhibition of the erroneous response tendency. The parallel saccade programming hypothesis is further supported by relatively short fixations during reading (Morrison, 1984; Radach, Heller, & Inhoff, 1999) and research on gaze behavior in natural scene viewing (Wu et al., 2013). However, the extent to which a correct and an incorrect saccade response are programmed in parallel is yet unclear (Hutton & Ettinger, 2006).

5.2.2 The LATER Model by Roger Carpenter

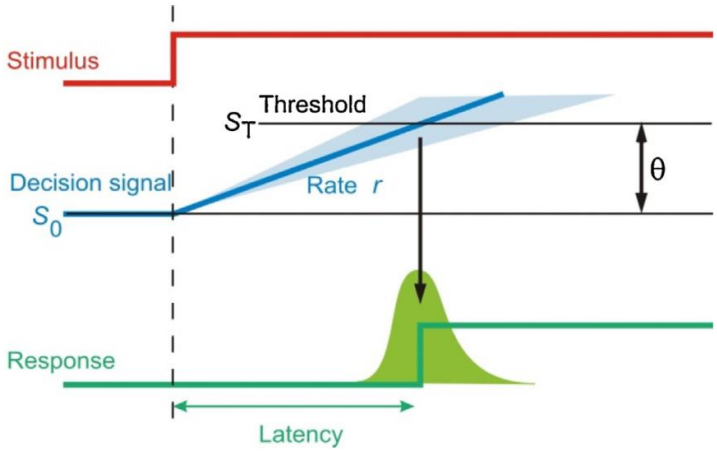
Average latencies of stimulus-guided saccades by far exceed the purely anatomical benchmark of 60ms from visual stimulus presentation to saccade initiation (Noorani & Carpenter, 2016). This observation suggests further time-consuming decision-making processes prior to saccade initiation beyond the simple transformation of a visual-spatial information into an appropriate motor signal. From this basic idea, the *linear approach to threshold with ergodic rate (LATER) model* emerged (Carpenter & Williams, 1995). The LATER model focused on reaction times and their variability to draw an economical and simplistic image of their underlying decision mechanisms and to explain behavior in simple and complex tasks. It proposed a stochastic decision mechanism that is driven by extraction of uncertain evidence from the noisy outside world, for example evidence regarding the presence of a visual stimulus (Carpenter & Williams, 1995).

In general, the LATER model assumed that a reaction time is the "*culmination of a process that proceeds at a certain rate towards completion*" (Noorani & Carpenter, 2016) (Figure 13). Upon onset of a stimulus, a decision signal S rises at a steady rate r from an initial value S_0 until it reaches a certain threshold criterion ($S_T = S_0 + \theta$) or likelihood level at which the target is presumed to be present ($S = S_T$). S_0 resembles the prior probability of the target being present. A decision is made when the decision signal is sufficiently strong enough to justify a decision, which then initiates an associated response (Carpenter & Williams, 1995; Noorani & Carpenter, 2016). Manipulations that cause changes in S_0, r (mean rate of rise μ and signal variance σ^2) or S_T could all result in changes in the response latency distribution (Figure 14). Such manipulating factors are (a) uncertainty regarding the urgency with which a response needs to be made, (b) prior response probability, or (c) the reward related to a response (Noorani & Carpenter, 2016).

Neurophysiological findings associated with the mechanisms of LATER and accumulator models in general (Munoz & Everling, 2004) underlined its validity as a decision-making model (for a summary refer to Noorani & Carpenter, 2013; Noorani & Carpenter, 2016).

Figure 13

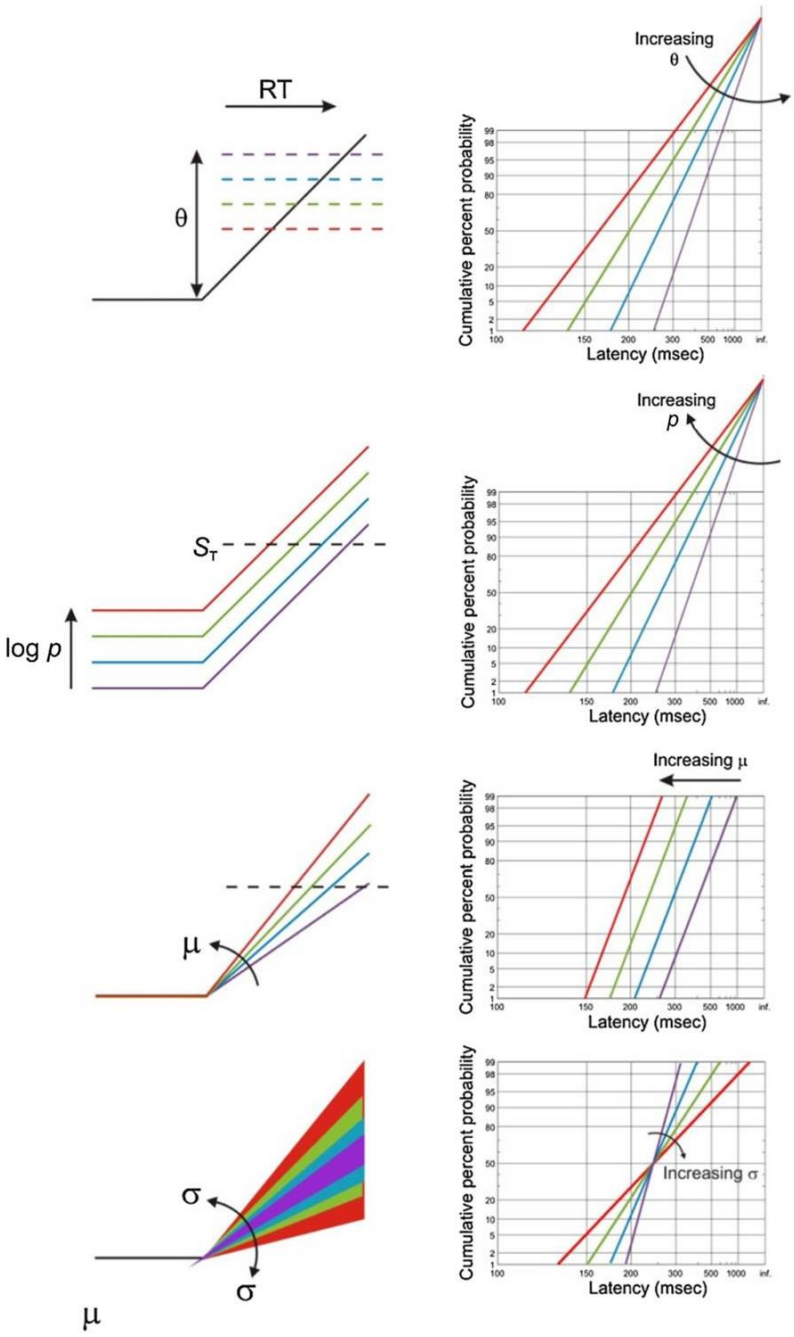
The LATER Model



Note. Schematic illustration of the process underlying response decision-making according to the LATER model. Upon stimulus onset, an initial decision signal S_0 begins to rise in a somewhat constant accumulation rate (r) until it reaches some decision threshold ($S_T = S_0 + \theta$), triggering an associated response. The accumulation rate varies from trial to trial in a Gaussian manner (mean μ, variance σ^2) resulting in a skewed latency distribution shown in green. Adapted from Noorani and Carpenter (2016).

Figure 14

Relationship of LATER Model Parameters and The Saccade Latency Distribution



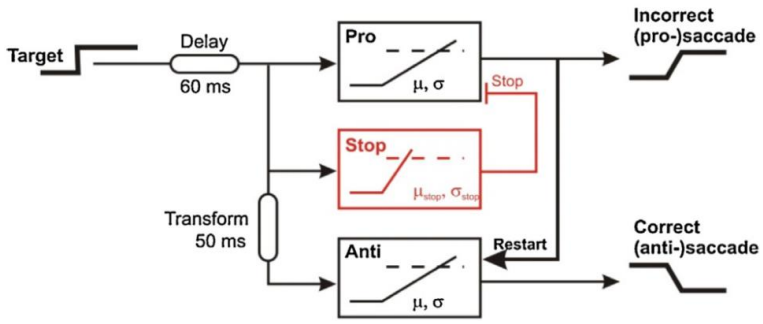
Note. Schematic that shows how variations of parameters in the LATER model (left column) effect parameters in a reciprobit plot of saccade latencies (right column). A reciprobit plot is a cumulative histogram that uses a probit scale on the y-axis and reciprocal scale on the x-axis to arrange data on a straight line if the data follows a Gaussian distribution. Top figure: changes in the urgency with which to respond (θ) alter reaction times (RTs) in proportion. Second top figure: as the prior probability (log p) of a certain movement vector increases, RTs decrease in proportion. Second lowest figure: variation in the decision signal's mean rate of rise (μ) leads to horizontal, self-parallel translation of the reciprobit plot. As μ increases, RTs decrease. Response distributions at different μ all follow a Gaussian shape. Bottom figure: alterations in the decision signal's variance (σ^2) generate changes in the slope of the reciprobit plot with no change in median response latency. Adapted from Noorani and Carpenter (2016).

LATER is a convincing model to predict different performance indicators in the antisaccade task on the basis of behavior in the normal prosaccade task. Predictable parameters include median latencies and latency distributions of correct antisaccades and incorrect prosaccades even at different target probabilities (Noorani & Carpenter, 2013) and corrective saccades (Noorani & Carpenter, 2014).

According to the LATER model, antisaccade decision making involves two *identical* accumulator units, one initiating the prosaccade and one initiating the antisaccade, and an independent stop unit that serves to suppress the prosaccade unit via a stop signal (Figure 15) (Noorani & Carpenter, 2013; Noorani & Carpenter, 2016). The model assumes that a signal is delayed for about 60ms after target onset due to non-decisional factors attributed to signal transduction by receptors and synaptic or signal conduction delays (Noorani & Carpenter, 2016). Then, the signal triggers a synchronic accumulation process in the prosaccade unit and in the stop unit at specific rates towards respective thresholds. Signal accumulation in the antisaccade unit – with parameters *identical* to the prosaccade unit - is triggered after a 50ms transformation delay during which spatial inversion of the saccade target vector takes place, as known from the LIP brain region in non-human primates (Zhang & Barash, 2004). The prosaccade and antisaccade accumulator units race against each other. A correct antisaccade is initiated when the stop unit's signal reaches threshold prior to the prosaccade decision signal, thereby sending out a signal that stops evidence accumulation in the prosaccade unit in favor of the antisaccade decision. It is speculated that the origin of the stop signal is in the basal ganglia, FEF or DLPFC (Munoz & Everling, 2004). An incorrect prosaccade results when the stop unit does not succeed in canceling the accumulation in the prosaccade unit before it reaches the response threshold. The amount of sensory evidence available to a subject to make a decision changes a signal's rate of rise in the accumulation process but not the initial level of the decision signal. Weaker evidence is best represented by slower accumulation, hence a flatter accumulation slope, and vice versa (Figure 14, second lowest illustration).

Figure 15

The LATER Model in Antisaccades



Note. Schematic of the LATER model in antisaccades with two identical units for prosaccade and antisaccade generation (mean rate of rise μ, standard deviation of the decision signal σ). A target signal triggers a synchronic accumulation process in the prosaccade unit and in the stop unit (μ_{stop}, σ_{stop}) at specific rates towards respective thresholds. In correct antisaccade trials, the stop unit cancels the erroneous prosaccade decision signal in favor of the antisaccade decision. An incorrect prosaccade results when the stop unit does not succeed in canceling the accumulation in the prosaccade unit before it reaches the response threshold. Initiation of an erroneous prosaccade restarts accumulation in the antisaccade unit to generate a corrective antisaccade response. Adapted from Noorani and Carpenter (2016).

5.2.3 Trial Frequency Manipulation by Cristina Massen

A central element of Carpenter's LATER Model in antisaccade generation is the stop unit to inhibit the prepotent prosaccade signal in antisaccade trials (Figure 15). A different accumulation model on antisaccade programming that does *not* depend on the existence of an explicit stop signal was proposed in a publication by Massen (2004).

In the model, prosaccade and antisaccade accumulation start simultaneously upon target onset. These decision signals compete and race against each other such as horses in a horse race until one of them reaches a threshold towards execution (Hutton, 2008; Massen, 2004). Both accumulation processes are thought to be independent from each other, and the *difference* between the two is attributed to their relative *speed* of accumulation, a key difference to identical saccade accumulator units in Carpenter's LATER model. That way Massen's model does not depend on the existence of a stop unit to cancel prosaccade generation in favor of antisaccade generation. In this framework inhibition errors are caused by the fact that the prosaccade signal reaches the execution threshold prior to the antisaccade signal as a result of a faster accumulation rate. Massen (2004) confirmed her model approach in a behavioral study. The author manipulated conscious attentional processes by varying the trial frequency respectively trial probability to generate expectations to either perform a prosaccade or an antisaccade. Subsequent studies employed the saccade-type frequency manipulation that followed the logic to selectively alter the accumulation speed, where a high stimulus frequency is associated with faster accumulation processes (Chiau et al., 2011; Pierce,

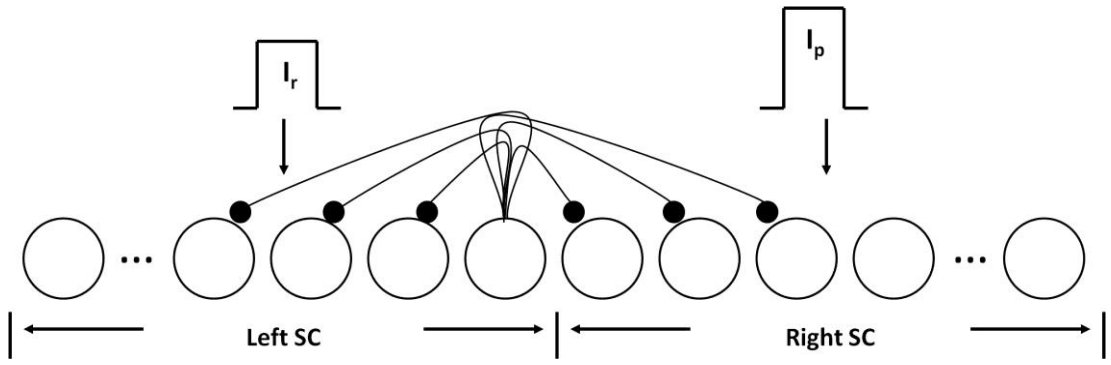
McCardel, & McDowell, 2015; Pierce & McDowell, 2016). Antisaccade latencies and antisaccade error rates decreased as the probability to perform an antisaccade increased. Hence, an antisaccade error is not the consequence of insufficient inhibition of the reflex-like prosaccade but of insufficient activation of the voluntary antisaccade (Eenshuistra, Ridderinkhof, & van der Molen, 2004; Hutton, Joyce, Barnes, & Kennard, 2002; Reuter, Herzog, Endrass, & Kathmann, 2006; Reuter & Kathmann, 2004). The frequency manipulation had little to no effect on prosaccade latencies. Massen (2004) did not report effects on prosaccade error rates.

5.2.4 Neural Decision-Making Model in The Superior Colliculus by Vassilis Cutsuridis

The group around Vassilis Cutsuridis published further research that drew on Carpenter's LATER model. Cutsuridis' competitive race account of antisaccade performance (Cutsuridis, Kahramanoglou, Smyrnis, Evdokimidis, & Perantonis, 2007; Cutsuridis, Kumari, & Ettinger, 2014; Cutsuridis, Smyrnis, Evdokimidis, & Perantonis, 2007; Cutsuridis, 2015) addresses several short comings of the LATER account, e.g., the fact that LATER is unable to produce *only* error prosaccades that are not followed by corrective antisaccades. As can be seen in Figure 15, a *restart* process always follows an erroneous prosaccade initiating accumulation of evidence in favor of the corrective antisaccade. Cutsuridis challenged the existence of a stop signal involved in decision-making processes underlying antisaccade performance. Instead his model proposed the competition via lateral inhibition between decision signals coding the volitional antisaccade and decision signals coding the erroneous prosaccade in build-up neurons in the intermediate layers of the SC during preparation of an antisaccadic eye movement (Cutsuridis, Smyrnis, et al., 2007; Cutsuridis, 2015) (Figure 16). The two decision processes are integrated at opposite SC locations. As opposed to LATER, the build-up neurons represent *non-linear* accumulators of incoming information that gradually build up their activity until reaching a threshold criterion. If the threshold criterion is exceeded, SC burst neurons are released from inhibition and their discharge results in the initiation of an eye movement. Short-range lateral excitation and long distance lateral inhibition was assumed between all neurons in the SC network (Cutsuridis et al., 2014). The model implied the assumption that a planned input of the antisaccade decision signal (I_p) originating from the frontal cortices is always stronger than the reactive input of the erroneous prosaccade decision signal (I_r) originating from the posterior parietal cortices. At a behavioral level, this means that the antisaccade is always expressed even in case an error prosaccade is expressed first. Cutsuridis' model accounted for latencies of error prosaccades, antisaccades and corrected antisaccades as well as for error rates of healthy and non-healthy subjects performing the antisaccade task (Cutsuridis, 2015).

Figure 16

Neural Network Model of The Superior Colliculus for Antisaccades



Note. Schematic of a neural network model of the intermediate layer of the superior colliculus (SC). Neurons are represented as rate nodes. The model assumes short-range lateral excitation and long-distance lateral inhibition between all nodes in the network. During preparation of an antisaccadic eye movement, the left SC is activated by a reactive input (I_r) (i.e., an error prosaccade decision signal), whereas the planned input (I_p) (i.e., the antisaccade decision signal) stronger activates the right SC ($I_p = 1.5* I_r$). The strengths of both inputs follow a Gaussian shape and compared to I_r, I_p is delayed by 50ms (not shown). The figure does not show the subsequent activity of build-up neurons encoding I_r and I_p competing in a *non-linear* race towards an execution threshold followed by response initiation when it is exceeded. Please refer to Cutsuridis, Smyrnis, et al. (2007) and Cutsuridis et al. (2014) for details on model parameters and mathematical formalisms. Adapted from Cutsuridis (2015).

5.3 The Neural Basis of Parallel Saccade Programming

Several behavioral accounts have supported the model assumption of parallel saccade programming in the antisaccade task as outlined in section 5.2 *Parallel Saccade Programming* of this dissertation. The next step is to examine whether this model assumption is also confirmed by evidence at the neuronal level. Single neuron studies (McPeek, Han, & Keller, 2003; McPeek & Keller, 2002) and brain imaging research (Hu & Walker, 2011) have investigated the neural basis of parallel saccade programming. This strand of research seeks to answer questions of (a) where the competitive integration of saccadic decision signals takes place in the brain, (b) whether it involves different brain activations within the underlying neural circuitry, or (c) if the two saccades are mediated by separate pathways (Walker & McSorley, 2006).

Single neuron studies emphasized the role of the SC in parallel saccade programming (McPeek et al., 2003; McPeek & Keller, 2002)**.** McPeek and Keller (2002) showed that neural activity of an initial saccade and a subsequent second saccade are simultaneously maintained on a common motor map in SC in the case of short ISIs. Their research supports the hypothesis of competitive integration of temporally overlapping saccade signals within the same neural system. Increased activity around the time of the second saccade may reflect preparatory processes of prior response selection or may

enhance the saliency of the saccade target location to enable advance response preparation. Behavioral findings support this competitive integration account (McSorley, McCloy, & Williams, 2016; Walker & McSorley, 2006).

It is plausible to assume that parallel saccade programming addresses distinct cortical pathways. When planning successions of reflexive and voluntary saccades, for example, the reflexive saccade is mediated by a subcortical/collicular circuitry, and the voluntary saccade rather relies on frontal cortex structures and the basal ganglia (Munoz & Everling, 2004) (Figure 10). Indeed, brain imaging has pointed to a vital role of the FEFs (Hu & Walker, 2011; Murthy et al., 2007) and PPC (Hu & Walker, 2011) in parallel saccade programming.

In FEF, visual and movement-related neurons may enable rapid and accurate correction of error saccades. In the rhesus monkey, timing of movement-related FEF activity predicted the latency of corrective saccades in visual search (Murthy et al., 2007), and visual FEF neurons established and maintained a representation of the saccade target location (McPeek & Keller, 2002; Murthy, Thompson, & Schall, 2001). Movement-related FEF neurons code the production of the corrective saccade (Murthy et al., 2007). Increased FEF activation in parallel versus serial saccade programming has been linked to processes underlying advanced temporal preparation and higher saliency of the second saccade goal (Hu & Walker, 2011). The authors suggested that these FEF activations mediate activity in other top-down areas, such as the SC – an assumption supported by the general understanding of the neural circuitry of saccadic eye movement control (see section 4.4.7 *Neural Correlates of Prepotent Response Inhibition in The Antisasccade Task* and Figure 10). Interestingly, movement-related activity which begins before an error signal arises in medial frontal cortex suggests a neural mechanism of saccade control that can correct saccade errors before performance monitoring signals or afferent visual processing detect the error (Murthy et al., 2007). This corrective mechanism thus involves at least partial parallel response preparation.

Parallel versus single saccade planning in double-step paradigms (Hu & Walker, 2011) is accompanied by elevated parietal cortex activations, which may reflect processes of spatial programming and spatial remapping of the saccade goal in preparation of subsequent saccades. The authors stated that spatial remapping compensates for the retinal displacement produced by the first saccade in the double-step task and thereby enabled the accurate saccade following a change of fixation. However, in line with the common understanding of the neural circuitry in eye movement control, it is rather likely to assume a processing funnel that involves *both*, separate yet parallel representations of saccade goals early in the processing stream *and* final response selection on a common SC motor map later in the downstream process (Findlay & Walker, 1999; Munoz & Everling, 2004).

The neural basis of parallel saccade programming has been investigated in the context of saccadic double-step paradigms (Hu & Walker, 2011; McSorley et al., 2016; Walker & McSorley, 2006), visual search tasks (McPeek et al., 2003; McPeek & Keller, 2002; Murthy et al., 2007) and investigations on corrective saccades (Murthy et al., 2007). However, the neural basis of parallel saccade programming had not been investigated by means of neural imaging in the *antisaccade paradigm*, yet. This was achieved in the first published project of this dissertation.

5.4 Publication I

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.

As outlined in section 5.2.3 *Trial Frequency Manipulation by Cristina Massen*, recent theoretical accounts explain performance in the antisaccade task in terms of parallel programming of exogenous and endogenous saccade signals. This approach is linked to the horse race metaphor. Behavioral research in the antisaccade task suggests that the trial frequency selectively alters endogenous or exogenous programming processes. More specifically, trial infrequency is thought to slow saccade generation, whereas trial frequency is thought to facilitate saccade generation (Massen, 2004; Noorani & Carpenter, 2016).

The current fMRI study investigated the neural mechanisms underlying inhibitory control processes in parallel saccade programming. An initial fMRI experiment aimed to assess effects on saccade programming processes and saccade performance induced by low versus high saccade trial frequencies. The study further explored the robustness of this frequency manipulation in a subsequent laboratory study. Here, a separate sample of healthy volunteers performed the same task as was used in the initial fMRI experiment. The research hypothesized to reveal cortical regions that significantly mediate executive control functions initiated by the competition of exogenous and endogenous saccade signals. It was further assumed to find consistent behavioral results in the initial fMRI experiment and in the subsequent laboratory experiment.

Sixteen subjects, half of them female, performed a mixed antisaccade and prosaccade task in an event-related fMRI task design. Antisaccade trial frequency (25% versus 75%) varied across blocks in pseudo-randomized order. Three experimental blocks respectively contained either frequent antisaccades (18 out of 24 trials) and infrequent prosaccades or infrequent antisaccades (18 trials out of 72 trials) and frequent prosaccades. Blocks were separated by 30 seconds of central fixation.

At the behavioral level, effects of *Condition* (antisaccade, prosaccade) and *Frequency* (infrequent, frequent) as well as their interaction on saccade latencies and directional error rates were analyzed. The study further analyzed the reactive BOLD signal of correctly performed saccades in a random effects flexible factorial design with the factors *Condition* and *Frequency*. It was assumed that the low saccade probability of a respective type of saccade within a block increases cognitive control demands to correctly perform that type of saccade (Pierce et al., 2015; Pierce & McDowell, 2016). Hence, the antisaccade versus prosaccade contrast as a function of antisaccade frequency served as

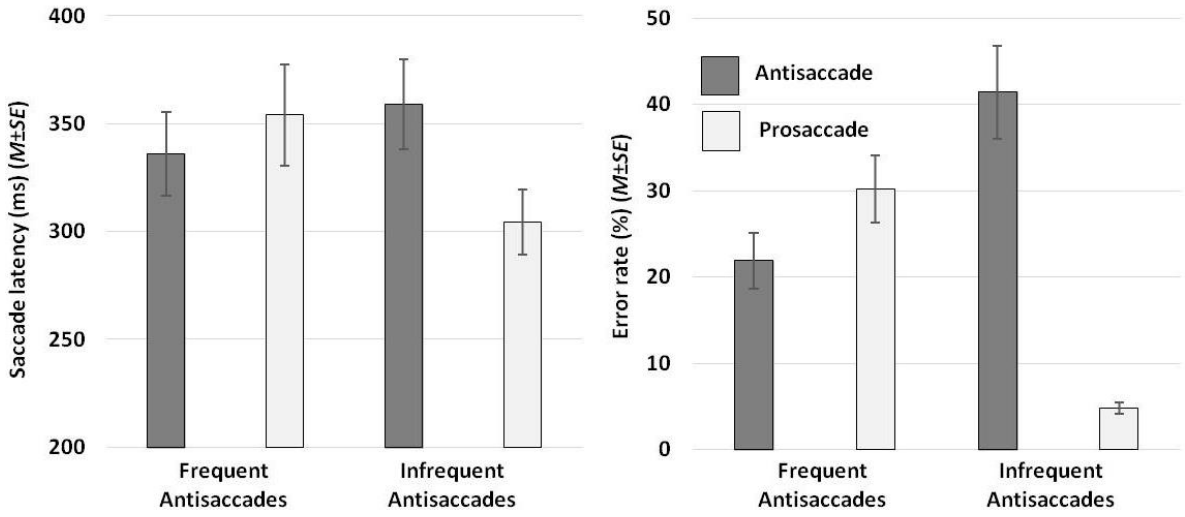
a marker of increased cognitive control in blocks of infrequent antisaccades relative to blocks of frequent antisaccades. The opposite pattern illustrated increased cognitive control in blocks of frequent antisaccades relative to infrequent antisaccades. Further contrasts assessed the main effect of antisaccade versus prosaccade performance and the main effect of performance in infrequent versus frequent saccade trials on the reactive BOLD signal.

The behavioral results confirmed that saccade programming processes were sensitive to the saccade frequency manipulation (Figure 17). Antisaccade latencies were lower and prosaccade latencies higher in frequent relative to infrequent antisaccade blocks. The same pattern is true for directional error rates. These findings were broadly replicated in the laboratory study. In line with the competitive integration model, these findings suggest that a saccade frequency reduction slows programming processes resulting in a relative disadvantage in the race to an execution threshold against an opposing facilitated decision signal (Hutton, 2008; Massen, 2004). At the BOLD level, increased cognitive control in blocks of infrequent antisaccades relative to blocks of frequent antisaccades were accompanied by BOLD signal increases in bilateral parietal cortex (inferior parietal lobule, IPL; SPL; IPS; supramarginal gyrus, SMG) and left precentral gyrus (PrCG), including medial frontal gyrus (MeFG) and inferior frontal junction (IFJ) (Figure 18). These areas reflect task-relevant components of a fronto-parietal network underlying cognitive control in saccades (Jamadar et al., 2013; McDowell et al., 2008). They are stronger activated because the slowed saccade signal requires additional cognitive control for correct saccade performance. Increased cognitive control in blocks of frequent antisaccades relative to infrequent antisaccades revealed BOLD signal changes in bilateral temporal cortex (superior temporal gyrus, STG; transverse temporal gyrus, TTG; rolandic operculum) extending into insula and in VMPFC. These areas comprise components of a *default mode network*, that is more activated during rest or non-task conditions than during task (Raichle & Snyder, 2007; Raichle, 2015; Raichle et al., 2001). Indeed, bilateral temporal cortex and VMPFC were deactivated or more strongly deactivated in cognitive control of infrequent antisaccades in the study (Figure 18), suggesting strengthened deactivations of non-task areas to suppress non-task related and task-goal distracting processes, thus facilitating performance (Gusnard, Akbudak, Shulman, & Raichle, 2001; Gusnard & Raichle, 2001).

To sum up, the current publication investigated the neural basis of saccadic decision making in the antisaccade task. The saccade frequency manipulation altered saccade-programming processes in favor of the parallel saccade programming account. The neural evidence suggested that saccadic decision-making operated in a way that increased BOLD signals within components of the saccade network may have contributed to additional cognitive demands required to bias saccade decisions. Task-irrelevant cortical areas were deactivated or more strongly deactivated.

Figure 17

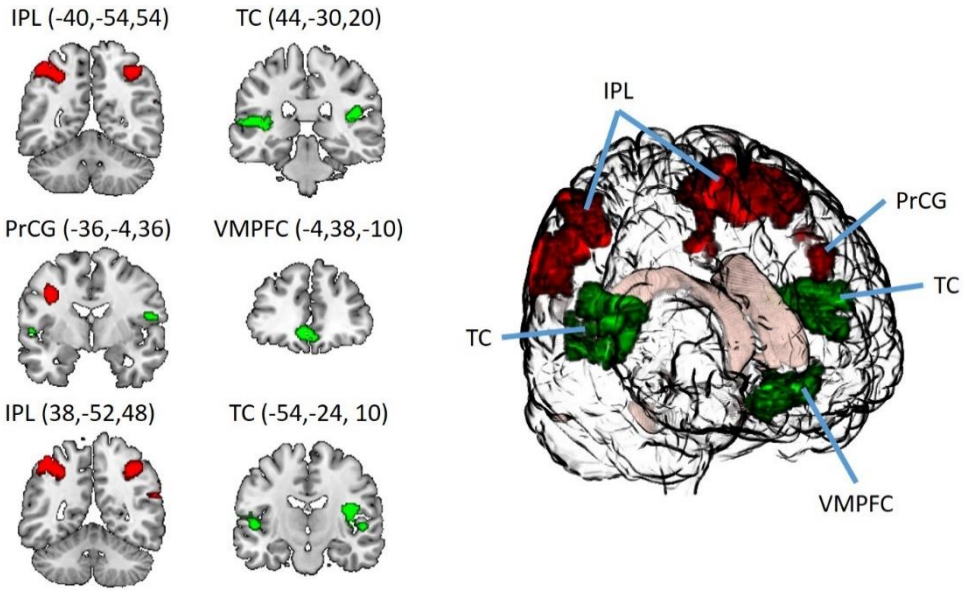
Publication I: Behavioral Results



Note. Mean latencies (ms) and directional error rates (%) of the fMRI study. Antisaccades and prosaccades are displayed as a function of antisaccade frequency per experimental block. Error bars illustrate the standard error of the mean (*SE*). Adapted from Talanow et al. (2016).

Figure 18

Publication I: fMRI Key Results



Note. fMRI activation map revealed by the *Condition* by *Frequency* interaction. Brain regions in red indicate greater activation differences between antisaccades and prosaccades for infrequent than frequent antisaccade blocks. The opposite pattern, i.e., greater activation differences between antisaccades and prosaccades for frequent than infrequent antisaccade blocks, is shown in green. Results are FWE corrected at a cluster-defining threshold of $p = .05$. MNI peak voxel coordinates and labels are displayed. IPL = inferior parietal lobe; PrCG = precentral gyrus; TC = temporal cortex; VMPFC = ventromedial prefrontal cortex. Adapted from Talanow et al. (2016).

6. Proactive Inhibition

To understand executive control and inhibitory control in its entirety, it is necessary to focus investigations (a) on the underlying mechanisms of stopping motor responses already in progress (reactive control) *and* (b) on mechanisms underlying preparatory processes that withhold a response before it is initiated (proactive control). In fact, successful inhibition involves learning the meaning of specific environmental cues which signal that a behavioral response should be withheld. These cues may also hold the information whether it is sensible to assume and to anticipate to stop (Meyer & Bucci, 2016). Such environmental cues enable us to adapt our behavior in advance of critical incidents and thus anticipate potentially relevant or even dangerous situations and to stop inappropriate behavior accordingly with foresight.

An everyday example illustrates the benefits of proactive processes in EF: imagine you are a pedestrian and you want to cross a busy road. You see a solid green pedestrian light not far away. As you approach the crosswalk, the green light begins to flash. The flashing green light signals that you only have a few seconds before the pedestrian light turns red and it will become potentially dangerous to cross the busy road. From this example, it should become apparent that the green flashing pedestrian light is a proactive cue that enables pedestrians to proactively stop walking or at least anticipate to stop prior to onset of the red stop signal. In some countries, the proactive traffic cue is a countdown until the onset of the red pedestrian light. We learn this important form of proactive motor inhibition at an early age and spend a great amount of time teaching our children to internalize this behavior: prepare yourself to immediately stop at a traffic light at any given moment!

With respect to the field of psychology, proactive inhibition is also discussed as a valuable concept of executive control in the context of clinically relevant psychological disorders. The construct of proactive inhibition may be a vital candidate to explain, for instance, the pathology of excessive gambling (Brevers et al., 2018; Brevers, He, Keller, Noël, & Bechara, 2017) and eating disorders (Bartholdy, Campbell, Schmidt, & O'Daly, 2016; Bartholdy, Rennalls, Danby, Campbell, & O'Daly, 2017).

6.1 The Distinction between Proactive and Reactive Cognitive Control

The following section outlines three views on the nature of the proactive inhibition control mechanism currently debated in the psychological literature to lay the theoretical foundation for publication II of this dissertation.

6.1.1 Dual Mechanism of Control

Cognitive control operates via two distinct modes in the *Dual Mechanisms of Control* (DMC) framework (Braver, Gray, & Burgess, 2007; Braver, 2012): *proactive control* is defined as an early selection mechanism to bias cognitive subsystems prior to the occurrence of a cognitively demanding event in order to achieve a behavioral goal. *Reactive control* on the other hand is thought of as a goal-driven late correction mechanism that biases cognition after detecting the onset of an interference event.

In line with this view, *proactive inhibition* refers to the active sustained maintenance of goal-relevant information, which biases cognitive subsystems in order to stop an upcoming response tendency prior to its evocation. Proactive control is developed on the basis of foreknowledge and upcoming demands and/or a subject's current goals (Lavallee, Meemken, Herrmann, & Huster, 2014). In contrast, *reactive inhibition* means a cognitive mechanism intended to stop a response tendency utterly motivated upon instruction of an external signal. Hence, proactive inhibition builds on the anticipation and prevention of interference which can be cued by contextual stimuli (Chikazoe et al., 2009). Reactive inhibition builds on the detection and resolution of interference after its initiation by a stimulus (Braver, 2012). Evidence derived from single-cell recordings in the rhesus monkey supports the notion of the DMC framework in response inhibition (Stuphorn & Emeric, 2012).

6.1.2 Tonic Inhibition As a Form of Proactive Control

Behavioral experiments by the groups around Marion Criaud and Magali Jaffard have contributed evidence on the hypothetical temporal dynamics of proactive inhibitory control (Criaud, Wardak, Hamed, Ballanger, & Boulinguez, 2012; Jaffard et al., 2008; Jaffard, Benraiss, Longcamp, Velay, & Boulinguez, 2007). Both research groups observed a paradoxical effect of warning signals in simple cued target detection tasks: reaction times *decreased* as the time interval between warning cue offset and target onset (stimulus onset asynchrony, SOA) increased from 100ms to 300ms (see Figure 19a). This enhancement effect was seen in cue trials of mixed-block designs but not in pure-block designs. Reaction times of non-cued trials were unaffected by the SAO and remained at a higher level in mixed-blocks than in pure-blocks. Thus, introducing warning signals randomly in blocks of non-cued trials increased reaction times. The authors suggested that this effect resembles the time required to release a *tonic inhibition* state after subjects identified the cue stimulus (see Figure 19c). According to this notion, tonic inhibitory control is set up already from the beginning of the trial and not after the instruction cue. This implies that executive control involves the temporary release from the inhibitory default mode when demands imposed by the environment become evident (Criaud et al., 2012). This state of tonic inhibition serves the purpose to control automatic but inappropriate

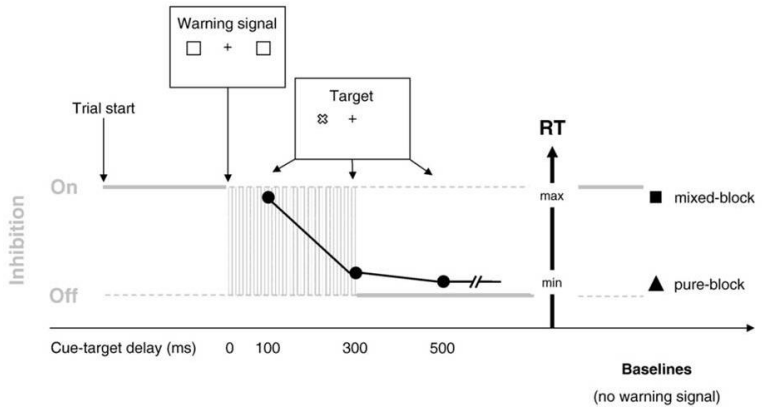
activations triggered by visual cues in the environment to prevent premature false responses (Jaffard et al., 2008). When the target is not preceded by a cue in a *mixed-block* design, tonic inhibition is not released until the target is presented and identified by the subject, resulting in relatively long reaction times (see Figure 19b). Reaction times in un-cued trials of *pure-block* designs remain unbiased because proactive inhibition is not required here, and movement initiation can be triggered shortly after target onset and target identification (see Figure 19a). According to the authors, alerting benefits or temporal costs were no potential explanations for the effect described above (Jaffard et al., 2008).

The research group around Jaffard and colleagues (2008) tested their concept of a proactive tonic inhibitory default state in a fMRI study. First, activations in medial prefrontal cortex (mPFC) and the IPC were observed in situations in which inhibition was present versus absent according to the model. This finding suggests a potentially active role of mPFC and IPC in tonic top-down inhibitory control. Second, putamen, SMA and primary motor cortex (M1) showed reduced activation when inhibition was expected to be present according to the model. The authors speculated that these regions resemble the target regions to be inhibited. Further evidence for a tonic proactive inhibition signal comes from computational work in the saccadic countermanding task (Lo, Boucher, Paré, Schall, & Wang, 2009). The authors detected strong tonic proactive activity of fixation neurons and their interactions with movement neurons before onset of a stop signal.

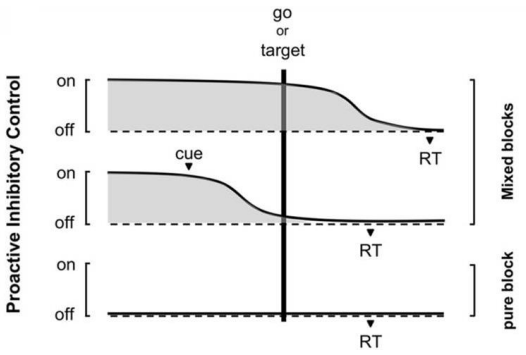
Figure 19

The Concept of Proactive Inhibition as a Default State in Warned Reaction Time Tasks

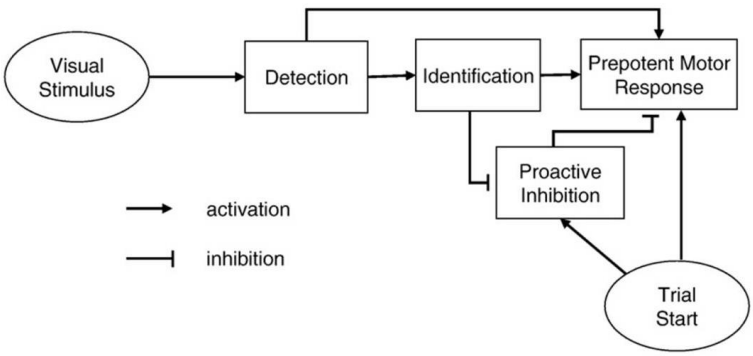
a.



b.



c.



Note. Schematic of the paradoxical effect of warning signals (a), hypothetical dynamics of proactive control (b) and processing steps in a simple warned reaction time task (c). (a) The release of inhibition (bold line: on; dotted line: off) after a warning signal accounts for reaction time (RT) decreases (represented in black). The level of inhibition decreases as the cue-target delay increases. (b) In un-cued mixed-block designs, tonic inhibition is only released after target stimulus identification to prevent response errors (upper part). A proactive warning cue reduces the tonic inhibition state prior to target onset in mixed blocks (middle part). No proactive inhibition is required in pure blocks in which only targets are presented (lower part). (c) Upon trial onset, a prepotent motor response is prepared and a default state of proactive tonic inhibition is active to prevent automatic, inappropriate motor responses that are triggered by the visual cue stimulus. Adapted from Jaffard et al. (2008) and Criaud et al. (2012).

6.1.3 Proactive Inhibition: A General Biasing Account

The research group around Elchlepp, Lavric, Chambers, & Verbruggen (2016) conducted a line of experiments on event-related brain potentials in which they investigated whether proactive inhibitory control underlies modulations of *both* attention settings and response settings. Hereby, the authors addressed the perceived shortcoming that recent work on proactive inhibitory control mainly focused on response-related processes (e.g., Aron, 2011; Stuphorn & Emeric, 2012) but neglected the role of attention in proactive control.

Results showed that the expectation of a stop signal modulated processing of the go stimulus, which is an indication of proactive inhibitory control. Specifically, an occipital negative reflection around 100ms after go stimulus onset (N1) and a broad negative event-related potential (ERP) around 140ms to 180ms post stimulus termed *selection negativity* (SN) (Hillyard & Anllo-Vento, 1998) were larger in a stop context relative to ignoring the go stimulus. The N1 reflects detection of the visual stimulus (Sur & Sinha, 2009), and the SN indexes selective sensory processing of attended visual features (Keil & Müller, 2010). Elchlepp and colleagues (2016) interpreted their findings in the light of the *biased competition* account of visual attention (Beck & Kastner, 2009; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). The biased competition theory assumes competitive interactions among neurons that code all stimuli in the visual field. These interactions can be biased by different processes – amongst them attention – to the benefit of behaviorally relevant stimuli over irrelevant stimuli (Desimone, 1998). Therefore, Elchlepp and colleagues (2016) suggested that detection of the stop signal was biased to the benefit of sensory neurons that code for specific stop-signal-related features. These biasing processes can be thought of as a form of proactive inhibitory control. Due to the bias, stop-related signals tend to win the competition against go response signals more often, resulting in a higher likelihood to stop successfully.

6.2 Experimental Findings on Proactive Inhibition

Proactive and reactive control mechanisms operate and interact in inhibitory control (Aron, 2011; Jahanshahi, Obeso, Rothwell, & Obeso, 2015) and involve separable yet overlapping neural networks (van Belle, Vink, Durston, & Zandbelt, 2014). The following section reviews behavioral and neural experimental evidence related to proactive inhibitory control.

6.2.1 Behavioral Findings on Proactive Inhibition

The stop signal task has been a popular paradigm to study inhibitory control because it provides an estimation of the latency to inhibit a proponent response, the so-called *stop signal reaction time* (SSRT). SSRT is an important marker of reactive inhibitory control (Verbruggen & Logan, 2008) but it is also used to draw inferences about proactive inhibition processes. Proactive inhibitory control

comes at a cost as shown by longer SSRTs when subjects anticipate at the beginning of a trial that they might have to stop their response (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Verbruggen & Logan, 2009b; Vink, Kaldewaij, Zandbelt, Pas, & du Plessis, 2015), a phenomenon termed *proactive response slowing*. Proactive response slowing is correlated with the stop signal probability as shown by more proactive inhibition and a reduction in SSRT when stop signals occur more frequently (Bissett & Logan, 2015; Castro-Meneses, Johnson, & Sowman, 2015). To be noted, other research reported no effect of stop signal probability on SSRTs (Lansbergen, Böcker, Bekker, & Kenemans, 2007; Ramautar, Kok, & Ridderinkhof, 2004). Proactive inhibition costs are further evident by longer go-response latencies after successful inhibition trials compared with go trials that follow no-stop trials (Verbruggen & Logan, 2008). All in all, these modulations in SSRTs suggest the presence of proactive inhibitory control. Interestingly, proactive inhibition aides reactive inhibition as evidenced by the fact that a greater level of preparation is associated with faster reactive stopping (Castro-Meneses et al., 2015).

Response-strategy adjustments in light of the *proactive-adjustment hypothesis* and at least partly dual task requirements (*dual-task hypothesis*) serve as a theoretical explanation for the proactive response-slowing effect (Verbruggen & Logan, 2009b): one theoretical approach suggests that stop signal task performance depends on a competitive race between a go process triggered by the go stimulus and a stop process triggered by the stop signal towards a response threshold (Logan & Cowan, 1984). Subjects inhibit their response in case the stop process reaches a certain threshold before the go process. According to the proactive-adjustment hypothesis, subjects increase their response threshold for go trials when they expect a relevant stop signal. As the response threshold increases, so does the finishing time of the go process that races against the stop signal. Hereby, the probability of responding given a stop signal decreases because the stop process is more likely to finish first (Verbruggen & Logan, 2009a).

According to the *dual task hypothesis*, prolonged reaction times in stop signal blocks result from increased cognitive demands that arise from the fact that stop signal blocks involve two potential task goals: going and stopping. In stop signal trials, subjects attend to the visual target stimulus and visual or auditory stop signal stimulus, whereas in non-stop signal trials subjects only attend and process the visual target stimulus.

6.2.2 Neuroscientific Findings on Proactive Inhibition

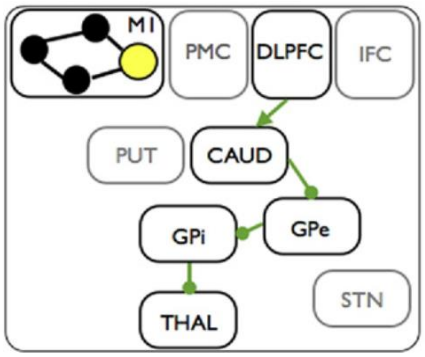
First and foremost, it should be stressed that it is, from an experimental perspective, a challenging undertaking to identify neural processes *purely* associated with proactive or reactive inhibition, i.e., clearly distinguishable brain activations. It is a challenge for the following two reasons: Firstly, randomized experimental protocols may induce proactive inhibition in inhibition trials as well as in

response trials. This is also true for certain variants of the antisaccade task, that cue the task-set simultaneously to onset of the target stimulus (Irving et al., 2009; Larrison, Briand, & Sereno, 2004). Here, upcoming task requirements remain unknown to the subject until target onset, which likely coincides with at least some amount of proactive inhibition in non-inhibition trials *and* inhibition trials (Ballanger, 2009; Criaud & Boulinguez, 2013). Furthermore, a tonic state of inhibition has been thought to operate permanently at target onset in mixed inhibition task designs (Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Jaffard et al., 2008, 2007). Therefore, inhibition-related activations in control trials likely contaminate the proactive inhibition versus control contrast. Consequently, in this context, proactive inhibition-related BOLD signal differences at least partially cancel each other out causing activation differences to be underestimated or even to be not significant. Secondly, some fMRI task designs may not clearly separate cue, target and response-related activations in inhibition tasks due to intervals between events being shorter than the time required for the BOLD signal to reach its peak (4 to 8 seconds; Kornak, Hall, & Haggard, 2011). For this reason, these fMRI task designs miss the opportunity to fully capture and dissociate proactive and reactive inhibitory neural mechanisms.

Proactive and reactive inhibition are mediated by common and unique neural networks (Meyer & Bucci, 2016; van Belle et al., 2014). Three frontal networks comprising (a) DLPFC and ACC, (b) VLPFC, pre-supplementary motor area (pre-SMA) and IPL and (c) right VLPFC and IPL are associated with proactive and reactive control. The brain network involved in reactive stopping (i.e., pre-SMA; right inferior frontal cortex, right IFC; STN) is likely also used in order to prepare to stop a response when a no-go or stop signal is anticipated (Aron, 2011). Indeed, variants of the stop signal task (Vink et al., 2005; Zandbelt et al., 2008) and the go/no-go task (Hester et al., 2004) revealed proactive activations of the reactive stopping network in pre-SMA, right IFC, STN, DLPFC and striatum. The assumption that the reactive stopping network is primed by the proactive network explains why people can stop so fast. A fronto-basal-ganglia circuitry (Figure 20) likely mediates proactive selective control by suppressing those channels specific to its motor representation in situations where subjects anticipate to stop (Aron, 2011). More precisely, DLPFC holds a stopping goal in working memory and sends a cortical signal coding this stopping goal to striatum (e.g., CN). This signal inhibits the GPe, that subsequently releases the globus pallidus pars interna (GPi) from inhibition directly or via STN, increasing inhibition of thalamocortical representations, e.g., M1. Another study also suggested that proactive inhibition is implemented via the basal ganglia (Majid, Cai, Corey-Bloom, & Aron, 2013). The indirect pathway model of proactive inhibition also applies to the context of eye movements where the suppression of a prosaccade in antisaccade trials may result from the inhibitory effect of the indirect basal ganglia pathway on the SC (Ford & Everling, 2009).

Figure 20

Hypothetical Fronto-Basal-Ganglia Circuit Underlying Proactive Selective Control



Note. Schematic of hypothetical fronto-basal-ganglia circuits that mediate proactive selective control via an *indirect* pathway. For example, inhibition of eye movements but not hand movements involves only weak activations of thalamocortical output to eye movements (black filled circles) but strongly activated primary motor cortex representations to hand movements (large yellow-filled circle). Green arrows indicate excitation and green lines with filled circles indicate inhibition. M1 = primary motor cortex; PMC = premotor cortex; DLPFC = dorsolateral prefrontal cortex; IFC = inferior frontal cortex; PUT = putamen; CAUD = caudate; GPi = globus pallidus pars interna; GPe = globus pallidus pars externa; STN = subthalamic nucleus; THAL = thalamus. Adapted from Aron (2011).

Studies have used EEG to investigate the time-frequency domain of proactive inhibition. Proactive control in the stop signal task (defined as trial-by-trial conflict anticipation) positively correlated with the power of low-theta band (3 - 5Hz) in the interval preceding the go signal but not in the interval after the go signal (Chang, Ide, Li, & Chen, 2017). Source analysis localized these time-frequency correlates of conflict anticipation to the pre-SMA and right SMG. Low-theta band modulates started shortly after trial onset, which suggests a preparatory process for the upcoming event. Behavioral slowing was reflected in delta-theta band (2 - 8Hz) power where longer go reaction times were related to lower power in delta-theta band (Chang et al., 2017). With regards to ERPs, proactive inhibition is reflected in a bilateral prefrontal negativity (located at prefrontal electrodes FP1 and FP2) during the decision and preparation stage when subjects freely decide whether or not to respond to an upcoming stimulus (Bianco, Berchicci, Perri, Spinelli, & Russo, 2017). Other studies showed that proactive inhibition is associated with modulations of N1 short-latency evoked potentials (Kenemans, 2015; Liebrand, Pein, Tzvi, & Krämer, 2017) and an increased contingent negative variation (CNV) (Liebrand et al., 2017). Here, the N1 likely reflects a mechanism of increased attention or detection of infrequent events. The CNV likely resembles processes of motor preparation and anticipatory attention towards the upcoming stimulus (Liebrand et al., 2017).

Single-unit recordings in non-human primates have further contributed to our understanding of the neurophysiology of frontal cortex in proactive inhibitory control (Stuphorn & Emeric, 2012). By use of single cell recordings, the authors overcame spatial and temporal limitations of the BOLD

signal. Their neurophysiological evidence favors dual mechanisms of control in response inhibition in the medial frontal cortex in line with the framework proposed by Braver (2012). Modest proactive changes in SEF and SMA neuronal activity have suggested that the medial frontal cortex is a vital component of the network underlying behavioral control (Stuphorn & Emeric, 2012). Also, longer reaction times following stop signals (proactive inhibition) were accompanied by increased power in low frequencies (1 - 20Hz). Beta frequencies (25 - 40Hz) in SMA shortly before target onset provided evidence of the vital role of medial frontal cortex in proactive inhibition (Stuphorn & Emeric, 2012). In the context of the stop signal task, proactive control likely adjusts the level of excitation and inhibition of the motor system (see proactive-adjustment hypothesis in section 6.2.1. *Behavioral Findings on Proactive Inhibition*), thus setting the threshold for a response.

In the context of saccadic eye movements, proactive inhibition in the go/no-go task is accompanied by increased activations in the posterior cingulate cortex (PCC), in the precuneus and in the right IPS as well as by deactivations in BOLD in the FEF and left insula (Brown et al., 2006). Antisaccade preparation involves a variety of processes likely including proactive inhibition. Preparation of antisaccades is mediated by a cortical network comprising DLPFC, FEF, SEF, PCC, IPS and parieto-occipital sulcus (Brown et al., 2006; Curtis & Connolly, 2008; DeSouza, Menon, & Everling, 2003; Ford, Goltz, Brown, Everling, & Kristen, 2005; Medendorp, Goltz, & Vilis, 2005). This proactive control network shares components of the well documented reactive antisaccade network, namely DLPFC, SEF, FEF, IPS and visual cortex (Brown et al., 2006; Curtis & Connolly, 2008; Ettinger et al., 2008a).

6.3 Foreknowledge and Uncertainty in Proactive and Reactive Inhibitory Control

6.3.1 Foreknowledge in Inhibitory Executive Control

An interesting gap in the inhibition literature becomes apparent when thinking about how to transfer the current knowledge of proactive executive control into everyday life: many studies on proactive control have provided subjects with little information on the context in which they are instructed to plan their behavior. For example, subjects might not be able to anticipate the required task-set, direction, or amplitude of the required response. Outside the laboratory context, however, we often appraise or even know what detailed behavioral needs everyday situations pose to us based on foreknowledge due to experience or environmental cues. This is also true in situations that require inhibitory control. Again, traffic events provide a good everyday example of how foreknowledge is used to prepare ourselves to adapt our behavior to changes in the environment: imagine you are playing basketball with your friends at a public basketball court. After a failed throw, the basketball bounces off the basket and rolls onto the nearby road. You start to chase the ball into

the street. Because you know from experience that suddenly a fast-moving car could appear on the road in your neighborhood, you prepare yourself *proactively* to stop running in order to avoid a potential traffic accident. It should become apparent that this decision context provides a sense of *certainty* regarding the upcoming response inhibition demand. Now image the same situation to be set in an unfamiliar neighborhood, in which you can hardly appraise the traffic conditions. Then the decision context is rather *uncertain* regarding the upcoming response inhibition demands, and it is difficult to appraise the potential need to proactively stop running.

Such everyday observations on proactive executive control were the motivation to conduct a line of experiments that aimed to investigate executive control mechanisms in situations that take into account contextual factors that may influence our response planning and decision making. In doing so, the research aimed to gain insights in mechanisms underlying the planning of inhibitory control.

A factor likely to interact with the mechanisms of proactive and reactive inhibition is the amount of foreknowledge in a decision situation. From a somewhat formalistic and experimental point of view, foreknowledge can be thought of as "*completely reliable information about some or all properties of an upcoming trial from the historical context of previous trials*" (Barton, Kuzin, Polli, & Manoach, 2006). Another form of foreknowledge is early advance information provided by explicit cues (*pre-cueing)*, although it does not rely on trial history information (Barton et al., 2006). Such pre-cues can provide information regarding the required task-set, the timing of the stimulus and/or response onset and response parameters including direction and amplitude, for example. It should be noted that proactive inhibition does not just depend on processing objective contextual task information but it is also influenced by subjective expectations of inhibition signals (Messel, 2017; Vink et al., 2015).

A few studies have investigated effects of foreknowledge on cognitive control in saccades. Generally, foreknowledge had beneficial effects on saccade performance and modulated neural processes underlying saccade generation (Abegg, Manoach, & Barton, 2011; Barton, Greenzang, Hefter, Edelman, & Manoach, 2006; Chang, 2015; Curtis & Connolly, 2008; Gagnon, Driscoll, Petrides, & Pike, 2002; Simó, Krisky, & Sweeney, 2005). On the behavioral level, knowledge of the target direction or target onset timing reduced saccade latencies (Gagnon et al., 2002). On the BOLD level, spatial saccade target predictability strengthened activations in FEF (Bär, Hauf, Barton, & Abegg, 2015; Chang, 2015; Curtis & Connolly, 2008; Gagnon et al., 2002), DLPFC, SEF, PFC, insula (Chang, 2015) and caudate (Gagnon et al., 2002) as well as in superior precentral sulcus (sPCS) and IPS (Curtis & Connolly, 2008). Predictability of when a target is shown (temporal prediction) activates the FEF (Gagnon et al., 2002), ACC, PCC (Chang, 2015) and the lenticular nucleus (Gagnon et al., 2002). In the antisaccade task, foreknowledge of stimulus location (FEF, PFC), saccade goal (FEF) and task-set

(orbitofrontal gyrus, OFG; superior frontal gyrus, SFG; and inferior temporal gyrus, ITG) increased activations in frontal, parietal and temporal areas but decreased activation in visual cortex (Bär et al., 2015).

6.3.2 Uncertainty in Inhibitory Executive Control

"*Successful interaction with the environment requires flexible updating of our beliefs about the world"* (Marshall et al., 2016). This statement nicely illustrates that subjective environmental factors determine successful executive control to a significant extent. Here, the terminology *belief* likely subsumes certainty and uncertainty regarding contextual elements of our environment when we make decisions regarding our course of action.

We know from our everyday life that there are indeed situations in which we do *not* know what behavior requirements are put on us due to a lack of experience, no memories of event frequencies or a lack of external cues. Often times, we do not expect one out of several options to occur with the same probability (Volz, Schubotz, & von Cramon, 2003). In those situations, we usually have several options for action that seem appropriate. However, we either do not know them or we do not know when to use them, or the options that we can think of are equally likely and therefore ambiguous. These circumstances result in behavioral *uncertainty*, which depends on the number of potential outcomes and their estimated probabilities (Huettel, Song, & McCarthy, 2005). A sub-categorical form of uncertainty that is relevant in the context of executive control is *task-set uncertainty*, where it is not entirely clear in what form to respond to a stimulus or whether to respond at all.

These effects of task-set uncertainty in the context of inhibitory executive control have been further explored in a research project of this dissertation. It was the goal to assess whether and how we prepare inhibitory control when we are sure (certain) and unsure (uncertain) about what behavioral inhibitory needs a situation poses to us. To be noted, research on uncertainty in decision making is a significant topic that has also been studied in domains other than executive control, such as in econometric decision-making (Goñi et al., 2011) and in the context of biopsychology to reveal neurotransmitters that contribute to successful decision making under uncertainty (Marshall et al., 2016).

Uncertain Task-Sets and Their Neural Correlates. Publications on the neural underpinnings of uncertain task-sets in decision making and executive control are rather rare. Decision making under uncertainty engages frontomedial cortex and subcortical components, namely midbrain, ventral striatum and dorsal thalamus, that are part of a striatal-thalamo-cortical network underlying reward-based learning (Volz et al., 2003). Work by Huettel and colleagues (2005) suggested that uncertainty in decision making addresses distinct cognitive processes depending on the decision task. Their data

pointed in the direction that uncertainty addresses frontomedial cortex when uncertainty influences the learning of stimulus-response-associations. When decision making depended on information-guided selection of plans for actions, uncertainty altered response selection processes coded by DLPFC and PPC. Brain imaging in the go/no-go task and stop signal tasks has suggested the involvement of proactive cognitive control, likely involving proactive inhibition of manual motor responses, when foreknowledge on task requirements is unavailable relative to conditions where an upcoming response demand is certain (Albares et al., 2014; Ballanger, 2009; Chikazoe et al., 2009; Jaffard et al., 2007; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013). Such uncertain information can be related to the task-set, i.e., it is unpredictable how to respond to a stimulus. In their experiment, Albares et al. (2014) introduced informative or uninformative task-set cues prior to onset of a target in a manual go/no-go task. Supplementary motor cortex (SMC) consisting of SMA proper and pre-SMA showed stronger activations when the task-set was unpredictable (uncertain > certain contrast) independent of the subsequent task requirement (go or no-go). No significant BOLD differences were found between responses to unpredictable no-go or go stimuli, leading the authors to conclude that inhibition might be an early, unspecific process when task-set requirements are unpredictable. Chikazoe et al. (2009) employed a stop signal task that cued subjects to be certain or uncertain whether to respond or whether a stop signal followed a go stimulus. Preparation-related activations in pre-SMA, IFJ and insula depended on the level of foreknowledge (uncertain go versus certain go), and reactive inhibition (stop versus uncertain go) triggered components of the well-known fronto-parietal inhibition network (pre-SMA; right inferior frontal gyrus, right IFG; IFJ; temporal parietal junction, TPJ; IPS; and insula). Further research in the stop signal task showed that the stop signal probability alters processing of the proactive inhibitory task-set and suggests different routes of implementing inhibition control in the basal ganglia (Leunissen, Coxon, & Swinnen, 2016). A high level of inhibitory task-set uncertainty was associated with increased sub-thalamic nucleus activity, but a lower level of uncertainty was related to increased activation in caudate. However, the work of Albares et al (2014) and Chikazoe et al. (2009) (a) missed a detailed analysis of BOLD signals time-locked to the onset of the task-set cue, i.e., proactive processes, and (b) lacked an inhibition condition with foreknowledge (Albares et al., 2014: certain no-go; Chikazoe et al. 2009: certain stop) to fully examine effects of task-set certainty and inhibitory demands as well as their interaction.

Overall, findings have suggested that activation increases in superior parieto-occipital cortex (Smittenaar, Guitart-Masip, Lutti, & Dolan, 2013; van Belle et al., 2014), right IFC (Chikazoe et al., 2009; Jahfari et al., 2010; Smittenaar et al., 2013; van Belle et al., 2014; Vink et al., 2015), SMA and pre-SMA (Albares et al., 2014; Chikazoe et al., 2009; Jahfari et al., 2010) and lateral IPC (Jaffard et al., 2008; Vink et al., 2015) support proactive inhibitory control in task-set uncertain conditions that do

not allow subjects to set up a selective inhibitory representation. With respect to the example situation at the basketball court, these cortical areas mediate proactive executive control in the *uncertain* context, in which it is difficult to appraise the need to proactively stop running on the street to avoid a potential collision.

Publication II of this dissertation enlarges upon the current understanding on proactive inhibitory control. It systematically assessed brain activations of proactive inhibition in the model system of saccadic eye movements and contrasted neural correlates related to uncertain and certain inhibition task-sets.

6.4 Publication II

Talanow, T., Kasparbauer, A.-M., Lippold, J. V., Weber, B., & Ettinger, U. (2020). Neural correlates of proactive and reactive inhibition of saccadic eye movements. *Brain Imaging and Behavior*, *14*, 72–88.

As outlined in section 6.1 *The Distinction between Proactive and Reactive Cognitive Control*, mechanisms involved in the dynamics of executive control can be formally separated into proactive and reactive processes. With respect to inhibition, proactive inhibition comprises top-down mental processes to prevent an inappropriate or undesired response in an upcoming situation. Reactive inhibition refers to mechanisms to refrain from a response when instructed to do so by the onset of an external stimulus (Braver, 2012). Although reactive neural processes of inhibitory control have been studied intensively, relatively few brain imaging studies have investigated proactive inhibition so far. Further, insights about factors that may interact with executive control are rare, such as the amount of foreknowledge provided by the environment in which we adapt our behavior. Previous studies have used variants of the go/no-go task and stop signal tasks to show that proactive inhibition of *manual* motor responses arises in conditions where upcoming task requirements are uncertain as compared to when they are certain (Albares et al., 2014; Chikazoe et al., 2009; Jaffard, Benraiss, Longcamp, Velay, & Boulinguez, 2007; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013). The current study hypothesized that proactive top-down inhibitory control may also arise in conditions where it is known at the beginning of a trial (pre-cueing) that a prepotent response to an upcoming stimulus will have to be inhibited. This aspect of proactive inhibition under task-set certainty has not hitherto been addressed in any published fMRI study. To the best of my knowledge, previous studies have not directly compared proactive inhibition due to task-set uncertainty with a condition of certainty regarding upcoming inhibition. The current research assessed proactive inhibitory mechanisms in saccadic eye movements. Certainty regarding upcoming inhibition in saccades likely generates stronger proactive control demands than in manual responses due to the strong demand to overcome an urge of reflexive covert orienting of the visual grasp reflex (see section 4.4 *Saccades: A Model System of Inhibitory Control*). Potentially relevant peripheral events in the visual field immediately attract visual attention and hereby make the inhibition of saccadic gaze shifts a demanding task (Laidlaw, Foulsham, Kuhn, & Kingstone, 2011; Theeuwes et al., 1998).

To assess these issues, a behavioral laboratory study on the effect of task-set foreknowledge on response inhibition was initially employed. Here, better inhibitory performance was expected on task-set certain than uncertain inhibition trials. Additionally, a separate study using BOLD fMRI was employed to investigate whether conditions of certain task-sets address a neural network different from conditions of uncertain task-sets in inhibition tasks. With reference to previous research,

proactive inhibition related BOLD signal modulations were expected in a network of occipital, parietal and frontal clusters (Albares et al., 2014; van Belle et al., 2014; Vink et al., 2015). Reactive inhibition was expected to evoke BOLD signal changes particularly in lateral parietal cortex, a region crucially involved in response inhibition (Brown et al., 2006; Ettinger et al., 2008).

Twenty-four subjects, most of them females, participated in the initial laboratory study. Here, subjects performed a saccadic go/no-go task (*N* = 22 included in the final analysis) and prosaccade/antisaccade task (*N* = 24 included in the final analysis) while an eye-tracking system recorded their eye movements. A color cue signaled the level of task-set *Certainty* (certain due to foreknowledge of the task-set versus uncertain due to no foreknowledge) and the instructed *Response* (go versus no-go; prosaccade versus antisaccade) prior to the onset of a peripheral target. Subjects were instructed to use the cue-color to actively prepare, if possible, the upcoming task response.

In a subsequent fMRI study, thirty-one other subjects, most of them female, engaged in event related fMRI-adapted versions of the saccadic go/no-go task (*N* = 19 included in the final analysis) and prosaccade/antisaccade task (*N* = 21 included in the final analysis) that were initially used in the laboratory study. Subjects' eye movements and proactive and reactive brain signals where simultaneously obtained using eye-tracking and fMRI at 3 Tesla. Such as in the laboratory study, the level of task-set *Certainty* and the instructed *Response* were manipulated.

At the behavioral level, both independent studies showed that inhibitory control was more successful under task-set certain than uncertain conditions in the go/no-go task (i.e., fewer erroneous responses in no-go trials) and the prosaccade/antisaccade task (i.e., fewer directional errors) (Figure 21). However, go-responding was less efficient (i.e., longer reaction times) under conditions of uncertainty than task-set certain responding. Task-set certainty likely promoted biasing or altering processes underlying (a) task-set and stimulus encoding, (b) selecting the appropriate action and (c) preparation to meet cued task demands (Braver, 2012; Elchlepp et al., 2016). Longer response latencies in uncertain conditions relative to certain conditions were likely related to time consuming processes that turn off a state of tonic inhibition upon target onset (Ballanger, 2009).

Task-set foreknowledge distinctly altered proactive and reactive BOLD signals. In the go/no-go task, certainty regarding upcoming inhibitory control relative to uncertainty increased activations in frontal, middle temporal and occipital regions. Under certainty, no-go cues relative to go cues elicited BOLD signal changes in postcentral and supramarginal cortex, a marker of proactive inhibition (Figure 22). Certain go trials relative to uncertain trials elicited activation differences in occipital cortex (OCC). Differences in proactive BOLD mostly resulted from deactivations in conditions of uncertainty. All other conditions showed little to no signal change.

In the antisaccade task, proactive BOLD signal changes in the superior temporal and postcentral gyrus (PoCG) were detected when contrasting certain antisaccades and saccades under task-set uncertainty. Here, effects resulted from stronger deactivations under uncertainty relative to deactivations when anticipating certain antisaccades. Under task-set certainty, antisaccade relative to prosaccade preparation showed BOLD signal changes in a widely distributed network comprising superior OCC, STG, MeFG and IFG (Figure 22). Differences in BOLD resulted from deactivations in certain prosaccade trials but little to no proactive signal change was detected in certain antisaccade. Reactive BOLD signal changes were revealed in inferior parietal lobe in no-go trials relative to go trials. The reactive BOLD signal was stronger in go trials relative to no-go trials in a widely distributed occipital cluster. The reactive BOLD signal did not differ significantly in the antisaccade task.

The fact that proactive BOLD signal differences mainly resulted from deactivation under conditions of task-set uncertainty (in the go/no-go task and antisaccade task) and conditions of task-set certainty regarding prosaccades (in the antisaccade task) was a first key finding of the study. It was hypothesized that deactivations in the uncertainty condition of the go/no-go-task reflect a task demand sensitive inhibition mechanism that facilitates performance by reducing potentially distracting neural processes as it has been discovered by research of other groups (Laurienti et al., 2002; Tomasi, Ernst, Caparelli, & Chang, 2006). Here, deactivations under uncertainty possibly reduced biases of premature response planning in the go/no-go task when task-set demands were yet unknown. Deactivations in the antisaccade task may likewise be related to the control of premature response planning because the response system may automatically prepare a prosaccade in the event of task-set uncertainty. It is plausible to assume that prosaccades are automatically generated in conditions of uncertainty because visually-guided prosaccades are a phylogenetically old core response mechanism of the human brain to detect sudden changes in the visual field (Theeuwes et al., 1998).

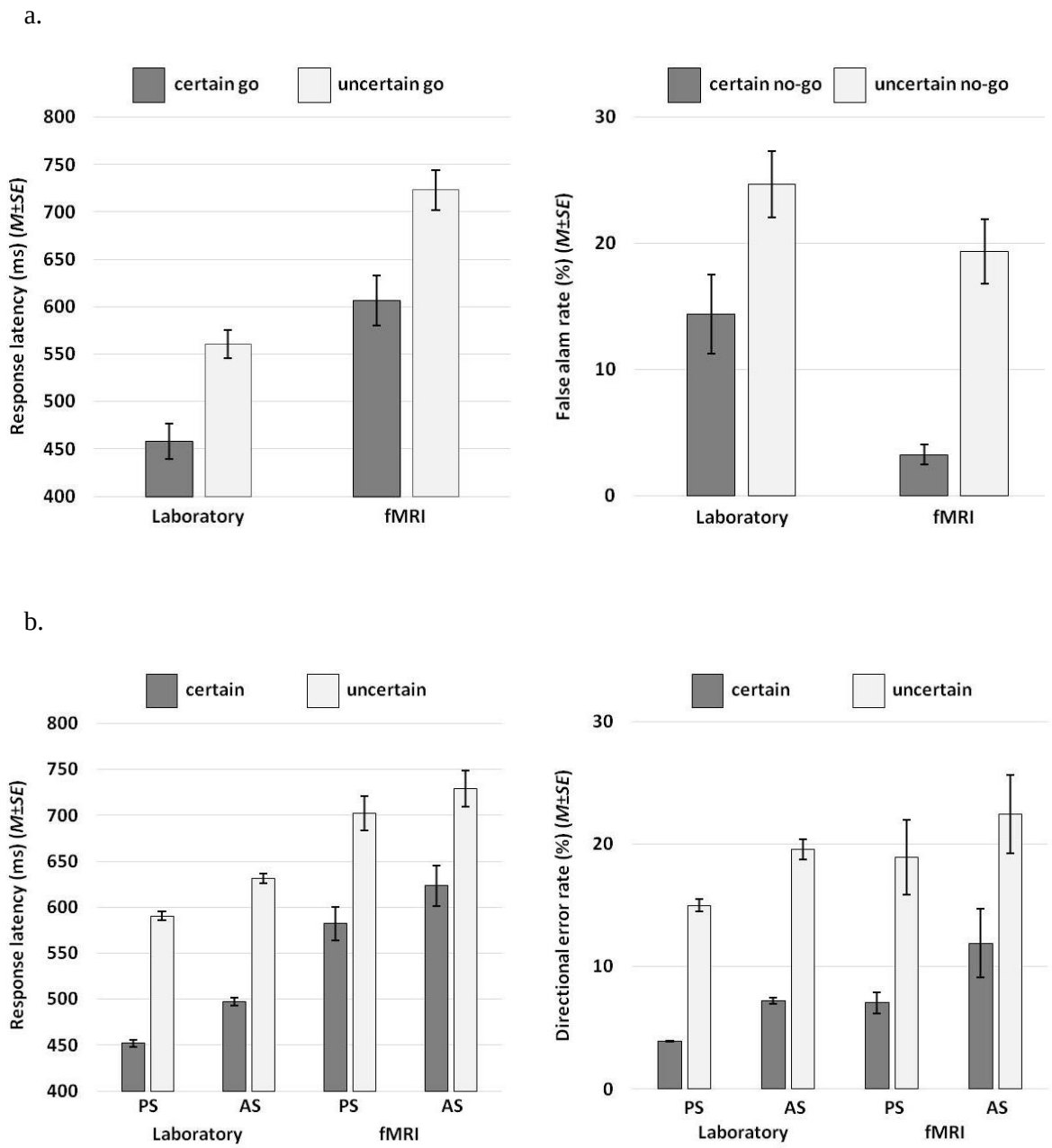
A second key finding concerned activations in SMG and a neighboring cluster in PoCG and IPL that proved to be the neural underpinnings of proactive inhibition under conditions of task-set certainty in the go/no-go task. The study also detected SMG activations related to reactive stopping in the go/no-go task, a finding in line with previous reports. This finding suggests that SMG does not mediate only inhibition demands in the task but SMG is also sensitive to stimulus driven attention (Corbetta & Shulman, 2002) and working memory demands (Criaud & Boulinguez, 2013) as well as saccade planning (Grosbras et al., 2001). The SMG/IPL effect was not observed in the prosaccade/antisaccade task. The lack of an effect probably depended on the fact that preparation of an antisaccade is conceptionally different from preparation of outright non-responding. Further, antisaccade trials with task-set certainty still contained an element of uncertainty because the target

location which is relevant in proactive response planning was unknown until target onset. No such target location uncertainty existed in inhibition demanding no-go trials.

To conclude, the study has extended existing knowledge of cognitive control by showing that proactive inhibitory control in a saccadic go/no-go task mediates situations of uncertainty in order to facilitate flexible responses to upcoming situational requirements and to prepare outright non-responding. These two processes can be differentiated at the neural level as suggested by our fMRI data. A region comprising SMG/IPL has a particularly important role in inhibitory control, both in proactively preparing for outright inhibition and during reactive inhibition in the go/no-go task. The study showed that inhibitory control is more successful in situations of certainty regarding the need to inhibit. Proactive inhibitory control involves focusing attention on the external environment to encode salient or alerting events as well as inhibitory mechanisms that reduce potentially distracting neural processes.

Figure 21

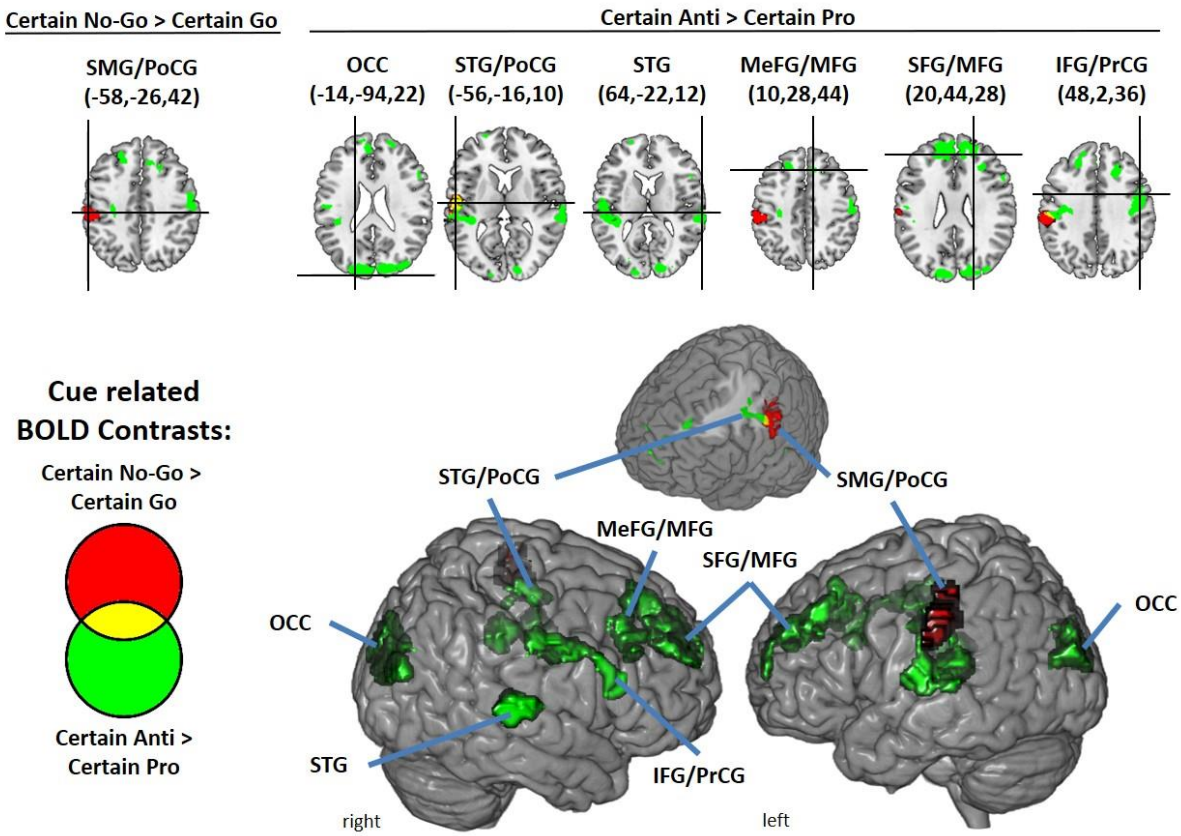
Publication II: Behavioral Results



Note. Mean response latencies (ms) and response error rates (%) of the saccadic go/no-go task (a) and prosaccade/antisaccade task (b) assessed in the laboratory and fMRI setting. Error bars illustrate the standard error from the mean (*SE*). PS = Prosaccade; AS = Antisaccade. Adapted from Talanow, Kasparbauer, Lippold, Weber, & Ettinger (2020).

Figure 22

Publication II: fMRI Key Results on Proactive Inhibition



Note. fMRI activation maps of proactive inhibition in the context of task-set certainty as assessed by the saccadic go/no-go task (red) and the prosaccade/antisaccade task (green). Overlapping activation patterns are displayed in yellow. SPM(T) maps were thresholded at the voxel-level of significance of $p = .001$ (uncorrected), corresponding to $T = 3.21$ and whole-brain FWE-corrected at the cluster-level threshold of $p < .05$. MNI peak voxel coordinates and labels are displayed. SMG = supramarginal gyrus; PoCG = postcentral gyrus; OCC = occipital cortex; STG = superior temporal gyrus; MeFG = medial frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; IFG = inferior frontal gyrus; PrCG = precentral gyrus. Adapted from Talanow et al., (2020).

7. Trainability and Transfer of Inhibitory Control

7.1 A Neuromyth: The Controversy of Cognitive Training

"*Humans mostly only use 10% of their brain…*" most likely one has come across this prominent assertion that triggers the vivid imagination of which mental achievements man is capable if he used the brain's whole potential, i.e., 100%. The greater is the disappointment to learn that this assertion is not supported by scientific evidence. In fact, it is one of many commonly-held false beliefs about how the mind and brain function, a so called *neuromyth.* Many myths about the brain result from biased expositions of scientific facts. Neuromyths particularly exist in relation to learning and teaching (Howard-Jones, 2014). For example, a survey among practicing teachers from the United Kingdom, the Netherlands, Turkey, Greece and China showed that the vast majority of respondents agreed that "*differences in hemispheric dominance (left brain or right brain) can help to explain individual differences among learners*" and "*individuals learn better when they receive information in their preferred learning style (e.g., visual…)*" (Howard-Jones, 2014). Around half of the respondents also agreed that humans mostly use only 10% of their brain. However, all three assertations are in fact misconceptions about neuroscience and are not backed up by scientific proof. Such misconceptions can fuel the belief that specific learning styles or training methods could potentially optimize brain functions and boost cognition, a topic closely linked to *cognitive training*. In fact, individuals, who are aware of the concept of cognitive training, commonly hold the misconception that those brain trainings are exercises or activities that improve memory, prevent memory loss and increase IQ (David & Gelfeld, 2014).

Cognitive training is defined as the intended improvement of cognitive functions by means of practice, i.e., repeated performance (process-based approach) and/or intentional instruction (strategy-based approach) (Jolles & Crone, 2012). Other definitions of cognitive training include a transfer of performance improvements from the training context and training task to other cognitive tasks, such as everyday tasks (Hertzog, Kramer, Wilson, & Lindenberger, 2008; Simons et al., 2016). Surprisingly, cognitive training has developed into a global market for commercially distributed software and hardware brain health "*applications designed to assess, monitor and/or enhance cognition and brain functioning*" (SharpBrain, 2019b). Indeed, marketing of these applications builds on the tempting belief that humans can easily improve their brain functions by practicing simple intervention tasks that will eventually unlock the full cognitive and intellectual potential of their brains. Cognitive training has apparently developed into a thriving business with an estimated volume of $210 million income generated from training membership fees in 2005 and a predicted volume of $6 billion in 2020 (SharpBrain, 2019a) or even around an estimated $8 billion in 2021 (Research and Markets, 2017). Popular commercial cognitive-training interventions (e.g., Nintendo, Lumos Labs, Posit Science, Cogmed, NeuroNation) have intensively advertised to improve *real-world*

performance on a wide range of tasks relevant for our academic, personal and professional lives (Simons et al., 2016). Such trainings follow the logic that (a) cognitive ability measures in training predict real-world performance, (b) training gains that result from engaging in a few simple tasks transfer to other untrained tasks and areas of cognition and (c) that practicing cognitive abilities improves the training outcome resulting in a, generally speaking, more successful life. Importantly, commercial cognitive trainings often claim that their advertised effectiveness is scientifically proven but often do not provide sufficient references with direct support for their claims (Simons et al., 2016).

It has been an ongoing controversy in the science community whether cognitive trainings are indeed effective: in October 2014, an international group of over 70 psychologists and neuroscientists signed an open letter on "*A Consensus on the Brain Training Industry*" issued by the Max Planck Institute for Human Development and the Stanford Center on Longevity (2014). In this open letter, the researchers stated that up to that date "*there is no compelling scientific evidence*" that cognitive trainings "*offer consumers a scientifically grounded avenue to reduce or reverse cognitive decline*". Only two months later, well over 100 scientists and therapists published their own open letter in response (Merzenich, 2016). These opposing researchers claimed that "*a substantial and growing body of evidence shows that certain cognitive training regimens can significantly improve cognitive function, including in ways that generalize to everyday life*". They further claimed that such training gains persist for a reasonable amount of time. However, they agreed that "*many brain fitness providers are subject to criticism for exaggeration, overstatement, and errors of omission in marketing their products*". In conclusion they encouraged continued comprehensive research and high methodological standards in the assessment of cognitive training effects.

In January 2016, the controversy on the effectiveness of cognitive trainings once more raised public awareness when the U.S. Federal Trade Commission (FTC) issued a $50 million judgment against *Lumos Labs Inc*., the company that runs the popular commercial cognitive training service *Lumosity*, for "*deceptive advertising*" (FTC, 2016; Nuechterlein, Rusk, Soberats, & Johnson, 2016) and "*suggesting their games could stave off memory loss, dementia, and even Alzheimer's disease."* These claims were not supported by scientific evidence (FTC, 2016). As part of the settlement, Lumos Labs paid $2 million in redress and changed its sales and advertisement practices.

At this point, it is reasonable to ask: is there compelling up to date scientific evidence on the effectiveness of cognitive training? Who might benefit from brain training and what are the limitations? What are characteristics of good training research?

Any sound scientific research is conducted objectively and independently of political and/or financial interests. Available efficacy studies commissioned or carried out by operators of commercial brain trainings may come into conflict with this critical ground principle of research and may even show serious methodological shortcomings, which question the credibility of the study results. To give an example, Lumosity's website (https://www.lumosity.com/en; last accessed on 2019/06/26) references an in-house study by Hardy, Nelson, Thomason, & Sternberg (2015) as supposed proof of quality and provides further information on the concept of Lumosity in a report by Hardy & Scanlon (2009).

The former authors tested effects of Lumosity's online cognitive training program in a large, online, randomized, active-controlled trial (Hardy et al., 2015). The study concluded that an intensive Lumosity training (i.e., 15-minute sessions on at least 5 days per week for 10 weeks) relative to solving cross word puzzles significantly improves a broad range of cognitive abilities including visual short-term memory, working memory, response inhibition, processing speed and problem solving. However, some aspects of the study have to be addressed critically:

First, subjects were covertly recruited from the Lumosity website, which likely introduced a selection bias on the study sample. Subjects who knew they engaged in a cognitive training and held positive expectations regarding the effectiveness of cognitive trainings per se were likely overrepresented in the study sample. Such expectations are known to evoke placebo effects related to aspects of motivation and commitment that can improve training performance (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016). Placebo effects should not be confused with true training effects. Overt recruitment of the study sample, which does not provide information on the training and study goals, is a more appropriate approach.

Second, Lumosity yield rather small performance gains in a variety of cognitive tests – between d = 0.003 and d = 0.255 – according to Cohen's conventions (Cohen, 1988). The large sample size (N = 4715) caused small differences to yield statistically significant effects. Importantly, the meaning and practical purpose of these statistical effects remain debatable and unclear.

Third, Lumosity's cost-benefit equation is in need of improvement. The training group invested 12.5 hours in training time to produce only small performance gains.

Lastly but likewise important, Hardy et al. (2015) provided no reliable evidence regarding the transfer of Lumosity's performance gains to everyday tasks and subjects' everyday lives. Though the authors suggested that subjects' training-related *self-reported* benefits in areas of specific cognitive failures, successes and emotions, reflect such everyday-life transfers. Again, effect sizes of between-group differences were small (d = 0.096 to d = 0.249) (Cohen, 1988), and it is debatable what the observed differences actually mean. Self-reported measures should be interpreted with caution due

to their potential inaccuracy and sometimes unsatisfying validity (Fan et al., 2006; Lelkes & Krosnick, 2012), but also see Short et al. (2009).

Lumos Labs Inc. explicitly acknowledges these methodological short comings on the Lumocity website by emphasizing the need for "*more research to determine the connection between improved assessment scores and everyday tasks in participants' lives*" (Lumosity, 2019). However, a recent comprehensive study challenges the effectiveness of Lumocity by showing neither significant differences in brain activity, nor choice behavior, nor cognitive performance measures between subjects who engaged in Lumocity training and active controls as well as no contact controls (Kable et al., 2017). The example above illustrates a need for theory-driven, scientifically and methodologically sound application-related training studies that explore the effectiveness of cognitive trainings in well-designed experiments in the field. At the same time, basic research is necessary (a) to investigate the underlying mechanisms that drive cognitive training effects in detail, (b) to identify factors of the training itself that drive its effectiveness and (c) to identify target groups for such applications where the training is effective. This knowledge could be applied in the development of new promising training methods to facilitate and/or maintain cognitive abilities.

Out of this motivation, a training study was conducted in the subject area of EFs as part of this dissertation. The study aimed to assess whether inhibitory control can improve through an intensive computerized training in healthy adults. Furthermore, the study examined if training gains transfer to an untrained inhibition task (near transfer) and to untrained tasks that demand updating, shifting and planning abilities (far transfer). The following section seeks to lay the theoretical foundation of the study.

It is important to address that the following literature review is likely skewed due to a publication bias. Training studies that do not report significant training effects are more likely not to be published in peer reviewed journals relative to training literature that has detected significant training effects. This can make a training intervention seem effective, although a number of unpublished studies will produce a different outcome. It is challenging to access this unpublished data to provide a comprehensive and objective review on the current state of knowledge on the effectiveness of cognitive training.

7.2 Cognitive Training Approaches

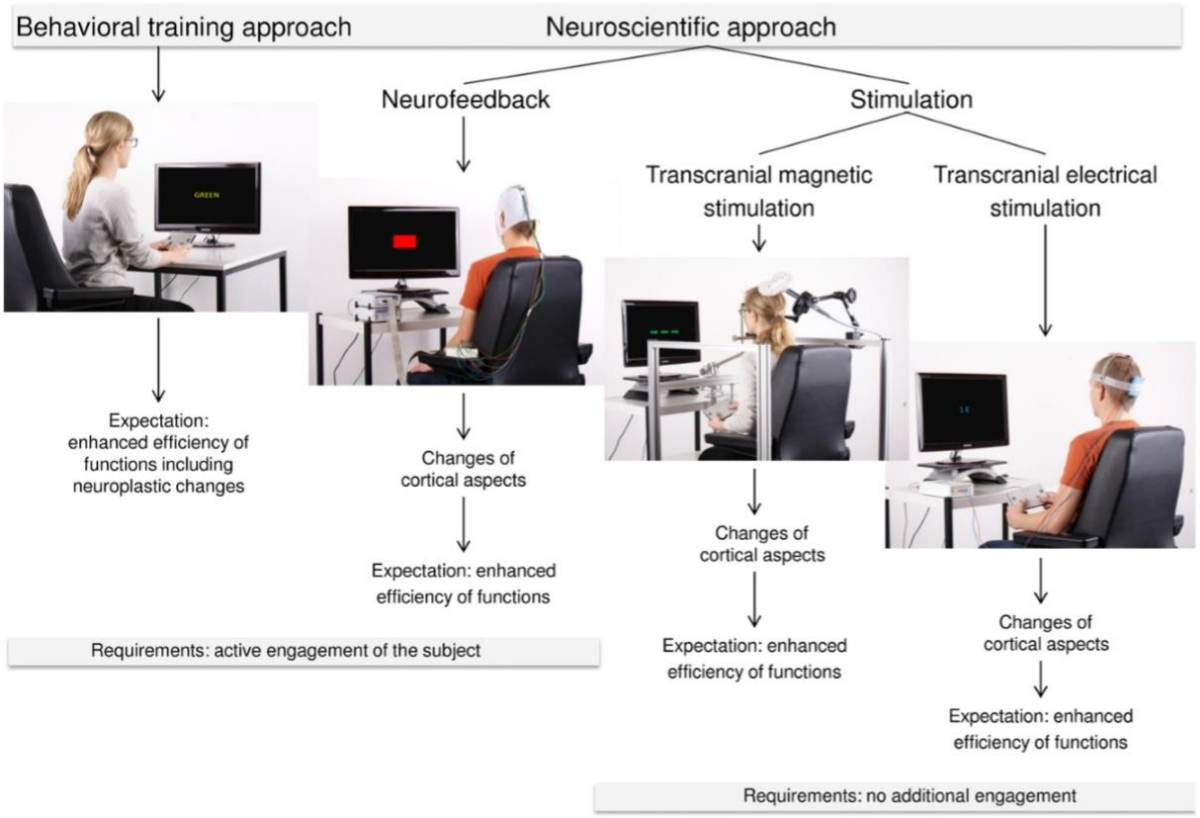
A range of theoretical training approaches to improve cognitive functions are investigated in the literature (Enriquez-Geppert, Huster, & Herrmann, 2013) (Figure 23). Indeed, enhancing the capabilities of EFs by (a) behavioral computerized training and (b) modulating approaches in clinical populations, such as patients diagnosed with ADHD (Cortese et al., 2015; Sonuga-Barke, Brandeis,

Holtmann, & Cortese, 2014) and non-clinical populations has been a research topic of great interest (Enriquez-Geppert et al., 2013; Karch, Albers, Renner, Lichtenauer, & von Kries, 2013; Strobach & Karbach, 2016). This dissertation focuses on research in the field of *behavioral training*. Behavioral training aims to achieve a temporally stable facilitation of specific skills or cognitive functions through repetitive engagement in behavioral tasks designed to address the skills or cognitive functions of interest (Enriquez-Geppert et al., 2013). Behavioral trainings are expected to enhance the efficiency of cognitive functions and to induce related neuroplastic changes (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). However, it is acknowledged that efficiency research on e.g., *neuroscientific methods*, aiming to improve cognition, is equally important.

Neuroscientific approaches, such as *neurofeedback* or *neural stimulation* have tried to achieve peak performance in skills and cognition by modifying their underlying neural activity. Neurofeedback is a method that feeds back a representation of one's brain activity in real time to self-regulate one's own brain activity in order to alter underlying neural mechanisms of cognition and behavior (Enriquez-Geppert, Huster, & Herrmann, 2017; Marzbani, Marateb, & Mansourian, 2016). Neurofeedback has been successfully applied in healthy individuals to boost measures of attention, memory and intelligence among other factors (Gruzelier, 2014; Wang & Hsieh, 2013). Theories and models to explain the underlying mechanisms of neurofeedback learning have been intensively studied (Sitaram et al., 2017). The application of neurostimulation enhances EFs in healthy and clinical populations (Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Sarkis, Kaur, & Camprodon, 2014). For a summary on this topic refer to Enriquez-Geppert et al., (2013). Common methods of neural stimulation are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). In tDCS (Brunoni et al., 2011) and tACD (Herrmann, Rach, Neuling, & Strüber, 2013), the brain is stimulated non-invasively but directly by electrodes attached onto the scalp that deliver low-frequency current. TMS stimulates the brain non-invasively via a magnetic field that is applied to the head by a coil (Nollet, van Ham, Deprez, & Vanderstraeten, 2003).

Figure 23

Theoretical Training Approaches to Improve Cognition



Note. Theoretical training approaches differentiated according to behavioral training, neurofeedback and stimulation techniques. Adapted from Enriquez-Geppert et al. (2013).

7.2.1 Effectiveness of Behavioral Cognitive Training: Training-Related Factors

The effectiveness of behavioral cognitive training is mediated by characteristics of the training task and the training protocol (Jolles & Crone, 2012). The authors listed relevant training-related factors, among others, the (a) *training intensity* (i.e., length, number of training sessions as well as the time interval between training sessions), (b) *training complexity* (i.e., to which extent does the training address the targeted cognitive processes of interest and possibly other processes due to task impurity), (c) *stimulus and task variability* (constant or variable across training, within and between cognitive domains) (Healy, Kole, & Bourne Jr., 2014; Schmidt & Bjork, 1992) and (d) *task difficulty* (i.e., degree of difficulty, adaptive versus non-adaptive training) (Enriquez-Geppert et al., 2013). Task difficulty adaptations can be used intentionally to introduce a mismatch between a subject's cognitive abilities and task demands placed on them. According to this mismatch model, the gap between cognitive functional capability and experienced demands are the driving force of neural plastic alterations related to cognitive training gains (Lövdén et al., 2010). A further factor is (e)

feedback (i.e., present versus absent, online feedback versus delayed feedback) (Bergman Nutley et al., 2011; Holmes, Gathercole, & Dunning, 2009; Klingberg et al., 2005) but some studies report no effect of feedback on training performance (Dowsett & Livesey, 2000; Wilkinson & Yang, 2012). Yet, further biasing factors are related to the subjects being trained, such as their age and motivation (for details on subject-related training confounds please refer to section 7.2.3 *Interpreting Cognitive Training Effects: Confounds and Counter-Measures*).

7.2.2 Markers of Effectiveness in Behavioral Cognitive Training

The quality of training research can be evaluated using a number of predominantly objective criteria. Needless to say, good training research should be unbiased by commercial or financial interests. It should use proper active control groups, although some research questions, such as "*Which target group responds best to training?",* may even justify the absence of a control group. Training studies should be sufficiently powered to be able to detect even small training and transfer effects. They should use proper samples for whom the training is designed and address potential limitations regarding the generalizability of training effects to other samples: a training that is effective in children may not prove suitable for elderly adults and vice versa. Training effects should sustain over time and transfer into everyday life.

To distinguish treatment from non-treatment effects (e.g., test-retest-effects and motivation), methodologically sound cognitive training studies employ a comparison of performance changes in the training group that receives a training intervention relative to an adequate control condition (Green, Strobach, & Schubert, 2014). A control group might also be matched to the training group on key characteristics, such as general cognitive abilities, sex, age or even familiarity with computer games (Jolles & Crone, 2012) to minimize non-treatment related cohort effects.

Some studies included an easy to implement passive control group, that received no treatment between pre-test and post-test sessions (Thorell, Lindqvist, Bergman, Bohlin, & Klingberg, 2009). Passive control groups account for effects of familiarity that result from repetitive task engagement. However, they do not control effects of expectation that increase a subject's confidence and motivation. Confidence and motivation gains lead subjects to put more effort in post-training tasks and thus bias the pre-treatment versus post-treatment comparison (Jolles & Crone, 2012). The proper control group is therefore the active control group.

Active control groups, that receive a placebo intervention, control for such biases. However, see Boot, Simons, Stothart, & Stutts (2013) for a critical discussion on active control groups. Ideally, a placebo intervention is highly similar, at best equivalent, to the cognitive training intervention regarding task design, stimuli and training protocol. The only difference is that the control

intervention is ideally ineffective and does not address the cognitive function to be trained or any particular cognitive ability that may bias the comparison of performance changes. Of course, it is difficult to design such a control task. In practice, studies have used several other placebo interventions including (a) engagement in an earlier version of the training intervention (Holmes et al., 2009), (b) watching videos (Rueda, Checa, & Cómbita, 2012), (c) playing computer games (Mackey, Hill, Stone, & Bunge, 2011; Thorell et al., 2009), (d) solving cross word puzzles (Hardy et al., 2015) or (e) two separate trainings that promote different cognitive processes (Mackey et al., 2011; Thorell et al., 2009).

To be noted, it is another option to employ a training without any control group, which might be appropriate when the training study aims to see which individual responds best to a training procedure. This study design is suitable to answer a research question, such as "*Do subjects with good general cognitive abilities benefit more from a cognitive inhibition training than those subjects with poorer general cognitive abilities?*". To answer this question, a sample with a wide range in general cognitive abilities should be trained.

A straight-forward index of cognitive training effectiveness are performance improvements on training tasks (e.g., shorter reaction times or reduced error rates) in process-based trainings. In strategy-based approaches, the trained strategy's frequency of use, speed and proficiency serve as an index of training effects (Jolles & Crone, 2012).

Changes in group differences and/or individual performance changes during the training by means of a learning curve provide further insights into training effectiveness (Jeter, Dosher, Petrov, & Lu, 2009; Jolles & Crone, 2012). A learning curve displays change in performance as well as changes in the learning rate over time and provides further indications on training effects when performance is assessed at multiple time points throughout training. Learning curves are sensitive to inter-subject variability (Heathcote & Brown, 2000). According to the mismatch model of cognitive plasticity, a typical learning curve is characterized by its initial rapid performance increase which then diminishes throughout the learning process until reaching an asymptotic level (Jolles, Grol, van Buchem, Rombouts, & Crone, 2010; Lövdén et al., 2010).

Follow-up measures reveal potential long-term training effects (Holmes et al., 2010; Wilkinson & Yang, 2016a; Willis et al., 2006) and give insight into the durability of cognitive training procedures beyond simple performance gains during the training period. They may also display secondary training effects, such as training-related increases in motivation to learn, which might even increase performance at follow-up assessment after the training phase (Jolles & Crone, 2012).

A further effectiveness index is the transfer of training-related performance gains to untrained tasks that require the same or other mental functions, or performance transfers to everyday life (near and far transfer, see section 7.2.4 *Transfer of Training Effects*).

7.2.3 Interpreting Cognitive Training Effects: Confounds and Counter-Measures

The interpretation of cognitive training effects is complicated by confounding factors – for a summary see Jolles & Crone (2012) and Green et al. (2014). The following section outlines potential confounds and their counter-measures in behavioral cognitive trainings including (a) task repetition effects, (b) placebo effects, (c) similarity between tasks, (d) aspects of motivation and expectation effects, as well as (e) cohort effects. For considerations and recommendations on the training design and training principles refer to Enriquez-Geppert et al. (2013), Nutley & Söderqvist (2017) and Operskalski & Barbey (2016), for example. For conceptual and methodological issues relevant in the study of training-related changes on the neural architecture and cortical functions refer to Church, Petersen, & Schlaggar (2010), Galván (2010) and Poldrack (2000).

It is important to separate test-retest effects from true training effects when assessing the benefits of cognitive training (Bors & Vigneau, 2003; Enge et al., 2014; Talanow & Ettinger, 2018). Task repetition during training sessions or baseline versus post-training comparisons increase task familiarity. Task familiarity could result in performance gains due to the promotion of task management processes or other processes apart from the cognitive function of interest. Thus, any performance gain due to task repetition is primarily not the result of facilitation in the underlying desired cognitive function, which the training intended to promote. A framework by Green et al. (2014) drew attention to the fact that the length of the pre-test and post-test session may determine learning at pre-test itself, which in turn influences the level of test-retest effects. According to the framework, large amounts of learning at pre-test leaves little room for improvement through training and little to no difference between treatment and control group performance at post-test. Learning at pre-test is minimized by reducing the number of pre-test trials, not providing any feedback and extending the time interval between test and retest (Green et al., 2014).

Further confounding factors closely related to task repetition are implicit memory effects of *priming*, where the exposure to one stimulus eases the response to another (Tulving & Schacter, 1990), and the development of *task strategies* (Kramer et al., 1999; Morrison & Chein, 2011). To minimize task repetition effects and accompanying priming and task strategies, (a) training conditions should be unpredictable, (b) training should be highly variable with respect to the presented stimuli and demanded response modalities and (c) use several training tasks that address the same underlying cognitive function to be trained (Enriquez-Geppert et al., 2013).

Positive performance changes in training interventions could potentially result from placebo effects (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Kermen, Hickner, Brody, & Hasham, 2010; Rabipour & Raz, 2012; Wager & Atlas, 2015), i.e., when subjects expect a training intervention to be effective (Green et al., 2014). Such expectations may increase either a subject's motivation to

engage in the training and/or to put more effort into training. This may cause performance improvements relative to a subject who does not expect the training to be effective. However, studies that have empirically tested placebo influences on cognitive training measures are rare (Foroughi et al., 2016; Stothart, Simons, Boot, & Kramer, 2014). It is striking that the majority of training studies inform potential subjects about the training nature of the study upon recruitment (overt recruitment), thus increasing the likelihood that subjects generate expectations about the effectiveness of the training (Foroughi et al., 2016). Indeed, the authors empirically showed that overt recruitment relative to no information about the training nature (covert recruitment) significantly increased fluid intelligence measures in Raven's Advanced Progressive Matrixes and in the Bochumer Matrix Test. Subjects who expected positive training results were overrepresented in the overt recruitment group. This finding illustrates the need for careful, non-suggestive communication and recruitment in the training context as well as random assignment of subjects to the intervention groups. Furthermore, placebo effects can be statistically controlled in the data analysis by including ratings of the subject's believe in cognitive training as a covariate (Rabipour & Davidson, 2015).

Task-difficulty adaptation can minimize confounds of a subject's motivation to engage in the training (Enge et al., 2014; Enriquez-Geppert et al., 2013; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). Task-difficulty adaptation ensures an individual, challenging level of task difficulty throughout the entire training session and thus ensures a rewarding high degree of motivation. At the same time, task-difficulty adaptation prevents automation processes at an early state of training. Such automation processes reduce the mismatch between training task demands and cognitive capabilities, resulting in constrained training gains (Enriquez-Geppert et al., 2013).

Similarity in context and stimuli between training and transfer tasks could also be a potential confounding factor on training gains (Jolles & Crone, 2012). Training gains in transfer tasks might be more related to familiarity with the type of task and stimuli rather than the trained cognitive mechanism.

Yet another issue is confounding influences of cohort effects (Jolles & Crone, 2012). Relevant factors here are, for example, the subjects' age (Bürki, Ludwig, Chicherio, & de Ribaupierre, 2014), their level of fluid intelligence (Jaeggi, Buschkuehl, Shah, & Jonides, 2014), their initial performance level at beginning of the training and whether they belong to a clinical or healthy sample (Johnstone, Roodenrys, Phillips, Watt, & Mantz, 2010). In summary, these factors have an impact on the room of potential improvement. For example, a child's current stage of development can influence training effects (Jolles and Crone, 2012). Children, whose cognitive abilities are still developing, provide substantial room for training gains as shown in measures of inhibition (Dowsett & Livesey, 2000; Liu, Zhu, Ziegler, & Shi, 2015; Thorell et al., 2009) and working memory (Holmes et al., 2009; Pugin et al.,

2015). Cognitive training benefits are found across age groups (Bherer et al., 2005, 2008; Karbach & Kray, 2009). Also elderly cohorts can improve inhibition abilities (Ji, Wang, Chen, Du, & Zhan, 2016; Wilkinson & Yang, 2012, 2016a, 2016b) and aspects of fluid intelligence (Günther et al., 2010) by training. Although age-comparative studies showed equivalent transfer effects in young and old adults (Bherer et al., 2005, 2008; Bürki et al., 2014; Karbach & Kray, 2009), other studies concluded that age modulates the amount of training transfer (Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008; Schmiedek, Lövdén, & Lindenberger, 2010) in support of the notion that cognitive plasticity declines throughout adulthood and old age (Brehmer, Westerberg, & Bäckman, 2012; Shing, Brehmer, & Li, 2008). Some training research suggested that older adults show constraints in the maintenance of training gains (Dahlin, Nyberg, Bäckman, & Neely, 2008; Li, Schmiedek, Huxhold, Ro, & Smith, 2008), other studies did not confirm this finding and reported maintenance effects across age groups (Borella et al., 2014; Brehmer et al., 2012).

7.2.4 Transfer of Training Effects

Enhancement of training task performance alone gives little insight into the extent to which cognitive training effects can be generalized. After all, it is a key goal of a cognitive training to facilitate cognition *outside* the somewhat artificial training and laboratory context and to achieve improvements in real life tasks and situations.

Transfer can be defined as effects of a training and learning experience on other explicitly not trained tasks, situations or processes (Perkins & Salomon, 1992; Sandberg, 2014). *Near transfer* refers to the facilitation in performance within a very similar context, the same domain or cognitive function that was trained (Enriquez-Geppert et al., 2013; Lussier, Gagnon, & Bherer, 2012; Perkins & Salomon, 1992). *Far transfer* effects define performance gains between contexts or in other untrained domains or functions (Enriquez-Geppert et al., 2013; Lussier et al., 2012; Perkins & Salomon, 1992).

The results of over a century of research on transfer effects of learning are diverging opinions and little agreement among scholars about its nature, extent and underlying driving mechanisms (Barnett & Ceci, 2002). At the beginning of the 20th century, Edward Thorndike's many works led him to claim that learning transfer is a rather rare phenomenon that broadly depends on highly similar, if not identical, training and transfer contexts (Barnett & Ceci, 2002; Thorndike, 1906). Opponents on the other hand, such as the researcher Charles Hubbard Judd, argued that "*every experience has in it the possibilities of generalization*" (Judd, 1908 in Barnett & Ceci, 2002).

The former view is in line with the assumption that transfer depends on the degree of structural and procedural overlap between training und transfer tasks. Such overlap is formally expressed by a significant correlation between training and transfer measures (von Bastian & Oberauer, 2014),

meaning that training and transfer tasks hold similar processing demands (Schmidt & Bjork, 1992). The larger the overlap, as signaled by a relatively high correlation coefficient, the more transfer should take place. The later view assumes that the brain's functions and organization are shaped by its experiences throughout the lifespan (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004).

7.3 Cognitive Inhibition Training

7.3.1 Behavioral Effects of Cognitive Inhibition Training

Given the popularity of cognitive trainings and the importance of inhibition in everyday aspects of life (Diamond, 2013), relatively few studies have explicitly addressed whether inhibition improves through training. Research suggests that inhibitory control can improve by training in healthy young children (Dowsett & Livesey, 2000; Liu et al., 2015; Thorell et al., 2009), healthy young adults (Berkman, Kahn, & Merchant, 2014) and healthy elderly populations (Wilkinson & Yang, 2012, 2016a, 2016b; Ji et al., 2016).

In children, such gains in inhibition performance were indeed induced by experience and training in a child-friendly version of the go/no-go task (Dowsett & Livesey, 2000). Even healthy 4-year-old preschoolers showed training effects of response inhibition (Liu et al., 2015). In that study, the children either received an inhibition training in the form of a computerized commercial game, which is a variant of the go/no-go task, or were assigned to an active control group that played a computerized coloring game. The post-treatment score of the commercial inhibition game significantly improved in the training group relative to the control group and this difference was not influenced by gender. Another study employed in preschool children by Thorell and colleagues (2009) reported significant improvements in inhibitory control measures through a diversified inhibition training. The authors employed two child friendly variants of the go/no-go paradigm[3] (Trommer, Hoeppner, Lorber, & Armstrong, 1988), two stop signal paradigms (Logan & Cowan, 1984) and a flanker paradigm[4] (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Children who underwent the five-week inhibition training showed significant improvements in interference control (i.e., reduced error rates) in a Stroop-like task and a significant increase in no-go commissions.

In comparison, research on training-induced plasticity of inhibition in healthy young adult populations is rather rare (Berkman et al., 2014; Enge et al., 2014; Maraver, Bajo, & Gomez-Ariza,

[3] The task instructed children to raise and lower the index finger of their dominant hand in response to the go signal and to refrain from any response to the no-go signal. Response error rates served as an index of inhibitory control.

[4] Subjects were instructed to indicate the orientation of a briefly presented left- or right-facing arrow by means of a button press. The target arrow was flanked by a set of distractor arrows. Distractor arrows pointed in the same direction as the target arrow on compatible trials (e.g., > > > > >) or pointed in the opposite direction on incompatible trials (e.g., < < > < <). The flanker effect, defined as the difference between reaction times of the incompatible and compatible condition, as well as error rates are markers of cognitive control. The flanker task involves conflict resolution and selection-for-attention.

2016; Millner, Jaroszewski, Chamarthi, & Pizzagalli, 2012). More recently, Maraver and colleagues (2016) employed a comprehensive training study that compared separate effects of a six-session working memory training or inhibitory control training (assessed by a test battery made up of a Stroop-like task, a conflict resolution task and a go/no-go-like task) relative to active and passive controls. Working memory training and inhibitory control training successfully showed specific pre-test to post-test enhancements in the n-back task and Stroop task as a marker of successful EF training. Further, Enge and colleagues (2014) employed an inhibitory control training study that followed a randomized, double-blind pre-test/post-test/follow-up design. Subjects either engaged (a) in an adaptive training of the go/no-go task and the stop signal task (training group), (b) in the same training procedure with fixed task difficulty (active control group) or (c) in no treatment between baseline and post training sessions (passive control group). Reaction times significantly improved in both training tasks in the adaptive and non-adaptive training group and exceeded performance increases of the passive control group. However, reaction time improvements came at the cost of increased response errors, suggesting a speed-accuracy trade-off and no true training effect of inhibitory control. Also, training gains neither transferred to an untrained Stroop Task (no evidence of near transfer) nor transferred to measures of fluid intelligence (no evidence of far transfer). Yet another study by Millner and colleagues (2012) came to a different result pattern by showing robust training-related improvements in the Simon task[5] (conflict monitoring) and the emotional go/no-go task (interference resolution) in healthy young adults. Bergman and colleagues (2014) analyzed neural mechanisms underlying successful adaptive inhibitory control training in the stop signal task using fMRI in healthy college students (see section 7.3.3 *Neural Effects of Cognitive Inhibition Training* for details). Inhibition training comprised ten sessions of engagement in the stop signal task across three weeks. At the behavioral level, stop signal training significantly reduced SSRTs from pre to post training, more than in active controls. SSRTs steadily improved across training and improved inhibition performance did not come at the expense of progressive slowing on go trials as a strategy to improve the stopping rate.

Elderly adults resemble a potential target group for brain training interventions aiming to counteract age-related cognitive decline and to maintain mental functions in old age. Also training effects in the domain of executive control are a popular research topic of interest. In elderly adults, Wilkinson and Yang (2012) reported performance gains in inhibition, indexed by a significant reduction in the Stroop interference effect, in a sample of volunteers who underwent a six-session

[5] The Simon task instructed subjects to respond to stimuli presented to the left or right of a fixation cross by means of button presses. In congruent trials, subjects had to press a button located on the same side as the target stimulus. In incongruent trials, subjects had to press a button at the opposite side of the target stimulus. The difference in reaction times and accuracy between congruent and incongruent trials is referred to as the *Simon effect*. Responses are generally slower and less accurate in incongruent trials due to interference in the response-selection stage of the decision making process (Simon, 1969).

Stroop task (Stroop, 1935) training. A follow-up study suggested that these Stroop training gains persisted over a period of up to three years (Wilkinson & Yang, 2016b). The same group of researchers also reported practice effects of three lab-based inhibition tasks in a different sample of healthy older adults (Wilkinson & Yang, 2016a). Furthermore, Ji and colleagues (2016) found training gains in inhibitory control after a four-week inhibition training in a group of subjects aged 60 and above.

Inhibition Training in The Context of Clinical Psychology. Deficits in inhibitory control are characteristic to a variety of clinically relevant psychological disorders, such as schizophrenia (Ettinger et al., 2018), ADHD (Barkley, 1999), eating disorders (Bartholdy et al., 2017), obsessive drinking (López-Caneda, Holguín, Cadaveira, Corral, & Doallo, 2014), problem gambling (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009) and substance abuse (Smith, Mattick, Jamadar, & Iredale, 2014). Given a key role of inhibitory control in psychological well-being, improving inhibition abilities by training might prove to be a useful addition to status quo treatment protocols in the future.

The following section addresses research on inhibition training in the clinically relevant context. Only few studies in this field of research are publicly available so far. The published research points in the direction of a certain potential for training-induced improvements in cognitive control in clinical samples of children (Johnstone et al., 2010) and adult populations (Thummala & Satpathy, 2009) diagnosed with ADHD. In the former study, a combined working memory and inhibition training reduced the frequency of inattention and expression of hyperactivity symptoms in a high intensity training group (adaptive task difficulty) but not in a low intensity training group (non-adaptive task difficulty). However, improvements in go/no-go performance failed to pass the level of significance. The later research by Thummala and Satpathy (2009) provided data of a sample of eight college undergraduates diagnosed with ADHD. Subjects engaged either in a battery of training tasks demanding prepotent response inhibition and resistance to distractor interference (i.e., antisaccade task, flanker task, variant of the Stroop task) or in an active control treatment comprising only control trials of the training battery that did not require inhibition skills. The authors reported training-induced improvements in response inhibition performance by means of reaction time decreases and response accuracy increases.

The effectiveness of cognitive inhibition trainings is further analyzed in applied clinical contexts of public health. For example, food-specific cognitive inhibition trainings map food cues onto stop signals. They significantly decreased food intake and bodyweight and reduced the desire to eat, as a measure of executive control and facilitation of automatic inhibition associations (Jiang, He, Guan, & He, 2016; Lawrence, Verbruggen, Morrison, Adams, & Chambers, 2015; Lawrence, O'Sullivan, et al., 2015). For instance, Houben & Jansen (2015) paired chocolate with no-go cues. A meta-analysis

confirms the efficacy of inhibitory control training for short-term appetitive behavior change in the laboratory to reduce food and alcohol consumption (Jones et al., 2016). However, food-specific cognitive trainings were not always successful and training effects are stimulus-specific (Lawrence, Verbruggen, et al., 2015). Another application field of cognitive inhibition training is the treatment of alcohol consumption in problem drinkers (Houben, Nederkoorn, Wiers, & Jansen, 2011; Jones & Field, 2013; Jones et al., 2014). Although some research reported significant training effects on reducing weekly alcohol intake (Houben et al., 2011), other research indicated that the observed influence on alcohol consumption in the laboratory seems to be transient (Jones & Field, 2013).

In sum, results on the effectiveness of inhibition training in the clinical context is rather mixed and inconclusive at this point. Considering the key role of inhibition in relation to the psychological well-being, it is indeed important that future research clarifies which training protocols might prove to be effective and which target groups may benefit from inhibition training.

7.3.2 Transfer Effects of Cognitive Inhibition Training

It is an important criterion for the effectiveness of brain training procedures that observed improvements in a trained cognitive domain are not limited to the training task and training context. Instead, training gains should rather be reflected in other cognitive tasks and in everyday life. In short: training effects should transfer.

Near Transfer. Some evidence supports the notion that training-related inhibition gains transfer to other untrained tasks that demand inhibitory control, a phenomenon termed *near transfer*. For example, a study by Zhao, Chen, and Maes (2018) in children and adults came to the conclusion that training-induced inhibition gains transferred from an adaptive go/no-go task to a similar response inhibition task with different stimuli. In young adults, Maraver and colleagues (2016) reported near transfer from a training battery that demanded response inhibition and interference control in a Stroop-like task, a conflict resolution task and a go/no-go-like task to an untrained stop signal task. Millner and colleagues (2012) showed near transfer effects from the Simon task and the emotional go/no-go task to interferences control in the Eriksen flanker task. In older adults, Ji and colleagues (2016) reported near transfer to an untrained inhibition task that demands deleting relevant information from the focus of attention (*deletion* according to 4.1.4 *Hasher's Classificatio*n). Lustig and colleagues (2007) as well as Wilkinson & Yang (2016a) demonstrated near transfer effects in digit and number variants of the go/no-go task.

However, other research has not confirmed the notion of near inhibitory control transfer (Enge et al., 2014; Johnstone et al., 2010; Liu et al., 2015; Thorell et al., 2009; Wilkinson & Yang, 2012, 2016a).

More precisely, Thorell et al. (2009) found no transfer from a successful inhibition training battery comprising tasks that demand inhibition of prepotent motor responses, stopping of ongoing responses and interference control to untrained child-friendly inhibition tasks, i.e., the Day-Night Stroop-like task[6] (Gerstadt, Hong, & Diamond, 1994) and a variant of the go/no-go task (Berlin & Bohlin, 2002). In another study in children, neither training a computerized child-friendly variant of the go/no-go task (Liu et al., 2015), nor engaging in an adaptive combined working memory and inhibition training (Johnstone et al., 2010) promoted near inhibition transfer to a different go/no-go task. Enge and colleagues (2014) reported a speed-accuracy trade-off (faster responses at the expense of higher error rates) in their go/no-go and stop signal training tasks that did not translate into the near transfer of inhibitory control abilities in the Stroop task. The speed-accuracy trade-off in training caused general improvements in Stroop reaction times over time as well as improvements in the Stroop congruency effect independent of training group. In older adults, Stroop task training gains did not transfer to an untrained go/no-go-task (Wilkinson & Yang, 2012).

Far Transfer. Research on transfer of improvements in inhibitory control abilities to untrained tasks that demand other cognitive abilities (far transfer) has shown diverging results.

Sometimes transfer is only short-lived and applies to only a part of the study sample (Zhao et al., 2018). Zhao and colleagues (2018) found a short-lived transfer from an adaptive go/no-go task to working memory, updating and task switching abilities in children but not in adults. Results by Liu et al. (2015) suggested that improvements induced by a computerized response inhibition training in children transfer to abstract reasoning abilities as illustrated by higher scores in Raven's Matrixes.

In older adults, research reports inhibitory control transfers to measures of fluid intelligence (g_f) (Ji et al., 2016). Work by Thummala and Satpathy (2009) suggested that training-related inhibitory control improvements (i.e., reaction time decreases and accuracy increases) have the potential to transfer to untrained EF tasks in adults diagnosed with ADHD. Maraver and colleagues (2016) detected a far transfer of inhibition training to reasoning abilities (Raven's Matrixes) in a sample of healthy college students.

Other studies failed to confirm the existence of far transfer effects of inhibitory control (Enge et al., 2014; Thorell et al., 2009; Wilkinson & Yang, 2012, 2016a). To be specific, Wilkinson & Yang (2012) detected neither transfer from Stroop task performance gains to perceptual speed, inductive reasoning, attention nor task-switching. Furthermore, results of a more recent study by the same group are inconclusive regarding *near-far* transfer of inhibitory control measures. Near-far transfer was assessed in transfer tasks that were different from the practiced tasks, but tapped the same

[6] The task instructed the child to verbally respond to a card that displays an image of the sun with the word "night" and to verbally respond to a card that displays an image of the noon with the word "day". Error rates and reaction times served as performance measures of interest.

underlying cognitive ability, such as the Stroop task, reading with distraction, and directed forgetting. The study also showed no evidence of *far-far* transfer assessed in tasks that were structurally different from the practice task and tapped different underlying cognitive abilities than those of the practiced task, such as working memory, episodic memory, reasoning and processing speed (Wilkinson & Yang, 2016a). It should be noted that the authors employed an intermingled EFs training (i.e., training of updating, shifting and inhibition abilities) which included inhibitory control rather than a purer inhibition training. The choice of a mixed training protocol could have contributed to the lack of transfer effects. Further, Thorell and colleagues (2009) found neither transfer of inhibition improvements on working memory nor attention while Enge et al. (2014) observed no far transfer on fluid intelligence measures (i.e., Raven's Matrixes; IST 2000–R matrices scales; Wiener Matrizen-Test). Nevertheless, the later result does not rule out the existence of transfer effects on fluid intelligence measures in case there had not been a speed-accuracy trade off in the training task.

In sum, more research is required to soundly confirm or falsify the hypothesis that inhibition training effects transfer to other EF domains beyond effects of repeated task engagement.

7.3.3 Neural Effects of Cognitive Inhibition Training

A further line of research is concerned with the question of whether cognitive training does not only cause changes in behavior, but also changes in the structure and functioning of the human brain. This strand of research is driven by the concept of *neural plasticity*, that builds on the idea that the human brain adapts its physical structure and functional organisation to its environment based on experience and training (Fuchs & Flügge, 2014; Galván, 2010; Hebb, 1949). It is widely accepted that cognitive and neural plasiticity takes place across the life span (Jones et al., 2006). A few studies have investigated potential effects of cognitive training and practice on mechanisms involved in neural plasticity (Karbach & Schubert, 2013; Kelly & Garavan, 2005). For a comprehensive summary of neuroimaging evidence regarding cognitive training-induced changes in brain activation, functional connectivity and brain structure refer to Jolles & Crone (2012).

Likewise, studies that have investigated the neural pathways of inhibition training effects are rare despite the critical role of the inhibition mechanism in executive control and despite the contibution of deficits in inhibition to psychiatric and neurological disorders (Berkman et al., 2014; Johnstone et al., 2010; Liu et al., 2015; Millner et al., 2012; Spierer, Chavan, & Manuel, 2013).

Berkman and colleagues (2014) assessed the underlying neural activity of an adaptive stop signal training relative to an active control condition in healthy adults. The authors employed fMRI before and after training. At the behavioral level, the pre-test versus post-test comparison showed that the

training group's performance improved in stop signal trials, more than in active controls. A pre-post comparison of brain images points to the vital role of a proactive control mechanism that was implemented by the inhibitory control training: from pre-test to post-test, acitvity in the IFG decreased while subjects implemented inhibitory control on stop-trials but IFG activity increased upon presentation of a cue that signaled the upcoming demand for inhibitory control. Further, control gains in the stop signal training group were related to activations in DLPFC, another key component of the inhibitory control network (Berkman et al., 2014; Dillon & Pizzagalli, 2008).

In a literature review on training-induced behavioral changes and brain plasticity in inhibitory control, Spierer and colleagues (2013) proposed that the quality of stimulus-response associations in inhibition trainings – stable or variable association – promotes either the development of automatic forms of inhibition or the modification of top-down controlled inhibition: (a) in the case of stable stimulus-response associations, such as in the go/no-go task, parietal cortical areas short cut inferior frontal areas in an *automatic inhibition state* leading to faster inhibition of motor activity. (b) In the case of variable stimulus-response variations in the training task, such as in the stop signal task, inhibitory control training modules activations of a *controlled inhibition state*. Here, parietal structures modulate IFG activation via a more time consuming route, that biases subcortical basal ganglia structures. As a result, thalamus and thus motor execution in M1 were inhibited in controlled inhibition with relatively longer SSRTs as compared to automatic inhibition (Spierer et al., 2013).

Evidence derived from EEG studies underscores the involvement of a central post-stimulus negativity component (N2) in inhibitory control training. The N2, sometimes refered to as N200, is a time-locked measure of electrical activity, a negativiation, at the surface of the skulls that is typically evoked 180ms to 325ms after the presentation of a specific visual or auditory stimulus. A great body of literature has linked the N2 to processes of stimulus evaluation, selective attention and conscious distraction (Patel & Azzam, 2005), strategic monitoring and control of motor responses (cognitive control) as well as mismatch, novelty (Folstein & van Petten, 2008) and conflict-effects (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010). In adults, a training comprising the Simon task and the emotional go/no-go task *reduced* the midline fronto-central N2 amplitude during incongruent trials of the flanker paradigm, which was interpreted as a neurophysiological marker of improvements in interference control (Millner et al., 2012). The N2 effect is also reported during a go/no-go near transfer task in children in a different study (Liu et al 2015). Here, the inhibition training induced neural changes during go/no-go performance, indicated by an *increase* in the midline central N2 effect. To be noted, these neural changes were observed in girls only, suggesting differences in neural plasticity between girls and boys. The results indicate that transfer effects of inhibition are not easily found in children.

Yet further insight into the neural effect of inhibition training derived from a clinical study in a sample of children diagnosed with ADHD (Johnstone et al., 2010). Subjects who engaged in a combined working memory and inhibition training showed changes in resting EEG oscillations namely increased delta, reduced alpha and reduced theta activity. Also, larger amplitudes in N1 and N2 event related potentials were observed post training. These findings may suggest improved attentional processes to go and no-go stimuli. However, behavioral improvements in go/no-go performance failed to pass the level of significance (Johnstone et al., 2010).

As outlined in section 7.3. *Cognitive Inhibition Training*, it remains to be determined if and to what extent inhibitory cognitive control improves through intensive computerized behavioral training in healthy adults beyond pure task-repetition effects. Further, research is yet inconclusive as to whether true training effects on inhibitory control may transfer to other, untrained inhibition tasks (near transfer) or even to other, untrained domains of EFs (far transfer). Furthermore, evidence on neural effects of inhibition training is rare at this point but the published studies show some first promising results. Publication III contributed to the development of theory-driven, methodologically sound inhibition training approaches by assessing effects of an intensive inhibition training protocol and potential related transfer effects.

7.4 Publication III

Talanow, T. & Ettinger, U. (2018). Effects of task repetition but no transfer of inhibitory control training in healthy adults. *Acta Psychologica*, *187*, 37-53.

The theoretical assumptions of the Unity and Diversity Model of EF (Friedman & Miyake, 2017; Miyake & Friedman, 2012) (please refer to section 4.2. *Executive Functions* for details) inspired the following published training study. The study aimed to explore potential transfer of an intensive computerized inhibition training within the Unity and Diversity framework. According to the Unity and Diversity model, improvements in inhibition abilities should result in facilitation of updating and shifting abilities and consequently in improvements in higher EFs. To investigate these model assumptions, a training study based on a randomized pre-test/treatment/post-test study design was employed in 102 healthy young adults. The study assessed the effectiveness of a three-week intensive repetitive inhibition training, which comprised eight training sessions on separate days. Furthermore, the study explored near transfer effects to an untrained task demanding predominantly inhibitory control (antisaccade task) and far transfer effects to untrained tasks demanding working memory updating (n-back task), task-set shifting (number-letter-task), and planning abilities (Stockings of Cambridge task).

The research hypothesized to detect training-related improvements in inhibitory control (i.e., faster and more accurate responses in inhibition trials) as well as near and far transfers of inhibitory control to untrained tasks that demand the cognitive abilities mentioned above.

While the experimental group (n = 38) was trained in a high-conflict Stroop task (80% inhibition trials), an active control group (n = 34) performed a simple stimulus-response mapping task during training sessions. The control task was designed to match the Stroop task as much as possible without demanding inhibitory control or other specific facets of EFs. A passive control group (n = 30) received no training intervention and engaged only in a pre-test and post-test session in the interval of three weeks.

Behavioral results of the Stroop training confirmed performance gains in inhibitory control indicated by a stronger reduction in incongruent reaction times relative to other trials (Figure 24). Inhibition-trial reaction times improved to the level of non-inhibition trials. Importantly, this improvement did not come at the expense of increased error rates (i.e., no speed-accuracy trade-off). The Stroop training also promoted processes beyond inhibition because reaction times decreased over time in congruent and neutral Stroop trials, too. The cause of these performance gains is unclear at this point but they could result from improvements in any stage of information processing from perceptual to motor processes. As expected, reaction time performance did not change during the active control training. However, the proportion of anticipatory responses

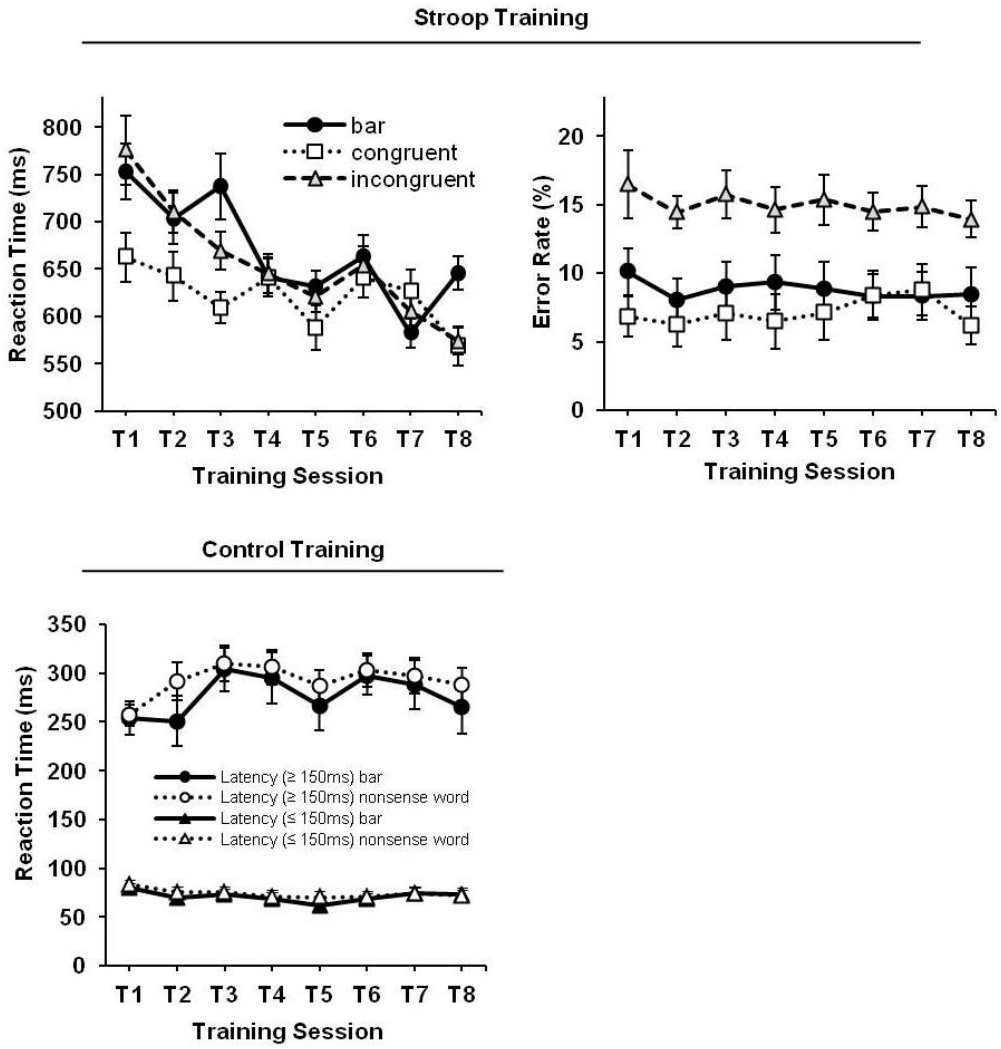
increased over training sessions, suggesting faster stimulus response mapping. Contrary to the study's expectations, which were generated on the basis of the Unity and Diversity Model, neither near nor far transfer effects of inhibition training were observed. Instead, the study observed significant task repetition effects independent of training condition in all transfer tasks (Figure 25, Figure 26). Interestingly, subjects who engaged in the Stroop training showed generally faster responses on Stroop trials, irrespective of trial congruency, which suggests that frequent task repetition during Stroop training seemed to have promoted stimulus-response-associations and task-management processes beyond inhibitory control. These reaction time improvements did not come at the expense of higher error rates.

What are potential explanations for the lack of a near and far transfer in this study? The a priori power analysis showed that the study design and sample size allowed to detect medium-to-large effects with sufficient statistical power. However, effect sizes of inhibitory control transfer are known to be rather small (Thorell et al., 2009) and the current study did not have sufficient statistical power to detect small transfer effects. Another critical aspect concerns the choice of the training task and the transfer tasks. The lack of near transfer effects could also be related to the difference in response domains between the Stroop training and the antisaccade near transfer task. Gains in inhibitory control might not transfer from one response domain to another. With respect to Stroop task parameters, a slow-paced variant of the Stroop task with rather long ISI (> 200ms) and verbal instead of manual responses might have induced stronger response prepotency and stronger related inhibitory control demands. Under these conditions, inhibitory control demands might be sufficient to evoke transfer effects. Further, it cannot be ruled out that near and far transfer effects of executive control might be task-specific. Furthermore, characteristics of the training protocol, presumably in particular the intensity, complexity and difficulty of the training, could be crucial factors for a successful transfer of inhibitory control abilities (for details please refer to section *7.2.1 Effectiveness of Behavioral Cognitive Training: Training-Related Factors*). A further explanation for the lack of near transfer effects could be the latent construct of inhibition itself. Inhibitory control comprises a sub-set of at least three distinguishable processes (Friedman & Miyake, 2004): (a) the inhibition of prepotent motor responses, (b) resistance to distractor interference and (c) resistance to proactive interference. Regarding far transfer effects, inhibition of prepotent responses might not be a suitable sub-set of inhibitory control to transfer to updating, shifting or planning abilities. Finally, training inhibitory control may have been sufficient to improve Stroop task performance, but it might not have affected what is essentially common among domains of EFs according to the Unity and Diversity Model, namely active goal maintenance, management of task goals in the face of interference and selective attention (Friedman et al., 2008).

In sum, the study results suggest that true training and transfer effects of inhibitory control might be smaller than expected in healthy volunteers. Instead, performance in the non-trained cognitive tasks significantly improved due to mere task repetition from pre-test to post-test, independent of the employed training procedure. The data raise the question if simple task repetition might be as effective as intensive training protocols in inhibition training. The lack of transfer effects of inhibition training in this study is in line with previous findings (Enge et al., 2014; Johnstone et al., 2010; Liu et al., 2015; Thorell et al., 2009; Wilkinson & Yang, 2012, 2016a). To be noted, the current study neither directly confirms nor directly falsifies the Unity and Diversity Model. Instead, further research on the effectiveness of cognitive trainings is encouraged. A multi-trait/multi-method approach is a gold standard to adequately analyze training and transfer effects of EFs.

Figure 24

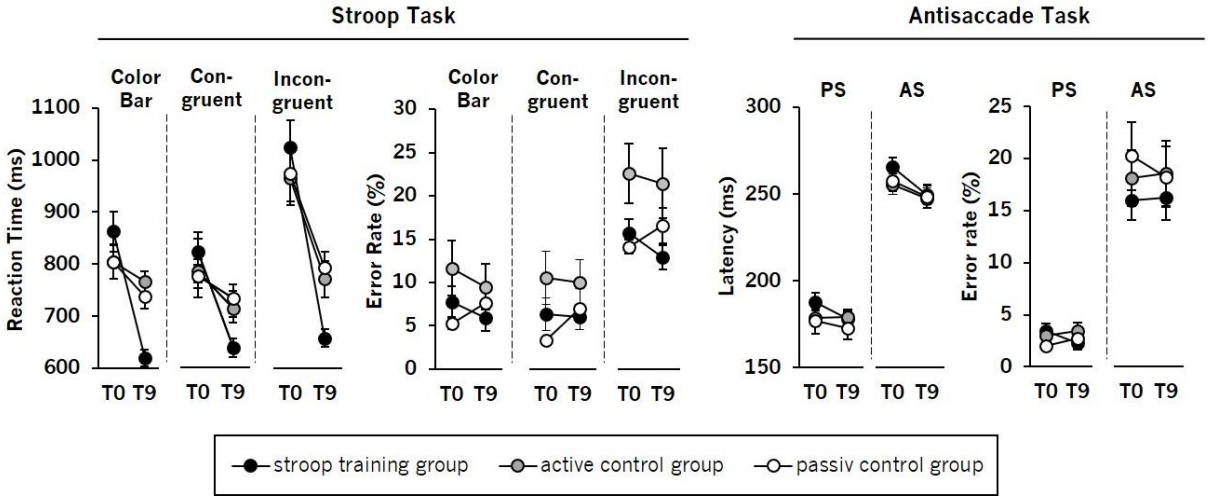
Publication III: Behavioral Results on Training Effects



Note. Stroop training performance (top section) and control training performance (bottom section) across training sessions (T1 to T8). For the Stroop training task, mean reaction times (left) and mean error rates (right) of color bar (black circle), congruent (white square) and incongruent (grey triangle) trials are displayed. For the control training task, mean reaction times of stimulus driven (≥ 150ms; circles) and anticipatory responses (< 150ms; triangles) of bar trials and nonsense word trials are displayed. Error bars illustrate the standard error of the mean (*SE*). Adapted from Talanow and Ettinger (2018).

Figure 25

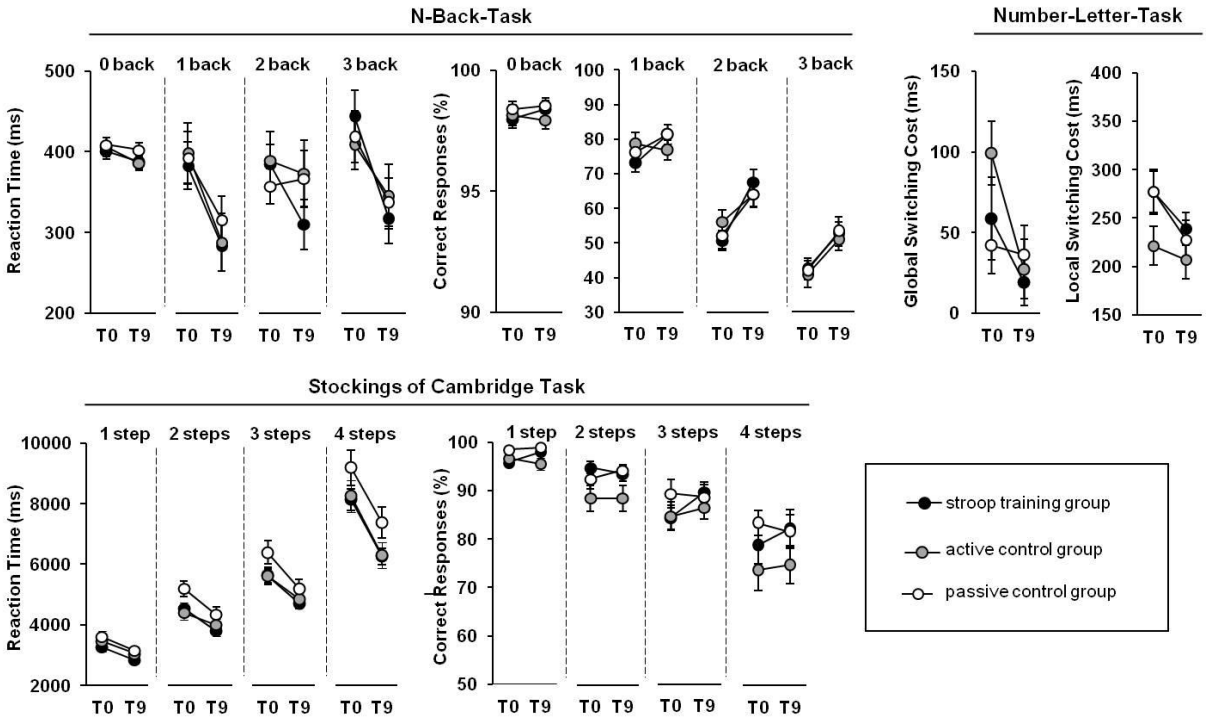
Publication III: Behavioral Results on Near Transfer Effects



Note. Mean group related Stroop task and near transfer antisaccade task performance at pre-test (T0) and post-test (T9). Error bars illustrate the standard error of the mean (*SE*). Latency = time interval between stimulus onset and eye movement onset; PS = prosaccade; AS = antisaccade. Adapted from Talanow and Ettinger (2018).

Figure 26

Publication III: Behavioral Results on Far Transfer Effects



Note. Mean group related task performance at pre-test (T0) and post-test (T9) in far transfer tasks: the n-back task, the number-letter-task and the Stockings of Cambridge Task. Error bars illustrate the standard error of the mean (*SE*). Adapted from Talanow and Ettinger (2018).

8. General Discussion

All three published projects presented in this dissertation investigated inhibitory behavioral control as a subcomponent of EFs within the model system of saccadic eye movements. In sum, the studies contribute to an improved understanding of the competitive, at least partially parallel nature of response generation during response selection in eye movements (publication I), demonstrated the impact of task-set context knowledge on planning, preparation and execution of inhibitory control (publication II) and showed that abilities in inhibitory control can be improved by training but do not seem to transfer to other EF domains (publication III).

8.1 Integration of Results

The antisaccade task is a reliable and well established tool to assess predominantly prepotent response inhibition in saccadic decision making (see section 4.4.4 *Prosaccades and Antisaccades*).

The precise nature of a saccadic decision mechanism in antisaccades remains not fully understood to date although the neural circuitry underlying antisaccade performance is intensively studied and well documented. It is a current matter of debate whether antisaccade performance is mediated by a distinct stop or inhibition signal or whether no such distinct stopping mechanism is involved in the accumulation of evidence in favor of prosaccade or antisaccade decisions (section 5. *Evidence Integration Models of Saccadic Inhibition in The Antisaccade Task*). Recent evidence favors the assumption that prosaccade and antisaccade decision signals compete in a parallel competitive accumulation process towards a response threshold with no distinct stopping mechanism at play. To test the assumption of competitive integration at the behavioral and neural level, a laboratory study and a brain imaging study were conducted in separate samples (publication I). A frequency manipulation altered the accumulation rate of prosaccade and antisaccade signals. Reducing the saccade frequency slowed response programming, which resulted in a relative disadvantage in the race to an execution threshold against an opposing facilitated decision signal. At the neural level, brain activation increases were detected in task-relevant components of a fronto-parietal network related to meeting additional cognitive control demands for correct saccade performance. Further, deactivations in brain regions were found coding non-task related and task-goal distracting processes to bias saccade decisions. In conclusion, the results favor a competitive parallel saccade programming account that is independent of a distinct stop or inhibition signal.

A significant proportion of research on inhibitory control focuses on mechanisms involved in stopping motor responses already in progress, i.e., *reactive* inhibition. However, one should think of executive control from planning to facilitation in order to fully grasp executive control in its entirety. Out of this motivation, a brain imaging study was conducted that assessed *both* proactive and reactive brain processes underlying planning and facilitation of inhibition respectively (publication II).

The study also included a variation of task-set certainty to do justice to the fact that humans often find themselves appraising or even knowing what detailed behavioral needs everyday situations pose to them. In fact, neural imaging data have suggested that proactive inhibition arises even when upcoming task requirements are uncertain (Albares et al., 2014; Chikazoe et al., 2009; Jaffard, Benraiss, Longcamp, Velay, & Boulinguez, 2007; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013). However, it is currently unclear how the brain prepares for top-down inhibition when it is clear from the beginning that responses to a stimulus will have to be inhibited. The results of the publication show that task-set certainty was related to more successful inhibition at the behavioral level, likely due to biases or altering processes in task-set and stimulus encoding, response selection and preparation to meet cued task demands (Braver, 2012; Elchlepp et al., 2016). Task-set foreknowledge distinctly altered proactive and reactive brain signals. We showed that proactive inhibitory control in a saccadic go/no-go task mediates situations of uncertainty in order to facilitate flexible responses to upcoming situational requirements *and* to prepare outright non-responding. A brain region in supramarginal gyrus/inferior parietal lobe was particularly important to proactive and reactive inhibition alike.

Many potential uses for inhibition training applications exist in case inhibition abilities could be specifically strengthened and promoted by training. For example, inhibitory control training (a) may support the development of inhibition abilities in children, (b) might slow down or even prevent cognitive decline in the elderly, (c) may support treatment of mental illnesses associated with inhibition deficits and (d) might possibly optimize cognitive control in healthy individuals. Commercial cognitive trainings seize on these hopes to market training interventions that supposedly improve EFs. They offer – against payment – easy to implement behavioral trainings. However, their effectiveness has not been clearly demonstrated by empirical, independent research to date. Therefore, a methodically sound training study was conducted that examined the effectiveness of inhibition training and assessed potential transfer of training effects to other facets of EFs (publication III). In this context, the publication refers to the framework of Miyake et al. (2000), that postulated that inhibition abilities are interwoven with other facets of executive control. Thus, it was hypothesized that training-induced improvements of inhibitory control drive improvements in other EFs. Indeed, the training intervention improved inhibition performance. However, these training gains neither transferred to an untrained inhibition task nor to other facets of executive control. To what extent the training effects are stable over time is a matter of further research. However, the results challenge the effectiveness of behavioral inhibition training for the purpose of cognitive enhancement in healthy young adults. The publication does not rule out that inhibitory control training could be a valuable contribution to the development of inhibition and the prevention of cognitive decline per se, but this too must first be empirically demonstrated.

8.2 Publication Limitations

Certain limitations need to be addressed with respect to the results of the three published studies presented in this dissertation.

A first concern is related to the assessment of inhibition in gaze control in the fMRI setting. In event-related fMRI task designs, the fMRI depends on rather long intervals between stimuli and trials in order to properly separate BOLD signal changes driven by stimuli or instruction from noisy background brain activity. For example, the fMRI adapted prosaccade and antisaccade task in publication II of this dissertation employed rather long inter-stimulus-intervals and inter-trial-intervals to optimally detect brain activations related to proactive and reactive inhibition. However, adapting the prosaccade and antisaccade task to the fMRI design somewhat alters the nature of the inhibition task: the highly reflex-like nature of the prosaccade is degraded and prosaccades become rather volitional delayed saccades. Prolonged prosaccade latencies – sometimes even to the level of antisaccade latencies known from laboratory studies, such as mean prosaccade latencies of ≥ 300ms in Talanow et al., (2016) and prosaccade latencies of ≥ 500ms in Talanow, Kasparbauer, Lippold, Weber, & Ettinger (2020) – are an indication that prosaccades have become more volitional in the MR scanner setting. The trade-off between a proper fMRI task design and the desired reflex-like nature of the eye movement response raises the question whether inhibition demands can be properly assessed by fMRI in the gaze model system. An increased volitional nature of prosaccades particularly imposes a challenge when contrasting antisaccade trials with prosaccade trials (AS > PS) to reveal brain activations related to cognitive control (refer to publication I and publication II of this dissertation). Brain activations related to voluntary executive control are more likely to cancel each other out in the AS > PS-contrast, as they are similarly prominent in both voluntary prosaccades and voluntary antisaccades. As a result, brain signals related to voluntary executive control in antisaccades could remain at least partially undetected. Due to this limitation, fMRI and laboratory research on gaze control should be linked with caution. Cognitive requirements may differ between tasks that are customized for the scanner setting and for the laboratory. Also, event-related brain activations may remain undetected by fMRI-contrasts.

A second limitation concerns the composition of the study samples in publication I, II and III of this dissertation. Samples were recruited amongst a population of healthy, highly educated, mostly female college students. For this reason, the external validity of the presented findings is limited and study results may not necessarily generalize. Indeed, it is an intensive ongoing debate that research in the social sciences is conducted to a great deal in Western, Educated, Industrialized, Rich, and Democratic (WEIRD) populations, and we should not assume that conclusions drawn from these WEIRD samples generalize to people as a whole (Henrich, Heine, & Norenzayan, 2010).

Third, female subjects were overrepresented in the gender-composition of publication II and publication III. One might address the potential concern that an uneven gender-distribution may bias the behavioral and BOLD signal results in these studies. However, it is the current opinion in the literature that neural characteristics are not reliably and distinctly different between genders (Jäncke, 2018; Rippon, Jordan-Young, Kaiser, & Fine, 2014). Hence, an uneven gender-distribution does not impose a problem to the validity of the results in publication II and publication III.

8.3 Future Research

Future research is encouraged to clarify the role of cortical areas outside the core saccade network in gaze control and saccadic decision making. Particularly the role of activations in bilateral temporal gyrus (publication I) and STG (publication II) revealed by response inhibition contrasts in this dissertation remain to be clarified. A working hypothesis is that these temporal activations may code the analysis of gaze cues (Hooker et al., 2003) or the direction of the saccade (Calder et al., 2007) but not inhibitory control per se.

Future research would benefit from studies on EFs in the context of gaze control in samples that are more representative to the general population, because young adult, mostly female, high performing western college students are not the best representatives of behavior and cognition of humanity per se. In fact, the psychology of undergraduate populations might be heavily influenced by environmental factors and the context in which subjects grew up. Therefore, undergraduates are likely not to be representative to the general population. One promising approach to increase the external validity of research on gaze control and EFs are population studies, such as the *Rhineland Study* in the city of Bonn, Germany. The Rhineland Study is one of the world's largest and most innovative multi center health studies that plans to recruit up to 30000 volunteers to assess their physical and mental health over the next years. The study recruits men and women aged 30 years and above regardless of their health status (JPND Research, 2017). The protocol of the Rhineland Study includes an oculomotor test battery that assesses parameters of gaze control and decision making during prosaccades, antisaccades and smooth pursuit eye movements.

What is unknown about the effectiveness and the limits of cognitive training in different target groups clearly exceeds what is known (Hertzog et al., 2008; Katz, Shah, & Meyer, 2018). Therefore, a main issue for future research is to clarify whether inhibition training effects are stable over time and whether inhibition training holds potential for use in cohorts with inhibition deficits, such as clinically relevant populations of ADHD and schizophrenia. Here, inhibition training may be a valuable component of treatment that may hold useful to addition to the status quo treatment protocols in the future. But this still has to be confirmed by future research. Research on inhibition training in healthy young adults presented in this dissertation came to the conclusion that training effects of

inhibition did not transfer. However, transfer effects may become apparent either (a) in cohorts with inhibition deficits, (b) in children, who still have to fully develop their potential in EFs, or (c) in aging populations, who are faced with age-related decline in inhibition abilities. It is too early to assume that inhibition training gains are short-lived and limited to the task in which they were learned. More methodically sound research on training and transfer of inhibitory control is required to answer these open questions. Also, future research is encouraged to contribute to a better understanding of the neural underpinnings of inhibition gains and transfer.

8.4 Concluding Remarks

Overall, the current thesis confirms that human gaze serves as a valuable framework to study the psychology of cognitive control and decision making. Despite certain limitations, the current theory-driven work is an opportunity to catch a glimpse through the metaphorical *window to the soul* when cleverly combining eye-tracking with brain imaging techniques and behavioral experiments. Thereby, the thesis revealed oculomotor markers of cognition and their neural underpinnings to gain an insight into the underlying nature and fundamental principles of reflex control and decision making. It is a strength of the current thesis that inhibitory control was assessed from planning to initiation across different tasks, a promising approach that aims to understand executive control in its entirety. A further positive contribution of the current thesis is the approach to study in what way executive control is sensitive to environmental information coded in a decision situation. Here, the thesis started by analyzing effects of task set knowledge on executive control. Everyday situations and life experience surely provide much additional choice relevant information whose interaction and impact on the decision process is still to be discovered. The theory-driven training study presented in this thesis adds to the quality of research in the domain of cognitive training. The training study challenges the neuromyth that an easily implemented inhibition training leads to an improvement of versatile mental abilities. It highlights that inhibition is subject to training (but not yet to transfer), which might one day in the future be effectively put to use for optimization and treatment in executive control alike. Ironically, something as simple as the movement of the eyes resembles the gate into the largely undiscovered world of the complex human psyche. The further one gets on the adventurous journey to discover the human mind, the more one realizes how much more there remains to be discovered on the other side of the *window to the soul*.

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10. Appendix A: List of Figures and Tables

Figures

Tables

11. Appendix B: List of Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
APA	American Psychological Association
B_0	Main magnetic field in the MRI scanner
BOLD (response)	Blood-oxygenation level dependent (response)
c	Constant in the general linear model
c.	Lat. circa, signifies “approximately”
CN	Caudate nucleus
CNV	Contingent negative variation
d	Cohen’s measure of sample effect size for comparing two sample means
DLPFC	Dorsolateral prefrontal cortex
DMC	Dual Mechanisms of Control framework according to Braver (2012)
e.g.	Lat. exempli gratia, engl. for example
EEG	Electroencephalography
EF/EFs	Executive function/executive functions
EPI	Echo-planer imaging
ERP	Event-related potential
F	*F* distribution, Fisher’s *F* ratio
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
FP1, FP2	Left, right prefrontal electrode on an EEG cap according to the international 10-20-system
FTC	U.S. Federal Trade Commission
FWE (correction)	Family-wise-error (correction)
g_f	Fluid intelligence according to Cattell (1963)
GLM	General linear model
GPe	Globus pallidus pars externa
GPi	Globus pallidus pars interna
GRFT	Gaussian random field theory
H_0	Null hypothesis, hypothesis under test
Hz	Hertz; a measure of frequency. One Hertz is defined as one cycle per second (1/s)
i.e.	Lat. id est, engl. that is to say
IFC	Inferior frontal cortex
IFG	Inferior frontal gyrus
IFJ	Inferior frontal junction
IOR	Inhibition of return
I_p	Planned neural input according to Cutsuridis et al. (2007)
IPC	Inferior parietal cortex
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
I_R	Reactive neural input according to Cutsuridis et al. (2007)
ISI	Inter-saccadic interval
ITG	Inferior temporal gyrus

LATER	Linear approach to threshold with ergodic rate according to Carpenter and Williams (1995)
LGN	Lateral geniculate nucleus
LIP	Lateral intraparietal area
M	Sample mean, arithmetic average
M, M_{xy}, M_z	Net magnetization in the MRI scanner in the plane as indicated by the subscript respective letter
M1	Primary motor cortex
MeFG	Medial frontal gyrus
MFG	Middle frontal gyrus
mPFC	Medial prefrontal cortex
MR/MRI	Magnetic resonance/Magnetic resonance imaging
ms	Millisecond
n	Number of cases in a subsample
N	Total number of cases in a sample
N1/N100	Timed-locked measure of electrical activity, a negativation, at the surface of the skulls that typically peaks around 100ms after stimulus presentation
N2/N200	Timed-locked measure of electrical activity, a negativation, at the surface of the skulls that is typically evoked 180ms to 325ms after stimulus presentation
OCC	Occipital cortex
OFG	Orbitofrontal gyrus
PCC	Posterior cingulate cortex
p	Probability
PrCG	Precentral gyrus
PoCG	Postcentral gyrus
PFC	Prefrontal cortex
PET	Positron emission tomography
PPC	Posterior parietal cortex
pre-SMA	Pre-supplementary motor area
r	Estimate of the Pearson product-moment correlation coefficient
RF	Radio frequency
RT	Reaction time
SC	Superior colliculus
SCi	Inferior segment of the superior colliculus
SCs	Superior segment of the superior colliculus
SE	Standard error
SEF	Supplementary eye field
SFG	Superior frontal gyrus
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SMC	Supplementary motor cortex
SN	Selection negativity
SNpr	Substantia nigra pars reticulata
SOA	Stimulus onset asynchrony
sPCS	Superior precentral sulcus
SPM	Statistical parametric mapping

SPM/SPMs	Statistical parametric map/statistical parametric maps
SSRT	Stop signal reaction time
STG	Superior temporal gyrus
STN	Subthalamic nucleus
T	Student's t-distribution
T1 relaxation	Time constant for the process by which the net magnetization (M) of the MR scanner returns to its initial maximum value
T2 (spin-spin) relaxation	Time constant for the process by which the transverse components of magnetization (M_{xy}) arising from *natural interactions* at the atomic level decay within a tissue of interest
T2 relaxation*	Time constant for the process by which the transverse components of magnetization (M_{xy}) arising from *inhomogeneities in the main magnetic field* of an MR scanner decay within a tissue of interest. *T2* relaxation* ≤ *T2 relaxation*
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TPJ	Temporal parietal junction
TR	Time of repetition/repetition time
TTG	Transverse temporal gyrus
VLPFC	Ventrolateral prefrontal cortex
β	Population values of regression coefficients, beta weight
ε	Error term
σ, σ^2	Standard deviation, population variance
θ	Response threshold level in the LATER model according to Carpenter and Williams (1995)
μ	Mean rate of rise of a decision signal in the LATER model according to Carpenter and Williams (1995)

12. Appendix C: Publications

This dissertation is based on three original publications. The published articles have been removed from the appendix section due to copyright regulations. The published articles can be found online using the following references.

Publication I

Published in

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. https://doi.org/10.1016/j.bandc.2016.05.006

Publication II

Published in

Talanow, T., Kasparbauer, A.-M., Lippold, J. V, Weber, B., & Ettinger, U. (2020). Neural correlates of proactive and reactive inhibition of saccadic eye movements. *Brain Imaging and Behavior*, *14*, 72–88. https://doi.org/10.1007/s11682-018-9972-3

Publication III

Published in

Talanow, T., & Ettinger, U. (2018). Effects of task repetition but no transfer of inhibitory control training in healthy adults. *Acta Psychologica*, *187*, 37–53. https://doi.org/10.1016/j.actpsy.2018.04.016