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Neural mechanisms of proactive and reactive motor inhibition

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Zusammenfassung

Motorische Inhibition kann definiert werden als die Fähigkeit motorische Aktionen zu hemmen, die entweder in einem spezifischen verhaltensmäßigen Kontext nicht angemessen sind oder inadäquat, da sie gegenwärtige motorische und/oder kognitive Prozesse behindern. Basierend auf aktuellen Zielen und Werten erlaubt uns motorische Kontrolle, flexibel gegenwärtige Bewegungen zu stoppen und anzupassen. In dieser Arbeit werden die Ergebnisse von drei Studien präsentiert, die proaktive und reaktive motorische Inhibition untersuchten. Begonnen wird mit einer allgemeinen Einleitung in aktuelle Konzepte, Modelle, Netzwerke und Herausforderungen im Bereich der Forschung zu Motorinhibition. Diese Einleitung fasst Daten aus bisherigen Studien zusammen und führt zu der Feststellung, dass die zeitliche Dynamik von motorischer Inhibition unzureichend verstanden ist und dass es Paradigmen, die sich mit motorischer Inhibition beschäftigen, an ökologischer Validität mangelt. Im Folgenden werden drei Studien präsentiert, in denen mit Hilfe von Elektroenzephalographie (EEG) versucht wird, die zeitliche Dynamik der relevanten neuralen Netzwerke zu klären. Die erste Studie (Kapitel 2) wurde speziell entwickelt um die Vorbereitung auf und die Implementierung von motorischer Inhibition zeitlich zu trennen. Hier wurden Korrelate von Oszillationen und ereigniskorrelierten Potentialen (EKP) bei proaktiver und reaktiver Hemmung von motorischen Handlungen untersucht. Die Ergebnisse zeigten, dass die Vorbereitung auf die Inhibition sowie deren Implementierung Aktivität in präfrontalen, sensomotorischen und okzipitalen Regionen modulierte. Dies spricht für die Beteiligung von kognitiver Kontrolle, von Aufmerksamkeit sowie von Aktivität im motorischen Kortex bei motorischer Inhibition. Darüber hinaus unterstreichen die Ergebnisse die Idee von Beta-Oszillationen als entscheidendem Mechanismus in einem Netzwerk, welches Motorinhibition zugrunde liegt. In der zweiten Studie (Kapitel 3) wurden Effekte von Läsionen in entscheidenden Zentren untersucht, auf denen motorische Inhibition basiert. Zu diesem Ziel nahmen Patienten mit Läsionen, die

entweder in den Basalganglien (BG) oder im präfrontalen Cortex (PFC) lokalisiert waren, an dem cued go/nogo Paradigma teil, welches in der ersten Studie etabliert wurde. Entgegen der Hypothesen unterschieden sich Patienten nicht von gesunden Kontrollprobanden, weder auf Verhaltensebene noch in Bezug auf EEG-Korrelate. Dies weist auf eine intakte Fähigkeit hin sowohl proaktive wie auch reaktive motorische Inhibition einzusetzen. Dieses Resultat steht im Widerspruch zu solider vorangegangener Evidenz, welche sowohl die BG wie auch den PFC mit Prozessen assoziiert, die in der Hemmung von motorischen Aktionen beteiligt sind. Dies führte zu der Schlussfolgerung, dass unsere experimentelle Manipulation nicht herausfordernd genug war um Limitationen in der inhibitorischen Leistung von Patienten zu Tage zu fördern. Demgegenüber konnten unsere Ergebnisse Reorganisation in sensomotorischer und visueller Verarbeitung in BG- und PFC-Patienten zeigen. Die dritte Studie (Kapitel 4) zielte darauf ökologische Validität in Experimenten zu erhöhen, die motorische Inhibition untersuchen. Zu diesem Zweck wurde ein Paradigma entwickelt, in dem die Probanden nicht nur eine habituelle motorische Handlung inhibieren, sondern in einigen Durchgängen gleichzeitig zu einer anderen Handlung wechseln mussten. Der Fokus lag hier auf oszillatorischer Dynamik von Prozessen im präfrontalen und sensomotorischen Cortex. Diese Studie bestätigte Ergebnisse der ersten Studie, die den PFC und den motorischen Cortex mit proaktiven und reaktiven motorischen Prozessen assoziierte. Darüber hinaus unterstreicht sie die Bedeutung des ipsilateralen motorischen Cortex in motorischer Kontrolle. Dieser scheint wie eine Schranke zu agieren, die spezifisch aktiviert ist, je nachdem ob eine Inhibition vorbereitet wird, ein Antwortwechsel oder eine habituelle Motoraktion. Diese Arbeit schließt mit einer allgemeinen Diskussion (Kapitel 5). Hier fasse ich die Ergebnisse der vorgestellten Studien zusammen, ziehe Schlussfolgerungen für Modelle der motorischen Inhibition und hebe zukünftige Ausrichtungen hervor, die aus den präsentierten Resultaten abgeleitet werden können.

Abstract

Motor inhibition can be defined as the ability to withhold motor actions that are either inadequate in a certain behavioral context or not appropriate because they impede current motor and/or cognitive processes. Motor control allows us to flexibly stop and change ongoing movement, depending on current goals and values. In this thesis results of three studies are presented, which investigated proactive and reactive inhibition of motor actions. It starts with a general introduction into current concepts, models, networks and challenges in research of action cancellation. This introduction summarizes previous research and leads to the conclusion that temporal dynamics of motor inhibition are still unclear and that paradigms investigating action cancellation lack of ecological validity. In the following three electroencephalographic (EEG) studies are presented which tried to clarify temporal dynamics of relevant neural networks. The first study (Chapter 2) was specifically designed to disentangle preparation for and later implementation of motor inhibition. Here, oscillatory and event related potential (ERP) correlates of proactive and reactive stopping were investigated. The results showed, that preparation for and implementation of inhibition modulated activity at prefrontal, sensorimotor and occipital sites. This speaks for involvement of activity in motor cortex, cognitive control and attention in motor inhibition. Furthermore, results underscore the concept of beta oscillations as a critical mechanism in a network action cancellation is based on. In the second study (Chapter 3), effects of lesions to crucial nodes in a network underlying motor inhibition were investigated. To this end, patients with lesions either to the basal ganglia (BG) or prefrontal cortex (PFC) participated in the cued go/nogo task established in the first study. Contrary to hypothesized, patients did not differ from control subjects, both on the behavioral and neural level, suggesting an intact ability to employ proactive and reactive inhibition. This finding stands in contrast to solid previous evidence implicating both BG and PFC in processes involved in action cancellation. This led to the conclusion

that our experimental manipulation was not challenging enough to reveal limitations in inhibitory performance in patients. However, our results revealed reorganization of sensorimotor and visual processing in BG and PFC patients. The third study (Chapter 4) aimed at increasing ecological validity in paradigms of motor inhibition. Therefore, a paradigm was designed in which participants not only had to inhibit a habitual motor response, but in some trials also had to switch to another action. The focus was on oscillatory dynamics of processes in prefrontal and sensorimotor cortex. This study confirmed findings of the first study, implicating PFC and motor cortex in proactive and reactive inhibitory processes. Moreover, it highlights the significance of ipsilateral sensorimotor cortex in motor control. It seems to act as a gate, being differentially activated when preparing to perform an inhibition, a switch or a habitual motor action. The thesis concludes with a general discussion (Chapter 5). Here, I integrate findings of present studies, draw conclusion for models of action cancellation and highlight future directions, which can be derived from presented results.

1 Introduction

1.1 General Outline

“Adapt or perish, now as ever, is nature's inexorable imperative” (H. G. Wells, 1945). Cognitive control refers to higher-level processes which allow for adaptive and variable information-processing and behavior depending on current goals and values. It encompasses a range of functions as maintaining and updating currently task-relevant information and shifting from one task to another(Miyake et al., 2000). An essential function of cognitive control is the capacity to flexibly inhibit inappropriate or maladaptive thoughts and behavior. The inhibition of actions can be considered as “the ability to withhold dominant motor responses that are either inappropriate in a given behavioral context or unwanted because they interfere with completion of motor and/or cognitive goals” (Simmonds et al., 2008). This inhibition of a motoric process can aim at switching to a more appropriate action alternative or be in favor of refraining from responding altogether. In daily life for instance, this capacity becomes critical when cycling on a street with a pedestrian suddenly stepping in the way or withholding your intention to grasp a hot pan falling from the stove. Research in clinical populations suggests that impairments in response inhibition may contribute to the development of psychopathological and impulse-control disorders, as for example evident in form of motoric tics in the Gilles-de-la-Tourette syndrome (Wylie et al., 2013; Thomalla et al., 2014). Deficits in inhibitory control have been linked to various psychiatric diseases as attention-deficit hyperactivity disorder (ADHD) (Barkley, 1999; Wodka et al., 2007; Senderecka et al., 2012), schizophrenia (Hughes et al., 2012), obsessive compulsive disorder (OCD) (Chamberlain et al., 2006; Lipszyc and Schachar, 2010), bipolar disorder (Weathers et al., 2012) and substance use disorders (Luijten et al., 2014; Moeller et al., 2016). Moreover, lack of inhibitory control has been ascribed to neurological diseases as Parkinson’s disease (PD) (Gauggel et al., 2004;

Mirabella et al., 2012) or Huntington's disease (Majid et al., 2013). Also, in the time course of normal cognitive aging, motor inhibition functions seem to decline (Gazzaley and D'esposito, 2007; Anguera and Gazzaley, 2012).

Conceptually and most relevant for this thesis, two variants of inhibitory motor control are distinguished, namely reactive and proactive control (Aron, 2011). Reactive motor inhibition refers to a process where an already initiated movement has to be withheld or stopped in reaction to an external signal. Proactive motor inhibition however, describes processes preparing to stop upcoming response tendencies, therefore being active before an action is actually in progress. Whereas reactive inhibition has been thoroughly studied in the past, proactive inhibition is a newer concept, introducing the element of endogenous preparation into theories of motor control. These two modes of inhibitory control will be discussed in deeper detail in Chapters 1.5 and 1.6.

Motor inhibition is not an isolated cognitive function. It is likely integrated within larger networks subserving cognitive control. Specifically, inhibitory performance has been shown to be altered by various domains as attention (Chatham et al., 2012; Aron et al., 2014a; Verbruggen et al., 2014), motivation (Leotti and Wager, 2010; Pessoa, 2014; Langford et al., 2016), expectancy (Vink et al., 2005; Verbruggen and Logan, 2009b; Zandbelt et al., 2013b), error monitoring (Li et al., 2008) and working memory (Redick et al., 2011; Barber et al., 2013) and is likely influenced by other cognitive functions. Especially the role of attention for motor inhibition will be discussed in more detail in Chapter 1.7.1.

To the present date, little effort has been invested in clearly separating proactive and reactive motor inhibition in the time-domain. This is what the current thesis aims at. We took advantage of the high time-resolution of EEG to study ERPs and oscillations underlying stopping at prefrontal, sensorimotor and occipital sites. In three cued go/nogo

tasks, dynamics of response inhibition were investigated in healthy subjects and in patients with lesions to critical nodes in a network underlying action cancellation.

1.2 Paradigms of Motor Inhibition

Motor inhibition is studied with various paradigms among which the stop-signal task (SST) and the go/nogo task are the two most frequently used. In the SST (Logan and Cowan, 1984; Logan, 1994), in all trials a go-signal is presented, to which participants are supposed to behaviorally react (e.g. with a button press or a vocal response). Occasionally, briefly following the go-signal, a stop-signal appears to which subjects have to inhibit the already initiated response. To avoid strategic behavior, such as delaying the response to the go-signal in order to increase the probability of successful inhibitions, the proportion of stop-signals is usually kept low (e.g. 25%). Moreover, the time between go- and stop-signal (stop-signal-delay, SSD) is dynamically adjusted during the experiment such that participants end up with a rate of about 50% successfully inhibited trials. A critical strength of the SST is that it allows researchers to estimate the latency of participants' internal stop process, termed stop-signal reaction time (SSRT), based on the horse-race model (see below). The SSRT is the time between occurrence of the stop-signal and the finishing of participants' endogenous stop process. The possibility of estimating the SRTT is a powerful aspect, as unlike other reaction times, the stopping latency cannot not be directly observed and thus remains a covert variable. The SST has been extensively used to investigate the cognitive and neural mechanisms underlying response inhibition (Aron and Poldrack, 2006; Verbruggen et al., 2014) and the SSRT has demonstrated proven to constitute reliable estimates of response inhibition efficiency (Verbruggen and Logan, 2008). One limitation of the SST might be that it is not entirely robust against subjects' individual task strategies, such as response adjustments following consecutive successful inhibitions or errors (Leotti and Wager, 2010).

In the go/nogo task (Donders, 1868/1969), the go-signal appears in most but not all trials. In some trials instead, a nogo-signal is presented, instructing the subject to cancel the response. Here, it is believed that a prepotent go-reaction is initiated in every trial and suppressed in case of nogo-signals. Regarding the percentage of nogo-trials used in go/nogo tasks, very heterogeneous values are used in the literature, ranging from 50% to less than 20%. A recent study probed different variants of go/nogo tasks and compared them with the SST as gold standard. It suggests a low share of go-trials and furthermore fast-paced tasks in order to specifically capture stopping-related brain activity (Wessel, 2018). In general, numerous variants of the SST and the go/nogo task have been used, including preparation for stopping and selective/nonselective inhibition (Majid et al., 2012; Zandbelt et al., 2013b). According to Schachar et al. (2007), two types of motor inhibition can be told apart, action restraint (putting a not-yet started action on hold) on the one hand and action cancellation (stopping an already initiated action) on the other. Go/nogo tasks seem to be more suitable to examine the former, while the latter is commonly studied using SSTs (Cohen and Lieberman, 2010).

Mathematical models have been developed to characterize motor inhibition, among which the *independent horse-race model* introduced by Logan (1981) and Logan and Cowan (1984) has been the most influential. This model is based on the SST. A typical observation in the SST is that subjects can reliably inhibit their response when the stop-signal is presented in brief succession to the go-signal, but fail to inhibit their response when the stop-signal occurs close to the moment where responses are executed. These observations led to the idea of a race between a go-process and a stop-process, similar to a horse race. The independent horse-race model states that the outcome of response inhibition depends on the relative finishing times of the independently developing go- and the stop-process. In case the stop-process finishes first the response is inhibited, whereas when the go-process is faster the response will be executed. According to the model, differences in inhibitory

performance can be entirely accounted for by the interplay between stop-signal delay (SSD), being the time between go- and stop-signal, the SSRT, and the go reaction time (RT) distribution. In healthy adults SSRTs have been shown to range around 200 ms, while in patients with neuropsychiatric diseases SSRTs were found to exceed 300 ms (Gauggel et al., 2004). Moreover, in accordance with developing and declining inhibitory abilities with age, longer SSRTs were also found in young children and elderly (Williams et al., 1999; Smittenaar et al., 2015). The independent horse race model describes stopping as a competition between two runners, but importantly does not specify the underlying structures and mechanisms of this race. The model thus cannot explain stopping on a deeper level and clarify why stopping behavior in certain patient groups differs from controls, differs across paradigms or on a trial-to-trial basis within one experiment. It nevertheless is capable of describing those differences and therefore can be and is used to formulate and test hypotheses regarding stopping-related behavior (Matzke et al., (in press)). For further details about the independent horse-race model see Verbruggen and Logan (2009a).

Recently, a general race model has been proposed that extends the independent horse-race model, incorporating the role of choice in processes of going and stopping (Logan et al., 2014). Here, all competing responses (and not just one go- and the stop-process) are modelled as independent runners. Moreover, a special race model was introduced, capable of explaining changes in RT with individual strategies and experimental conditions (Logan et al., 2014). This RT variability occurs as a result of stochastic accumulation and the model can predict shapes of RT distributions.

1.3 Validity of Motor Inhibition Paradigms

When referring to real life situations in which motor inhibition is needed, often traffic situations are described, as stopping a car when a pedestrian suddenly runs onto the street.

Without question, such a situation is far more complex than what is investigated in the SST, the go/nogo task or other paradigms tapping into motor inhibition. To stop the car in the above described setting, the driver not only has to stop an ongoing movement, as releasing one foot from the gas pedal, but also has to engage in another action, namely pulling the break. Moreover, a clear stop-sign as evident in most stopping-related paradigms, is usually not present in complex real life environments. Conversely, the driver has to detect the pedestrian and decide based on intrinsic models that there is a meaningful reason to stop the car. Also, if the pedestrian is further away, the driver might only break and not fully stop his vehicle, leaving him enough time to cross the street. Finally, in case of warning signs, for instance of animals crossing the street, the driver might prepare to stop his car and not only rely on external stop-signals. Mentioned aspects, although relevant to everyday life, are not investigated with widely used standard SST and go/nogo tasks. However, novel paradigms are beginning to investigate these cases. One first step to come closer to real life situations was to introduce proactive inhibition to theoretical concepts of stopping (Aron, 2011). This refinement included the important aspect of endogenous preparation into research of stopping (see Chapter 1.6). A second aspect is response change. As evident from abovementioned example, everyday life rarely calls for the complete suppression of motor tendencies without subsequent behavioral adjustment (Böcker et al., 2013). Stopping and changing motor actions are thus closely intertwined and often occur in common. Studies investigating action changing suggest that the same network underlying simple motor inhibition also is recruited for the stopping part when having to change (Böcker et al., 2013). Third, in standard tasks, motor output has to be inhibited globally, whereas in reality often only selective movements have to be suppressed. Novel paradigms started to address this issue (Aron and Verbruggen, 2008; Claffey et al., 2010). As a fourth point, the complexity of stop-signals in real life scenarios has been addressed (Wessel and Aron, 2014). In this study, participants had to match visual

features of a multidimensional go-stimulus to a complex stopping template. Independent component analysis (ICA) of EEG data was used to show that the same network explaining motor stopping in the SST also implements inhibition in this complex stopping task. However, as spatial resolution of EEG is limited, claims about network similarities have to be taken cautiously.

Some work linked response inhibition to behavior in everyday life. In one study, cigarette smokers performed in a go/nogo task before and while attempting to quit (Berkman et al., 2011). Here, activity in a putative response inhibition network at baseline was coupled with a reduced association between craving and subsequent smoking. Also, in overweight adults training with go/nogo food stimuli lead to significant weight loss, reductions in daily energy intake and a reduction in rated liking of high-energy density food, compared to a control go/nogo task containing non-food stimuli (Lawrence et al., 2015). Finally, response inhibition has been linked to sports performance, as both in soccer and tennis, experienced compared to less or non-experienced athletes showed a shorter SSRT, speaking for more effective motor inhibition (Wang et al., 2013; Verburgh et al., 2014).

Summarizing, some evidence points to the fact that results from simple stopping-task are generalizable to real life scenarios and first attempts have been made to move stopping-related research closer to everyday life. However, this evidence needs to be extended, and in particular novel paradigms might help in order to increase ecological validity in research of motor inhibition.

1.4 Prefrontal-Cortex Basal-Ganglia Working Memory Model

Zooming out of the rather narrow perspective of considering motor inhibition an isolated cognitive domain, the inhibition of actions or inhibition in general can be considered as one piece of the more overarching and general ability to employ cognitive control. Cognitive control refers to “the ability to perform task-relevant processing in the face of

other distractions or other forms of interference, in the absence of strong environmental support" (O'Reilly et al., 2010). There is strong consensus that key nodes of cognitive control are located in prefrontal cortex (PFC) (Hazy et al., 2007). This claim is supported by findings that patients with lesions to the PFC, among other cognitive functions, have limitations in attention, learning, decision making and inhibitory, emotional and social control, which all can be considered as being under the influence of cognitive control (Szczepanski and Knight, 2014). O'Reilly and Frank (2006) established a framework, the prefrontal-cortex basal-ganglia working memory (PBWM) model, in which the PFC together in interplay with the basal ganglia (BG), underlies cognitive control (see also Hazy et al., 2007). Cognitive control ensures the balance between stability and flexibility, at their core, two opposing aspects of information processing. In the PBWM model, the BG are acting as a gate, enabling to switch between stable and flexible behavior (Figure 1.1A).

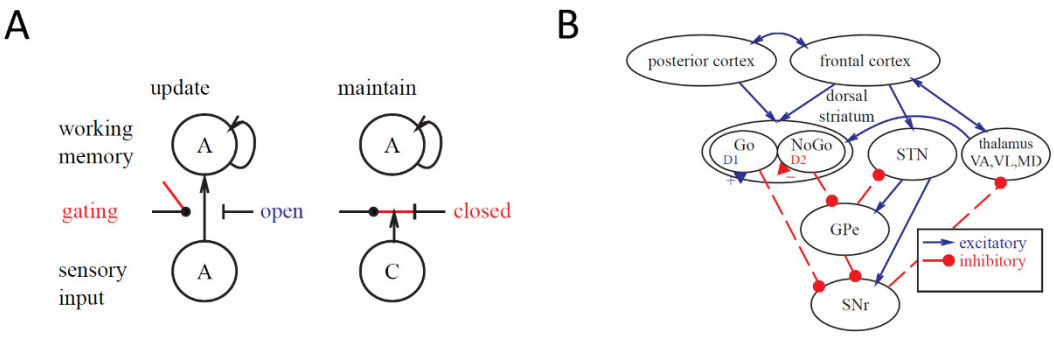


FIGURE 1.1 | Prefrontal-cortex basal-ganglia working memory (PBWM) model. (A) When the gate is open working memory representation can be updated, e.g. from sensory input. When it is closed, information is maintained and shielded from interference. (B) Schematic depiction of involved regions and excitatory/inhibitory cortico-basal ganglia connections in the PBWM model. Central regions are the frontal cortex and dorsal striatum, which opens the gate via Go neurons and closes it via NoGo neurons. Figure adapted from Hazy et al. (2007).

When the gate is open, sensory input can update working memory (e.g. encoding novel items into memory), but it cannot when the gate remains closed. Closing the gate prevents interference from task-irrelevant distracting information (e.g. distractor C), while maintaining previously encoded stimuli or task rules. This gating mechanism is thought

to be implemented in dorsal striatum where Go neurons, which through inhibition of substantia nigra pars reticulata (SNr) and subsequent disinhibition of the thalamus, enable updating of working memory representations in PFC (Figure 1.1B). NoGo neurons in dorsal striatum counteract this effect by inhibiting globus pallidus externus (GPe) and thereby disinhibiting SNr, effectively closing the gate for updating PFC representations. Working memory representations are thought to be stored in PFC "stripes", small and relatively isolated groups of interconnected neurons, of which about 20.000 are assumed to be present in frontal cortex (Frank et al., 2001). Learning what and when to gate is accomplished by a dopamine-based reinforcement-learning mechanism which updates activity in striatal Go and NoGo synapses. Recently, the PBWM has been refined, extending the basal ganglia controlled input gate to PFC. Specifically, a second striatal based output gate was proposed, determining which PFC-maintained active representations are utilized for behavior (Chatham et al., 2014). Finally, a third striatum dependent mechanism was suggested that reallocates working memory capacity when representations are no longer needed (Chatham and Badre, 2015). Summarizing, the core idea of the PBWM model is that cognitive control emerges out of the interaction between PFC and basal ganglia. In the following, similar concepts will be presented for reactive and proactive motor inhibition, both of which, are thought to be based on an interplay between cortical nodes in PFC and connected subcortical basal ganglia nuclei.

1.5 Reactive Motor Inhibition

Reactive inhibition is the type of inhibitory control which has been most commonly studied. It refers to the stimulus-triggered stopping of a response that already has been initiated. An influential model postulates a triangulate network of pre-supplementary motor area (pre-SMA), right inferior frontal cortex (IFC) and subthalamic nucleus (STN) to be critical for inhibiting motor output (Aron, 2011) (Figure 1.2).

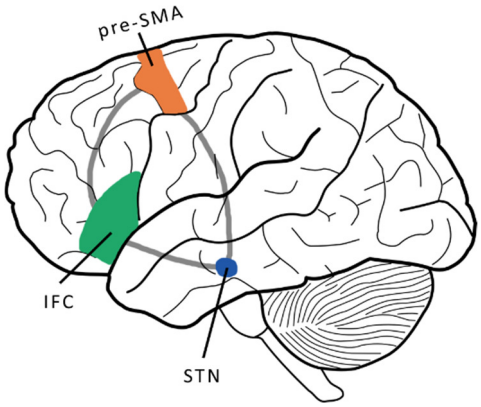


FIGURE 1.2 | Schematic representation of the triangular network underlying reactive inhibition, comprised of IFC, preSMA and STN. (Note that this is more a schematic display of the network than an exact anatomical depiction of involved nodes. STN is located subcortical and pre-SMA is mostly a medial brain structure).

From a temporal perspective, in the process of stopping, sensory information about the stop-signal is passed to the prefrontal cortex, where the stopping command is presumably generated. Two subregions of the PFC, preSMA and right IFC, work together to send an inhibitory command to intercept the prepotent motor process. This command is passed via the STN with suppression of basal ganglia output as a consequence. Finally, downstream inhibitory effects on premotor (Mattia et al., 2012) and primary motor cortex (M1) are produced (Stinear et al., 2009; Swann et al., 2009). The triangular network likely extends to other regions as dorsolateral PFC (DLPFC) (Menon et al., 2001; Mostofsky et al., 2003; Zheng et al., 2008), parietal areas (Menon et al., 2001; Rubia et al., 2003), anterior insula (Swick et al., 2011) and other basal ganglia nodes such as striatum (Vink et al., 2005; Aron and Poldrack, 2006; Aron et al., 2007; Ray Li et al., 2008).

It has been suggested that distinct regions in this broader network exercise subspecialized functions. Whereas the IFC is recruited to implement response inhibition, especially in more demanding situations, top-down control of action-selection areas might be implemented by DLPFC. The pre-SMA could be relevant for actual selection of specific actions and basal ganglia might keep all responses in check, until signals from upstream cortical areas are received whether to implement action or inhibition (Ridderinkhof et al., 2011). In the following, the two main brain structures involved in reactive motor inhibition will be discussed, PFC and basal ganglia.

1.5.1 Prefrontal Cortex

Early studies on the PFC, both in human and human primate brain, concluded it to be functionally insignificant; they reported that large parts of it could be removed without significant harm on cognitive abilities or on behavior (Hebb, 1939; Teuber et al., 1951). Several decades of neuroscientific research, including a wide range of experiments, turned this view around: now the general consensus is that the PFC is most important for control of goal-directed thought and behavior (Luria, 1966; Fuster, 1989; Stuss and Knight, 2013; Szczepanski and Knight, 2014). Functions ascribed to the PFC are subsumed under the general term of cognitive or executive control. These processes can be divided into three core cognitive factors, which are (i) inhibition and switching, (ii) working memory and (iii) sustained and selective attention (Alvarez and Emory, 2006). Given its extensive reciprocal connections with nearly all cortical and subcortical regions (Ilinsky et al., 1985; Selemon and Goldman-Rakic, 1988; Croxson et al., 2005), the PFC is placed in a unique position for monitoring and controlling a broad range of cognitive and affective functions.

Specifically, the right IFC, located at the lateral inferior part of the frontal lobe, has been proposed to house the core inhibitory module for reactive inhibition (Aron et al., 2004b; Aron et al., 2014a). Evidence for this claim is stemming from numerous brain imaging studies (Rubia et al., 2003; Zandbelt et al., 2013b; van Belle et al., 2014), mostly contrasting go-trials and successful stops or successful with unsuccessful inhibition. Further support is coming from lesion (Leimkuhler and Mesulam, 1985; Aron et al., 2003; Rieger et al., 2003) and brain stimulation studies (Chambers et al., 2007; Verbruggen et al., 2010). For instance, in one study, the disruption of right inferior frontal gyrus (IFG) pars opercularis with transcranial magnetic simulation (TMS) harmed inhibitory performance, as evident by an increased SSRT (Chambers et al., 2006). In another study excitation of right IFG with transcranial direct current stimulation (tDCS) led to an decrease in SSRT, speaking for more efficient motor inhibition (Jacobson et al., 2011). Still, tDCS is a rather novel brain

stimulation technique, and results are restrained by its limited focality. Recent frameworks see the role of right IFC as a brake (Aron et al., 2014a), which can be triggered by both external signals and internal goals and can modulate responses on different levels, i.e. pausing them until final decisions are made or stopping them completely.

Even though most studies highlight the role of the right IFC in inhibitory control, some studies also see its left homolog region implied in response inhibition. Significant activation of the left IFC has for instance been reported in functional magnetic resonance imaging (fMRI) studies using the go/nogo task and contrasting go- with nogo-trials (Rubia et al., 2001; Tamm et al., 2002; Steele et al., 2013). Moreover, patients with lesions to the left IFC show deficits in inhibitory performance compared to healthy control subjects (Swick et al., 2008). One explanation for these results is that bilateral IFC is recruited for successful employment of inhibitory control, with at the same time lateralization of this function to the right side. Alternatively, these findings might be attributed to using different experimental paradigms since most studies underscoring the role of left IFC are based on go/nogo-tasks, while work highlighting the importance of the right IFC is largely based on the SST. One idea is that right IFC activation depends on the effort of inhibitory processes. For instance, inhibiting a response, which already is in progress, likely is more effortful than cancelling one that is on hold. This would explain why activation in right IFC is more consistently observed in SST, which is believed to be more demanding than go/nogo tasks. Alternatively, recruitment of right IFC might depend on task complexity (Ridderinkhof et al., 2011).

However, critique has been addressed to the concept of a specialized hub coding motor inhibition, thought to be located in the PFC. The functional role of right IFC might not be specific, as in the broader literature aside its implication in response inhibition, it also has been reported to be involved in target detection (Hampshire et al., 2007), working memory (Shivde and Thompson-Schill, 2004; Kumar et al., 2016), in attentional tasks (Hampshire et

al., 2012; Cieslik et al., 2015), in decision-making (Sherman et al., 2016) and even in successful lying (Vartanian et al., 2013). In a modified SST, controlling for engagement of attention, activation of pre-SMA but not right IFC was found to be related to inhibition per se (Sharp et al., 2010). In another study by Erika-Florence et al. (2014) participants performed four variants of the classic stop-signal task, of which only one included the necessity to inhibit a motor action. Activity in PFC subregions was not specific to motor inhibition and further results of data-driven ICA did not concur with the idea of functionally specific nodes within the PFC. On basis of these findings, the idea was developed that the same set of frontoparietal networks subserve a broad range of control processes, among which response inhibition is only one of many (Hampshire and Sharp, 2015a). To date there is vivid ongoing debate about whether stopping can be localized to frontal subregions or not (Aron et al., 2014b; Aron et al., 2015; Hampshire and Sharp, 2015b).

One possibility, reconciling opposing findings of right IFC being involved in inhibition or rather in attentional monitoring, might be that the frontal cortex houses distinct subregions subserving specific functions respectively. Limitations of spatial resolution in brain imaging might have prevented a sharp separation of those regions. In line with this idea, a TMS study found the ventral-posterior part of the right IFC to be involved in updating action plans, as triggering the stop process, while the dorsal-posterior part (or IFJ) was important for monitoring the visual environment to detect rare stop signals (Verbruggen et al., 2010). Similarly, a recent meta-analysis states that, whereas the right IFC is critical for implementation of inhibition, the right anterior insula is more important for detecting behaviorally salient events (Cai et al., 2014).

The second major hub in PFC subserving response inhibition is the pre-SMA/SMA region. It is frequently activated in fMRI paradigms investigating motor stopping (Simmonds et al., 2008; Sharp et al., 2010; van Belle et al., 2014). Macrostimulation of subdural electrodes

over pre-SMA in epileptic patients resulted in arrest of speech and manual movements (Lüders et al., 1988; Fried et al., 1991; Swann et al., 2012). Patients with lesions to the SMA/pre-SMA showed impairments in stopping, indexed by prolonged SSRT (Floden and Stuss, 2006) and an increased number of failed inhibitions in nogo-trials (Picton et al., 2007). When perturbing activity in pre-SMA with TMS, SSRT and failed inhibitions similarly increased (Chen et al., 2009; Obeso et al., 2013). Pre-SMA seems to be directly connected to the right IFC, as observed by diffusion tensor imaging (DTI) (Aron et al., 2007). During successful stopping, increased functional connectivity between right IFC and pre-SMA has been observed (Duann et al., 2009), and in a large sample fMRI study, resting state functional connectivity between these two regions was predictive of inhibitory performance as measured with SSRT (Wang et al., 2016). There is less consensus about the role of pre-SMA in the context of stopping than about other regions. It has been associated with motivation (Scangos and Stuphorn, 2010), resolution of response conflict (Isoda and Hikosaka, 2007) and modulation of response thresholds (Bogacz et al., 2010). Still, most evidence speaks for a role of pre-SMA in selection of action sets (Rushworth et al., 2004; Ridderinkhof et al., 2011).

1.5.2 Basal Ganglia

The basal ganglia are comprised of a group of subcortical nuclei primarily underlying motor control. Influential frameworks implicate the basal ganglia in action selection, i. e. the question which behavior to execute out of several possible action alternatives (Chevalier and Deniau, 1990; Gurney et al., 2001; Humphries et al., 2006). Deficits in motor behavior result from basal ganglia disorders such as Chorea, Dystonia and Parkinson's Disease (PD) (Mink, 2003; DeLong and Wichmann, 2007). Apart from their substantial role in the motor system, the basal ganglia are engaged in other cognitive functions such as learning, attentional control and reward processing via dopaminergic mechanisms

(Lingford-Hughes and Kalk, 2012). From a functional perspective these nuclei are comprised of the striatum, consisting of caudate nucleus und putamen, the pallidum, substantia nigra and STN (Herrero et al., 2002).

Among these, two nodes seem to be particularly relevant for motor inhibition, STN and the striatum. In rodents, lesions to the STN led to reduced stopping accuracy at all stop-signal delays in a SST (Eagle et al., 2008). A monkey single cell unit recording study showed that STN neurons increased in firing rate when monkeys inhibited and switched responses (Isoda and Hikosaka, 2008). In a high-resolution human fMRI study, activity in STN was increased when subjects successfully stopped motor responses (Aron and Poldrack, 2006). Deep brain stimulation of STN led to increased stopping speed in PD patients (van den Wildenberg et al., 2006; Swann et al., 2011), but see (Ray et al., 2009). In a further study, direct recordings from STN revealed go-units firing selectively before motor execution and stop-units which were selectively active in preparation of a successful stop (Benis et al., 2016). Moreover, recordings of STN local field potentials in patients with PD demonstrated an increase of oscillations in the beta band for successful stopping (Kühn et al., 2004; Alegre et al., 2013; Wessel et al., 2016a). These and related findings led to the hypothesis of a beta-driven cortico-subcortical circuit underlying response inhibition (Aron, 2011; Aron et al., 2016). This beta-associated circuit will be discussed in deeper detail in Chapter 1.7.2. Supporting the abovementioned idea of a triangular network, the STN receives direct input from pre-SMA and right IFC (Inase et al., 1999; Aron et al., 2007). Recent work has led to the idea that the STN modulates decision making, in raising the decision threshold to allow more evidence to be accumulated before responding (Aron et al., 2016). This effectively leads to a pause of behavior, which is thought to be realized by suppression of basal ganglia output, resulting in global inhibitory effects on behavior.

Besides STN, evidence points to involvement of the striatum in stopping circuits. Increased striatal activation has been observed in the SST (Vink et al., 2005; Chevrier et al., 2007) and

in go/nogo tasks (Durston et al., 2003; Kelly et al., 2004). In rats, lesions to the striatum resulted in impaired inhibition, as seen by increased SSRT and an altered behavioral profile of inhibiting actions (Eagle and Robbins, 2003). One study directly recorded activity from the striatum while monkeys performed in a go/nogo task (Apicella et al., 1992). In the time period between a cue and an imperative target stimulus, increased activity in striatal neurons was observed, suggesting preparatory engagement of this region. Another study investigated neurons in monkey caudate nucleus and reported increased activity when selectively stopping a prosaccade and engaging in an antisaccade (Ford and Everling, 2009). This and further data led to the conclusion that the striatum is less of importance for reactive inhibition but more so for proactive (and selective) stopping (Aron, 2011). Therefore, it will be discussed in deeper detail in the next section.

1.5.3 Circuits of Reactive Stopping and Conclusion

As introduced above, motor output can be inhibited globally (i.e. all motor responses) or selectively (i.e. one action of a broader set). It has been suggested that these distinct forms of reactive stopping are realized by independent pathways (Aron, 2011). In reactive global stopping the *hyperdirect pathway* is thought to be recruited (Figure 1.3A). In this circuit, the STN, triggered by IFC, has a broad inhibitory effect on globus pallidus internus (GPi). This results in global suppression of thalamocortical motor programs. Reactive selective stopping however, might be realized by the *indirect pathway* (Figure 1.3B). Here, inhibitory commands are transferred from IFC to caudate nucleus, and over globus pallidus externus (GPe) to GPi, which itself inhibits thalamocortical output. Importantly, here only one, but not all motor representations in primary motor cortex are suppressed. For proactive selective stopping the same circuit as for reactive selective inhibition has been suggested with caudate nucleus receiving input not from IFC but from DLPFC (Figure 1.3C).

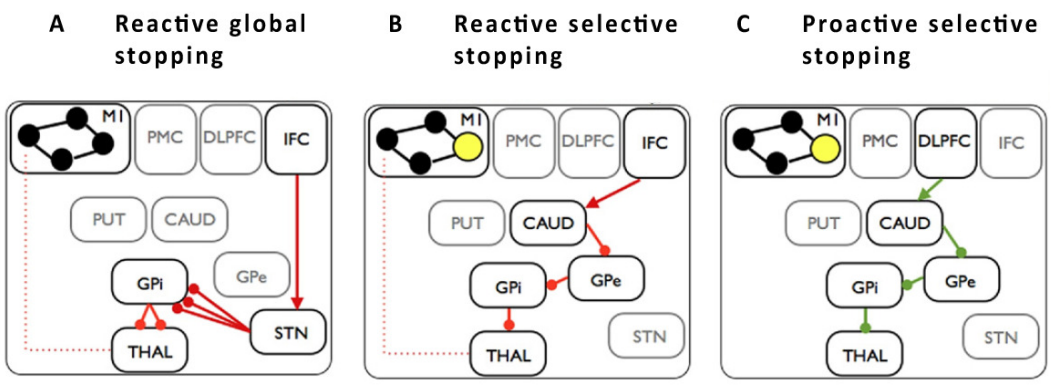


FIGURE 1.3 | Schematic representation of specific pathways underlying global and selective reactive and selective proactive inhibition. (A) Reactive global stopping recruits the hyperdirect pathway where the STN over broad inhibition of the pallidum inhibits thalamocortical output. (B) In reactive selective stopping the indirect pathway is activated, where the striatum via caudate nucleus downstream inhibits pallidum and thalamocortical connections. (C) Proactive selective stopping is realized with involvement of caudate nucleus and DLPFC. Figure adapted and modified from Aron (2011).

Taken together the abovementioned various and to some degree inconsistent findings, substantial evidence points to recruitment of PFC and basal ganglia nuclei in processes involved in reactive motor inhibition. These regions seem to be organized in a network with right IFC, pre-SMA and STN as critical nodes. Future research might resolve the close intertwinement between attentional processes and stopping using elaborated experimental designs. Also, the exact functional roles of specific stopping-related nodes might be further delineated.

1.6 Proactive Motor Inhibition

Proactive inhibition is a top-down process, which is endogenously activated by internal goals, as opposed to being exogenously triggered by the external environment. It is implemented before outright cancellation of actions, restraining action initiation in preparation for potential upcoming stopping. In everyday life and in disorders resulting in impaired stopping capacity, top-down, endogenous, preparatory and thus proactive inhibitory processes are frequently involved. Human beings do not only stop behavior as a result of external signs as stop-signals. There could be numerous endogenous reasons

why people inhibit actions, as expectations, learned behavior or the internal urge to do so. Proactive inhibition has been even proposed to be the default state of executive control (Criaud et al., 2012). Nevertheless, the most commonly used paradigm in studies of motor inhibition, the SST, is targeted to understand reactive processes and the vast majority of stopping research focused on reactive mechanisms. Following this discrepancy, a shift in the direction of proactive inhibition was suggested to better understand basic aspects of motor control in daily life (Aron, 2011; Schall and Godlove, 2012). Indeed, in past years proactive control has gained increasing attention and valuable insights were gained from studies of proactive inhibition.

1.6.1 Proactive Slowing

One major finding of studies investigating proactive motor inhibition is that participants slow down on go-trials when the likelihood of having to stop is increased (Verbruggen and Logan, 2009b; Zandbelt and Vink, 2010). This observation has also been referred to as response delay effect (Jahfari et al., 2010; Greenhouse et al., 2012). Two opposing explanations have been put forward for the phenomenon of behavioral slowing. The first states that slowing is implemented as a strategic process to delay the motor process until the time-point when it is apparent that any stop-signal will occur (Sylwan, 2004). Following this hypothesis, no inhibitory process is assumed to underlie proactive slowing, it results rather from a holdup of excitatory processes. Alternatively, an active inhibitory process might be involved in what can be behaviorally observed as a delay of an overt response, suppressing motor tendencies in order to facilitate inhibition when actually needed. Evidence for the second hypothesis is stemming from TMS studies showing that corticomotor excitability in selective SSTs, as measured with MEPs, is reduced in anticipation of an upcoming stop (Claffey et al., 2010; Cai et al., 2011). This clearly speaks for an active inhibitory mechanism and notably only task-relevant muscles are inhibited

while MEP amplitudes of irrelevant effectors remain unaffected (Greenhouse et al., 2012; Majid et al., 2012), but see (Greenhouse et al., 2015). The proactive slowing has been quantified as preparatory cost, which is the RT difference of go-trials with and without need for anticipation of stopping (Chikazoe et al., 2009). Alternatively, the cost can be defined as a function of change in go-trial RT per increase of stop-signal probability (Vink et al., 2005; Zandbelt and Vink, 2010). Those studies show consistently that subjects become slower the higher the likelihood they might have to stop.

Linking proactive and reactive inhibitory control, a negative correlation between SSRT, the standard measure of reactive inhibition, and the preparatory cost has been reported (Chikazoe et al., 2009; Jahfari et al., 2010; Castro-Meneses et al., 2015). As increased preparatory cost is interpreted as enhanced proactive control and decreased SSRTs are assumed to reflect better reactive control, this negative correlation points to a positive relationship between proactive and reactive inhibition. Thus, proactive control might be strategically implemented to facilitate reactive control in helping to withhold responses more quickly and effectively when needed. Support for this idea is coming from studies showing increased accuracy in stop-trials as a function of stop-signal probability (Verbruggen and Logan, 2009b; Zandbelt and Vink, 2010). Moreover, one study using TMS to investigate motor cortex excitability, demonstrated that those subjects who prepare to stop, showed selective suppression of the motor system, while those who do not implement proactive control displayed global inhibitory effects on motor effectors (Greenhouse et al., 2012). This finding suggests that preparation for stopping also allows to inhibit more selectively.

1.6.2 Network of Proactive Inhibition and Prefrontal Cortex

Above, the notion of a triangular network underlying reactive inhibition was introduced. fMRI studies, using novel paradigms to investigate proactive inhibition, reported a similar network being involved in preparation for stopping (Hester et al., 2004; Chikazoe et al., 2009; Jahfari et al., 2010; Smittenaar et al., 2013). The right IFC, as part of this network, has been proposed to be a central hub not only for reactive, but also proactive motor control (Aron et al., 2014a). Two studies using tDCS support this idea in showing that stimulation of right IFG led to both enhanced proactive and reactive inhibition (Cunillera et al., 2014; Cai et al., 2016), displayed by decreased SSRT and increased go reaction times (RTs) respectively. The right IFC was also target region in the first study using direct electrical stimulation (DES) to excite a cortical region in human subjects (Wessel et al., 2013). Direct stimulation of right IFC resulted in slowing of motor responses and importantly, more so when stopping could be anticipated compared to when not. However, evidence from these studies is limited to a certain degree, as the rather indirect measure of slowing of RT in go-trials is interpreted as correlate of engagement of proactive control. As detailed above, behavioral slowing is a key finding of proactive processes. This nevertheless does not imply that once slowing is observed, this necessarily has to be caused by preparatory inhibition. Several mechanisms could result in increased RTs, such as disruption of attentional mechanisms, interruption of active maintenance of task goals or of processes directly involved in motor preparation.

In contrast to abovementioned evidence, results from several studies argue against a role of prefrontal regions in proactive inhibition (Verbruggen et al., 2010; Zandbelt et al., 2013a; Zandbelt et al., 2013b; van Belle et al., 2014; Vink et al., 2015). A major limitation of most fMRI studies on proactive inhibitory control is that they do not distinguish between cue-related and target-related activity, therefore hardly can differentiate between activity related to the preparation for and implementation of motor inhibition. As an exception

Zandbelt et al. (2013b) and Vink et al. (2015) performed experiments which were specifically designed to disentangle activity related to cue- and target-stimuli. They found that part of the stopping-network, including right IFC, was not activated until target signals were presented, speaking for reactive rather than proactive engagement. This finding is supported by electrocorticography (ECoG) studies, showing that the right IFG was not activated until stop-signals appeared (Swann et al., 2009; Swann et al., 2012). Moreover, studies stimulating right IFC with TMS found no effect on measures of proactive inhibition (Verbruggen et al., 2010; Zandbelt et al., 2013a). Further questioning the view of similar neural networks underlying proactive and reactive inhibition, a large sample size study using ICA to distinguish proactive and reactive activations, found common as well as distinct networks underlying both stopping modes (van Belle et al., 2014). The authors observed right lateralized frontal and frontoparietal activity, including right IFC, uniquely associated with reactive inhibition while activity in dorsal premotor cortex and putamen was specifically ascribed to proactive processes. These findings challenge the view that comparably to reactive inhibition, right IFC also plays a key role in proactive processes and that similar networks are involved in both stopping modes. They also speak against the idea that during preparatory periods regions of the stopping network are primed for later implementation of inhibition (Chikazoe et al., 2009; Aron, 2011).

Another candidate region for proactive stopping might be DLPFC. Several fMRI studies found engagement of DLPFC in preparation for action inhibition (Chikazoe et al., 2009; Smittenaar et al., 2013; van Belle et al., 2014; Leunissen et al., 2016). The DLPFC however, does not seem to be exclusively recruited in proactive settings. Using spatial ICA to separate circuits for reactive and proactive stopping, one study found that networks underlying both stopping modes overlapped primarily in DLPFC (van Belle et al., 2014). This is consistent with findings of DLPFC activation in studies of reactive stopping (Menon et al., 2001; Mostofsky et al., 2003; Criaud and Boulinguez, 2013). Work from patients with

ECoG coverage of PFC regions ascribes dissociable roles to DLPFC and to its neighboring ventrolateral PFC (VLPFC) (Swann et al., 2013). For DLPFC a role in maintenance of task goals was suggested and for VLPFC in actual implementation of response inhibition. In accordance with this idea longstanding evidence points to a major role of DLPFC in working memory (Curtis and D'Esposito, 2003; Fregni et al., 2005; Mostofsky and Simmonds, 2008; Barbey et al., 2013). It might thus be that DLPFC stores stopping goals, both in contexts of reactive and proactive inhibition, but presumably more so in settings of proactive stopping where future action cancellations are specifically anticipated.

1.6.3 Striatum and Conclusions on Networks Underlying Proactive Inhibition

A good, already abovementioned candidate for proactive stopping is the striatum. When the likelihood of inhibiting a motor response increases, striatal activity was increased likewise (Vink et al., 2005; Zandbelt and Vink, 2010; Leunissen et al., 2016), speaking for a role in preparatory processes. Also, subjective expectation of stop-signals led to higher striatal activation in an anticipatory period before the imperative target appeared (Vink et al., 2015). When participants were informed about which of two simultaneous button presses selectively to inhibit, thus enabling the possibility to prepare for stopping, enhanced activity in right putamen was observed (Smittenaar et al., 2013). A TMS-fMRI study showed that the degree of proactive motor suppression, as indexed by corticospinal excitability, corresponds to striatal activation in a proactive SST (Majid et al., 2013). The study further investigated subjects with premanifest Huntington's disease, a disorder which leads to significant loss of brain volume in striatum and pallidum, and found absence of proactive motor suppression in patients, as measured by motor evoked potentials (MEPs). Striatal activity has also been implicated in studies and one meta-analysis of reactive inhibition (Vink et al., 2005; Simmonds et al., 2008). Very recent work concluded that this activation during periods of reactive stopping can, similarly to proactive

inhibition, be linked to expectancy of stopping, as striatal activity in a time period of actual action cancellation was increased for expected compared to unexpected withdrawals (Pas et al., 2017). This data further strengthens the implication of the striatum in preparatory inhibition.

While likely ecologically of higher relevance than reactive control, the underlying structures of proactive inhibition are far less clear. It might be subserved by a similar network as reactive processes, but several findings point against this view. Whereas quite clear evidence implicates recruitment of basal ganglia nuclei, the striatum in particular, the role of prefrontal areas in anticipation of stopping, especially of right IFC, has yet to be clarified.

1.6.4 Proactive Inhibition in Movement Preparation

Based on TMS research, the idea evolved that proactive inhibition is not only constrained to processes resulting in complete abortion of actions, but also involved in more general mechanisms of movement preparation as action selection. For instance, in an early phase of manual reaction time tasks, directly following go-signals broad inhibition of selected and non-selected finger muscles can be observed, as measured with MEPs. In a later phase however, while task irrelevant finger muscles are still inhibited, MEPs in the task relevant finger increase, speaking for movement facilitation (Leocani et al., 2000; Duque et al., 2014; Klein et al., 2016). Further evidence stems from instructed-delay reaction time tasks, in which a specific movement is cued, but subjects have to delay responding until an imperative target stimulus appears. In such paradigms inhibition of the selected effector can be observed in the timeframe closely preceding target signals (Touge et al., 1998; Hasbroucq et al., 1999). This suppression also occurs in task-irrelevant muscles and often is stronger when a specific muscle is selected compared to not (Duque and Ivry, 2009; Klein et al., 2016; Lebon et al., 2016). Several hypotheses have been developed, explaining these

and related findings. One hypothesis is that action selection is accomplished via preparatory inhibition. Here, selection might be achieved by suppression of competing but non-selected action alternatives (van den Wildenberg et al., 2010b; Tandonnet et al., 2011). A second hypothesis states that preparatory inhibition serves to counteract premature responding, inhibiting task-relevant muscles while preparatory activity evolves (Duque et al., 2010; Labruna et al., 2014). Following a third hypothesis, proactive inhibition increases the signal-to-noise ratio in the motor system in order to modulate gain of specific motor processes (Greenhouse et al., 2015). A very recent review concludes that current data does not provide sufficient evidence to discriminate between these hypotheses (Duque et al., 2017). Moreover, these are not mutually exclusive. Further research might clarify the role of proactive inhibition in action selection.

1.6.5 Isolating Proactive Inhibition

Generally, to tell proactive apart from reactive inhibition is a complex endeavor. Even in very simple go/nogo tasks or SSTs, commonly thought to specifically target reactive inhibition, proactive aspects seem to be involved (Criaud et al., 2012; Meyer and Bucci, 2016). For instance, after a few stop-trials subjects likely will prepare for upcoming inhibitions. One indicative for the close intertwinement of both stopping modes is that subjects can adjust their response speed on a trial-by-trial basis, with response slowing and speeding of SRTT after stop-signals (Bissett and Logan, 2012b; a) and faster RTs after successive go-trials (Emeric et al., 2007). Stopping in these paradigms thus does not happen in a completely unexpected, reactive fashion. Subjects presumably create internal models of stopping likelihood and will adjust internal systems as an efficient balance between stopping and responding. One way to address this issue is to clearly separate activity in early preparation for and later implementation of stopping, which is feasible with the fine time-resolution of EEG.

1.7 Electrophysiological Signals of Motor Inhibition

The most prominent EEG correlates associated with motor inhibition are the ERPs N2 and P3. Usually in nogo- or stop-trials compared to go-trials an increased frontal-central negativity can be observed (N2), followed by an enhanced fronto-central to central located positivity (P3) (Jodo and Kayama, 1992; Bokura et al., 2001; Donkers and van Boxtel, 2004; Smith et al., 2007; 2008). N2 emerges about 200-300 ms after the stop-/nogo-stimulus, and P3 is observed about 150 ms later. Moreover, when comparing successful to failed stop-trials, amplitude of P3 was reported to be increased (Ramautar et al., 2004; Senderecka et al., 2012), or peaked earlier in accomplished in contrast to failed inhibitions (Kok et al., 2004; Bekker et al., 2005). A recent study suggests P3 to be a solid marker of inhibitory behavior. Across several SSTs, the onset latency of P3 was shorter when stopping was successful and furthermore P3 latency was strongly correlated with SSRT (Wessel and Aron, 2015). In contrast to these findings, two recent reviews question the role of N2 and P3 as valid markers of motor inhibition (Huster et al., 2013; Albares et al., 2015). First, both components are observed in a wide range of experimental conditions, also in circumstances that do not call for cancellation of motor responses. Second, both potentials seem to emerge too late to be able to reflect inhibitory processes. Therefore, N2 and P3 were suggested to be markers of conflict-resolution and evaluation processes than of inhibition per se. The reviews conclude that data from the time-frequency domain, as beta oscillations, might be more suited to capture inhibitory processes.

1.7.1 Brain Oscillations Underlying Motor Inhibition

Ever since the human EEG was first described in 1929 by Hans Berger, oscillations play a significant role in research of brain activity. Berger was the first to note that in subjects with closed eyes, large and slow fluctuations of neural activity emerge over occipital areas, and that these are replaced by faster oscillations once the eyes are opened (Berger, 1929).

Brain oscillations are clustered in distinct frequency bands, namely delta (~1-4 Hz), theta (~4-8 Hz), alpha (~8-12 Hz), beta (~15-30 Hz), gamma (~30-90 Hz) and high gamma (~>50 Hz) (Cole and Voytek, 2017). As the number of cognitive functions exceeds these five frequency bands, obviously a specific band cannot be directly tied to a certain brain function. Specific properties of an oscillation can be defined, as frequency, amplitude and phase. Thus, cognitive functions might relate to modulations of these parameters and by the cerebral area in which the oscillation emerges (Herrmann et al., 2016). However, certain relationships seem to be very consistent, as for instance the linkage between theta and memory (Colgin, 2013), beta and sensorimotor processing (Neuper et al., 2006; Kilavik et al., 2013) and alpha and the inhibition of cortical areas (Jensen and Mazaheri, 2010). High-frequency oscillations, specifically gamma, are assumed to underlie local processing in small time-scales, while activity in lower frequencies (theta, alpha, beta) might subserve longer distance communication between connected brain areas in larger time windows (Kopell et al., 2000; von Stein and Sarnthein, 2000; Canolty et al., 2007; Scheeringa et al., 2011). An influential theory states that communication between separated neuronal groups is most effective when they coherently oscillate, sharing similar time windows for in- and outgoing information (Fries, 2005). Also, oscillations of different frequency bands have been suggested to interact with each other, a phenomenon called cross-frequency coupling (Canolty and Knight, 2010). Oscillations offer a very powerful tool to understand neural processing, as they seem not only to be able to explain which brain regions are involved in a certain cognitive process, but also how processing is organized. They can describe neural computation in terms of excitation, facilitation, inhibition and in specific forms of information transfer. One putative oscillatory signature of motor inhibition is prefrontal theta power. Theta has been reported to be increased over PFC regions when inhibiting motor responses (Kirmizi-Alsan et al., 2006; Yamanaka and Yamamoto, 2010; Harper et al., 2014). As theta increases in a similar timeframe as the N2, it was suggested that both reflect

a similar process (Huster et al., 2013; Harper et al., 2014). However, it is unclear what underlying process theta is an indication for. In the context of motor inhibition theta has been associated with motor inhibition directly (Wessel and Aron, 2014), but also with conflict monitoring (Huster et al., 2013), or has been proposed to play a role in stimulus coding and response selection (Mückschel et al., 2017). Therefore, in the following, I will focus on the alpha and beta band as activity in those frequencies has most consistently been associated with motor processes and motor inhibition.

1.7.1.1 The Role of Prefrontal Beta Oscillations in Motor Inhibition

Above, the PFC was highlighted as one of the central structures in a network recruited when inhibiting motor actions. Delineating a network underlying stopping tells us *what* regions might be relevant for successful withdrawel of movements, but not *how* information is transferred within this network. Filling this gap, oscillations in the beta band were suggested to underlie communication between critical fronto-basal ganglia stopping nodes (Aron, 2011; Aron et al., 2016). This idea is based on the concept that oscillations offer a potential mean for information transfer between brain regions (Fries, 2005). In healthy subjects, an increase of beta over fronto-central regions was observed when subjects were engaged in reactive inhibition (Alegre et al., 2004). A recent EEG study, using independent component analysis (ICA) to single out stopping-related activity, found a right-lateralized frontal beta signature for stopping (Wagner et al., 2018), corresponding to abovementioned studies highlighting the role of right IFC in reactive inhibition. Similar findings were obtained from intracranial recordings in epileptic patients, where beta power over right IFG was enhanced for successful compared to unsuccessful stopping (Swann et al., 2009; Wessel et al., 2013), but see (Fonken et al., 2016). These studies established a link between reactive inhibition and increased beta oscillations over prefrontal regions. Extending these findings, not only PFC but also preSMA, STN and M1 display enhanced beta when stopping is implemented. An increase of the beta rhythm for

action stopping has been reported in direct recordings from STN in PD patients (Kühn et al., 2004; Alegre et al., 2013; Benis et al., 2014; Wessel et al., 2016a). In preSMA, beta power increased for successful inhibitions as suggested by one ECoG study (Swann et al., 2012). Increased beta over sensorimotor cortex has been associated with action cancellation, as outlined in the following subsection. Finally, one study, using combined TMS and EEG, showed that motor cortex excitability follows a beta oscillation after stimulation of pre-SMA or right IFG (Picazio et al., 2014), suggesting beta-driven network interactions. In sum, this work, centered on reactive stopping, underpins the idea of beta oscillations as a communication mechanism within a putative stopping network.

When turning from reactive to proactive inhibition, the picture becomes less clear. One study using magnetoencephalography (MEG) reports increased beta power over DLPFC when subjects prepared for an anti- compared to a prosaccade (Hwang et al., 2014). In few epileptic patients, right IFC and DLPFC were reported to display increased gamma but not beta activity, contrasting trials where subjects might have to stop, with trials where no stopping was required (Swann et al., 2012; Swann et al., 2013). Swann et al. (2012) however, studied a single subject and Swann et al. (2013) focused on gamma and did not specifically report results of in the beta band activity. As only few studies investigated oscillatory dynamics of proactive inhibition, data remains limited and more work is needed to clarify whether prefrontal beta plays a similar role in preparatory compared to reactive stopping.

1.7.1.2 Mu and Beta Oscillations over Sensorimotor Cortex

The final relay for stopping signals is the sensorimotor cortex. Here, the corticospinal tract begins, which over spinal nerves innervates the muscles, the target structure of motor inhibition. Numerous studies showed a decrease of sensorimotor alpha (which over this region is referred to as mu) and beta oscillations during action preparation and execution, with an increase after movements have been performed (Pfurtscheller et al., 1996; Neuper

et al., 2006). The initial decrease is stronger over the contralateral hemisphere in relation to the performed action (Babiloni et al., 2004; Kajihara et al., 2015). Evidence for a link between sensorimotor processing and mu oscillations was found in a local field potential study, in which monkeys performed a vibrotactile discrimination task (Haegens et al., 2011). A decrease in mu over sensorimotor cortex led to enhanced behavioral performance and an inverse relationship between mu power and neuronal spiking was found. This suggests a role of mu in modulating sensorimotor excitability. Further supporting this idea, in a TMS study a negative relationship between MEPs and sensorimotor mu directly preceding M1 stimulation was found (Sauseng et al., 2005). Also in humans, an association between sensorimotor mu and behavior was established. In a go/nogo task, prestimulus mu was predictive of errors as it was increased before subjects failed to successfully withhold a button press (Mazaheri et al., 2009).

There is longstanding evidence for a central role of beta in motor control (Jenkinson and Brown, 2011). Major support for this idea is stemming from patients with PD, a disorder leading to significant impairments in motor control as tremor, rigor and hypokinesia. Such patients display strongly elevated beta oscillations, both in cortical and subcortical areas, which were shown to correlate with motor deficits (Hammond et al., 2007; Brittain and Brown, 2014). Beta over sensorimotor regions, similar to mu, has been associated with motor cortex excitability (Mäki and Ilmoniemi, 2010), as central beta oscillations were weaker before large-amplitude MEPs. When successfully inhibiting a preplanned response, compared to failed inhibitions, beta over central regions was increased, with this increase being observed around the time of the erroneous response (Krämer et al., 2011). In one ECoG study, in electrodes directly over M1, a relative increase for beta in correct stop-trials compared to failed inhibition was reported (Swann et al., 2009). Results from another study in epileptic patients point in the same direction, reporting that beta power decreased over M1 for go-trials and unsuccessful stops and increased for successful inhibitions

(Fonken et al., 2016). Sensorimotor beta oscillations also seem to be related to specific movement preparation and thus proactive processes. When subjects were given increased certainty about where to pull a joystick (within a range of 90° instead of 180°), prestimulus beta power over sensorimotor regions was decreased (Tzagarakis et al., 2015). Concluding, sensorimotor mu and beta are most important for preparation and implementation of motor actions and for motor inhibition. Studies investigating mu and beta in go/nogo tasks and the SST focused on reactive stopping and their role in proactive inhibition has yet to be clarified.

1.7.1.3 The Role of Alpha Oscillations in Attentional Networks

The constant monitoring of the environment is essential for motor inhibition in daily life, as for instance in traffic situations, in interpersonal encounters or at work. We would not be able to stop our bike, if we would not have paid attention to the pedestrian suddenly crossing the street. There is extensive evidence for visual attention being related to oscillations in the alpha band. Posterior alpha oscillations originate from occipito-parietal areas, where they are modulated by incoming visual information (Berger, 1929; Adrian and Matthews, 1934; Hari et al., 1997). Alpha oscillations decrease over occipital visual areas during preparatory attention (Sauseng et al., 2005; Thut et al., 2006), when critical target stimuli are anticipated. Occipital alpha on the opposite increases, when processing task-irrelevant information (Kelly et al., 2006) and in time-windows when distracting stimuli are presented (Payne et al., 2013). Spontaneous fluctuations of alpha over occipital areas were predictive of following perception (Ergenoglu et al., 2004; Hanslmayr et al., 2007; van Dijk et al., 2008), with higher alpha leading to decreased likelihood of detecting visual targets. This is in line with the finding that when occipital cortical areas were stimulated specifically in the alpha frequency (10 Hz) with TMS, impaired visual detection in the visual field opposite to the stimulated hemisphere was observed (Romei et al., 2010). Direct recordings from visual areas V2 and V4 in macaque monkeys also showed an inverse

relationship between alpha amplitude and visual performance (Bollimunta et al., 2008). Moreover, alpha phase seems to play an important role, as increased phase locking, the phase variability at a given point in time, has been observed prior to successful target detection (Hanslmayr et al., 2005). In addition, targets are less likely to be detected with the cycle of the alpha wave being at its through during visual target presentation (Mathewson et al., 2009). Linking visual alpha to motor inhibition, the prestimulus alpha rhythm over occipital regions was increased before errors in a go/nogo task were committed (Mazaheri et al., 2009), speaking for decreased chances of successful target detection. Earlier theories interpreted alpha as an idling rhythm, observable in brain areas free of task-processing and therefore "non-activated" (Pfurtscheller et al., 1996). This view has been refined in recent years. Novel theories suggest a gating role of alpha, suppressing brain activity which is non-beneficial in a given context and facilitating processing of relevant information (Klimesch et al., 2007; Jensen and Mazaheri, 2010). Such a gating mechanism might be very relevant for successful selection of stop-stimuli in a context of motor inhibition.

1.8 Outline of the Thesis

The aim of this thesis is to further our understanding of the neural mechanisms underlying motor inhibition. The experiments targeted proactive and reactive processes, tapping both into early preparation for and subsequent implementation of motor inhibition. Three EEG studies focused on alpha/mu and beta power over prefrontal, sensorimotor and occipital sites with the following research questions:

I. The first study aimed at developing a deeper understanding of the time course of proactive and reactive motor inhibition (Chapter 2), disentangling the preparation for and later implementation of motor control. Here, healthy participants performed in a novel cued go/nogo task.

II. In the second study, I was interested in the specific role of prefrontal and basal ganglia nodes in the time course of proactive and reactive inhibition (Chapter 3). To this end, patients with focal lesions in PFC and BG performed the cued go/nogo task established in Study I.

III. The third study was conducted to increase ecological validity in a proactive motor inhibition context in including motor adaptation (Chapter 4). To do so, I designed a novel paradigm in which participants not only had to inhibit motor actions, but in specific trials also had to change to a rare non-standard motor response.

2 Temporal Dynamics of Proactive and Reactive Motor Inhibition [1]

2.1 Introduction

Motor control is one of the key executive functions in daily life, allowing us to flexibly adapt or inhibit our behavior to a changing environment according to our current goals. Two variants of inhibitory motor control can be distinguished, reactive and proactive control (Aron, 2011). Whereas reactive motor inhibition refers to a process when a prepotent movement has to be withheld or stopped in reaction to an external signal (for instance a stop sign), proactive motor inhibition describes a condition in which preparatory processes facilitate motor inhibition which might be required at a later point in time (for example a street sign warning of bears crossing).

Most behavioral and neuroscientific research on motor control has focused on reactive inhibition. However, the transferability of this model to daily life is limited as stopping usually does not happen in a purely exogenous, stimulus-driven way. Most often, context-dependent, top-down endogenous processes are involved. This for instance can be observed in psychiatric patients having deficits in urge-control, supposedly linked to a lack of such top-down signals. Proactive inhibition thus seems a more ecologically valid model and therefore promising in order to understand fundamental aspects of motor control in everyday life as well as in psychiatric and neurological disorders (for review see Aron (2011)).

The dual mechanisms of control (DMC) framework states that cognitive control can be either proactive or reactive depending on costs or benefits of the respective processes. Whereas proactive control is based upon the anticipation and prevention of interference

[1] This chapter corresponds largely to: Liebrand, M., Pein, I., Tzvi, E., & Krämer, U. M. (2017). Temporal Dynamics of Proactive and Reactive Motor Inhibition. *Frontiers in Human Neuroscience*, 11. The study was conceived and designed by UMK. I analyzed the data and wrote the manuscript.

before it occurs, reactive control relies upon the detection and resolution of interference after its onset (Braver et al., 2008; Braver, 2012). The DMC framework makes specific predictions about proactive and reactive control. During proactive control the lateral prefrontal cortex (lPFC) is believed to be activated in a sustained way, reflecting maintenance of task goals. Furthermore, attention and action are thought to be biased proactively in a goal-driven manner. Regarding reactive control, the lPFC is believed to be activated transiently in reaction to external signals. That is, according to the DMC framework three networks can be assumed to be implicated in motor control: PFC mediating cognitive control, sensorimotor cortex executing motor actions and a visuo-attention network.

In this study, investigating proactive and reactive inhibitory control, we specifically focused on these three networks. We used a cued go/nogo paradigm with cues indicating whether participants might have to stop later in response to target signals or not, thereby manipulating the need for proactive control. We took advantage of the high time-resolution of electroencephalography (EEG) and measured both event-related oscillatory activity (prefrontal beta, sensorimotor alpha/beta, occipital alpha) and event-related potentials (ERPs; contingent negative variation (CNV), N1/P1, P3). In the following paragraphs, we will outline for each of the three networks, visual-attention areas, sensorimotor cortex and PFC, what previous literature has identified as relevant ERP and oscillatory measures of reactive and proactive motor control.

In a context like the go/nogo task, in which visual targets need to be detected to successfully inhibit a preplanned response, visual attention becomes critical. In attention research, great emphasis has been put on oscillations in the alpha band (Hanslmayr et al., 2011; Klimesch, 2012). Alpha oscillations over occipital visual areas decrease during preparatory attention and increase in regions processing task irrelevant information. Moreover, visual alpha has been linked to behavioral performance in demanding tasks

requiring visual attention (Ergenoglu et al., 2004; Hanslmayr et al., 2005). Lavallee et al. (2014) highlighted the role of attention in proactive motor control by showing increased delta power in trials involving proactive control, presumably reflecting the engagement of a posterior attentional network. Another marker of attentional preparation is the CNV. This slow negative potential with its maximum over central regions, is the most common ERP component when studying preparatory (i.e., proactive) cognitive processes. Schevernels et al. (2016) reported in a cued go/nogo-study that in cued nogo- compared to cued go-trials the CNV was reduced, speaking for less employment of attentional resources. Here, we expected proactive motor control to be accompanied by increased activity in attentional networks, reflected in changes in occipital alpha, the CNV and the P1/N1-complex, as ERP correlate of early visual processing in extrastriate cortex (Hillyard and Anllo-Vento, 1998).

With respect to sensorimotor cortex, oscillations in the alpha (9–13 Hz) and beta (14–25 Hz) frequency bands have frequently been associated with motor control. Sensorimotor alpha, also referred to as mu, desynchronizes during anticipation and execution of movements and synchronizes afterwards (Neuper et al., 2006). The same pattern can be observed for sensorimotor beta oscillations (Neuper et al., 2006). Previous response inhibition studies (Krämer et al., 2011; Picazio et al., 2014) have shown that beta is relatively increased during reactive motor inhibition. However, little is known about the role of sensorimotor mu and beta in proactive motor inhibition. In our study, we thus focused on mu and beta with respect to both proactive and reactive motor control.

Prefrontal regions have consistently been associated with motor inhibition (Aron et al., 2004b; Aron et al., 2014a). Moreover, prefrontal beta oscillations have been implicated in reactive motor inhibition. For instance, in healthy subjects (Alegre et al., 2004) and in epileptic patients using intracranial recordings over the right IFG (Swann et al., 2009), higher prefrontal beta power has been observed in trials where reactive inhibition was

called for. Investigating proactive inhibition, two studies using a modified stop signal task (SST) in a limited sample size of epileptic patients reported increased gamma but not beta power over prefrontal electrodes (Swann et al., 2012; Swann et al., 2013). In the present study, we measured reactive and proactive prefrontal beta power to clarify whether proactive inhibitory control, similarly to reactive control, is reflected in increased prefrontal beta oscillations.

Finally, the most-studied ERP components of reactive response inhibition are the N2 and P3 (Huster et al., 2013). Although it remains controversial whether the stopping-related N2 and P3 reflect inhibition per se, recent evidence suggested that the onset of the P3, presumably stemming from PFC, is indeed linked to the success of response inhibition (Wessel and Aron, 2015). As a prominent marker of reactive inhibition, linked to the PFC, we included the P3 into our analysis.

To investigate proactive inhibition, we contrasted activity occurring in the cue-target interval, comparing trials in which subjects prepared for an upcoming inhibition with trials in which no response inhibition could occur. This comparison reflects processes modulated by the context of knowing that the default action can be implemented or that an alternative action, in this case the inhibition of an action might be required. As a second measure for proactive inhibition, we investigated how activity after target-signals was affected by the context (for a similar approach see Swann et al. (2012); Swann et al. (2013)). Specifically, we asked how response execution was modulated by proactive control instigated by the cue. For reactive inhibition, we contrasted target-related activity in trials where subjects had to stop with trials where they executed a default motor action (for a detailed description of contrasts see “Materials and Methods” section).

Based on the DMC framework and previous findings, we expected that proactive inhibition would lead to increased employment of attention (indicated by decreased occipital alpha,

an increased CNV and P1/N1), sustained higher levels of prefrontal control (reflected in increased prefrontal beta) and a modulation of sensorimotor activity (indicated by altered mu/beta power). Reactive inhibition was expected to be mediated by transiently increased prefrontal control (higher beta power), an increased P3 and increased sensorimotor mu/beta power.

2.2 Materials and Methods

2.2.1 Subjects

Twenty-five right-handed participants participated in the study. Three participants were excluded from analysis due to extensive EEG artifacts (see below for further explanation). All of the remaining 22 participants (20–32 years, mean: 24.5 years, 14 females) were by self-report free of neurological or psychiatric disorders. The participants had normal or corrected to normal vision. They gave informed consent and received money (8€/h) or course credit for participation. The study was performed in agreement with the Declaration of Helsinki and had been approved by the ethics committee of the University of Lübeck.

2.2.2 Design and Stimuli

The participants performed a cued go/nogo-task (see Figure 2.1). The cue-stimuli were a square and a circle, the following target stimulus a triangle. If the triangle followed the square, it was in 75% of the trials presented in the center of the screen and in 25% lateralized to the right side (5°). If the triangle followed the circle, it appeared in 75% of the trials in the center of the screen and in 25% lateralized to the left side (5°). The probability of the two cues was 50% each.

The participants were instructed to press the right button (go) with their right index finger after the triangle following the square and the left button with their left index finger after

the triangle following the circle. Additionally, before each block they were told to refrain from pressing the button either when the triangle appeared on the right side (block: stop right) or on the left side (block: stop left). These two types of trials were alternated from block to block. Participants were instructed before each block which side they have to attend and possibly stop.

This design results in two different conditions, which we refer to as Maybe Stop (MS) and Certain Go (CG; see Figure 2.1). In the MS condition, the cue indicated that the participant might have to stop afterwards, whereas in a CG condition no stop was required in any case. In the MS condition participants had to stop in 25% of the trials (Stop-trials), but were instructed to press the button in the remaining 75% (No Stop-trials). In terms of probability and visual stimuli the trials in the CG condition were matched to Stop- and No-Stop-trials. Trials in the CG condition which are matched to Stop-trials, thus including lateralized target stimuli and 25% probability, are referred to as Rare Go-trials. The remaining 75% of trials, matched to No Stop-trials, are referred to as Frequent Go-trials. For instance, if the current block was a "stop-left" block and a circle was presented followed by a triangle on the left side, the response had to be withheld (MS condition, Stop-trial). However, if in the same block a square was presented followed by a triangle on the right side, the participant had to press the right button (CG condition, Rare Go-trial). Also, in the following we refer to trials with 75% probability as frequent trials (No Stop and Frequent Go) and to those with 25% probability as rare trials (Stop, Rare Go).

Both cue (square, circle) and target (triangle) appeared for 100 ms. The target followed cue-onset after an interval of 1100 ms. The time between two subsequent trials was jittered (1.3–1.6 s). The experiment was divided into six blocks with 160 trials each, resulting in 960 trials. The to-be-stopped side of the first block was counterbalanced among participants. Throughout the whole experiment a fixation line was presented underneath the stimuli, which participants were instructed to fixate. Participants were instructed to

respond as fast and accurate as possible and not to press the button until the triangle had appeared. Before the start of the experiment the participants practiced the task in three short blocks with each 16 trials.

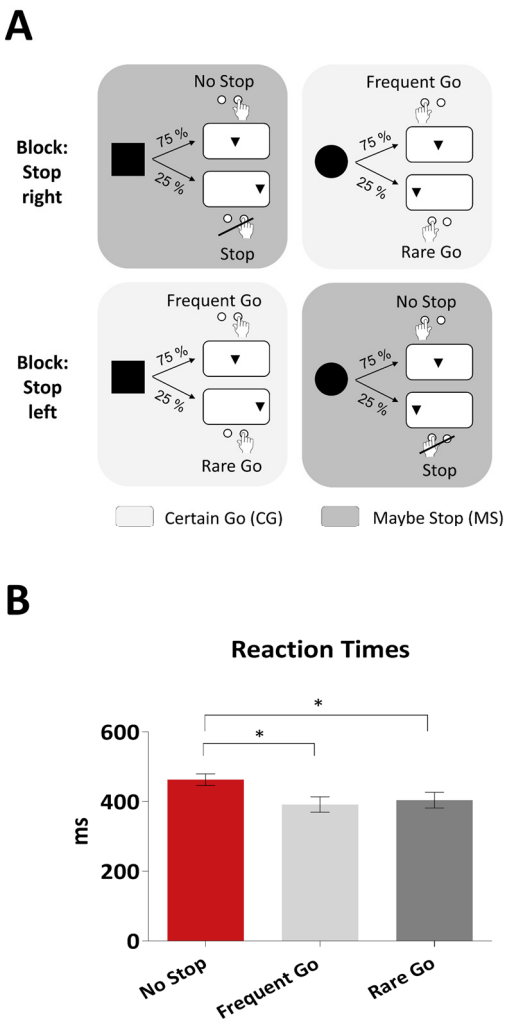


FIGURE 2.1 | Design and behavioral results. (A) Design of the cued go/nogo task. On the upper row a block is illustrated where subjects had to refrain from pressing the button when the target (triangle) appeared on the right side of the screen. Similarly, in the block displayed in the lower row a stop was required when the target appeared on the left side. In the Maybe Stop (MS) condition (dark gray) the subject was told by the cue (square, circle) that he might have had to stop later on, while in the Certain Go (CG) condition (light gray) he was informed by the cue that he always could press the button when the target appeared later on. (B) Behavioral results showing mean reaction times in No Stop-, Frequent Go- and Rare Go-trials. As error bars the standard errors of the mean (SEM) are displayed. Significant effects are stressed with asterisks.

2.2.3 Procedure

The experiment was controlled using the Presentation® software (Version 14.5). Stimuli were presented on a 17″ screen, about 1 m away from the participant. Participants were sitting in a comfortable chair and in the middle and after each of the experimental blocks they had a short break of 20 s where they were able to relax. The total duration of the experiment was about 50 min.

2.2.4 EEG Recordings and Data Preprocessing

The EEG was recorded with a 64-channel BrainAmp MR plus amplifier with a sampling rate of 250 Hz. Electrodes were placed according to an extension of the international 10–20 system (Nuwer et al., 1998). Vertical and horizontal eye movements (vEOG and hEOG) were recorded, the former using an electrode placed below the right eye and a frontopolar electrode, the latter using electrodes located on the outer canthus of each eye. The EEG was recorded against a reference electrode placed on the right earlobe.

2.2.5 Behavioral Data Analyses

Mean reaction times, overall error rates and premature error rates (button presses before the triangle had appeared) were computed for each subject and submitted to paired sample *t*-tests comparing Stop-, No Stop-, Frequent Go- and Rare Go-trials.

2.2.6 EEG Data Analyses

EEG data analysis was performed with EEGLAB (Delorme and Makeig, 2004), ERPLAB (Lopez-Calderon and Luck, 2014) and custom written MATLAB (Natick, MA, USA) scripts. EEG data were re-referenced offline to the average of the signal from the two earlobe electrodes. The data were high-pass filtered with 0.5 Hz in addition to a notch filter of 50 Hz. The data were segmented into epochs for the different conditions. Epochs included 1 s before and 2 s after the stimulus. The baseline was defined as the 100 ms preceding the stimulus, with the stimulus being either the cue or the target, depending if effects in the cue-target interval or target-related activity was analyzed. An Independent Components Analysis (ICA), as implemented in EEGLAB (Infomax extended), was performed on the epoched data including all conditions. Independent components accounting for blink artifacts and horizontal eye movements were identified and removed from the data (Jung et al., 2000). Trials affected by other artifacts caused, e.g. by muscle tension, were rejected from further analysis with a threshold for rejection of ±80 μV. If more than 30% of the data

of one participant were rejected, this subject was excluded from analysis (three subjects). Current source density (CSD) interpolation of the data was estimated through Laplacian computation based on a spherical spline interpolation (with a spline order of four; Kayser and Tenke (2006)) using a toolbox for MATLAB (Kayser, 2009). We took advantage of the Laplace transformation, as it improves the spatial resolution of EEG, especially in combination with higher density recordings (≥64 electrodes; (Babiloni et al., 1995)).

2.2.7 Event-Related Potentials (ERPs)

We analyzed the amplitude of the CNV in the cue-target interval and the target-related P1, N1 and P3. As measure of the amplitude, we computed the area under the curve (AUC) in a given time-window, zeroing negative values in positive waveforms and vice versa. The AUC is a rather new approach but has the critical advantage of minimizing the problem of selecting an appropriate measurement window (Luck, 2014). Also, when computing our statistics based on mean amplitude measures, all reported significant effects were replicated. P1 and N1 were measured at PO7 and PO8 and in the following time-windows after target-onset: P1 (50–150 ms), N1 (100–250 ms). The CNV was measured in an interval directly preceding the target (–100 to 0 ms relative to the target), as its amplitude is expected to be more stable later during a preparatory process (Boehm et al., 2014) and most representative of the preparatory state directly before target-onset. The CNV was measured at Cz, as this slow negativity has been shown to be highest over central sides in a motor preparation context (Filipović et al., 2001; Smith et al., 2013). P3 was measured between 300 ms and 500 ms after target-onset, a common time-range for P3 in go/nogo tasks (Verleger et al., 2006; Smith et al., 2008). We decided to measure P3 at central midline electrodes (C3, C4, Cz). This decision was data-driven and based on the topography of the go-P3 (Figure 2.5), which had two lateralized maxima over the sensorimotor cortex. This topography is likely due to application of CSD transformation to our data, as data without

transformation show a central topography. For P1 and N1, data of trials requiring left-handed responses were flipped along the midline to be able to measure activity over the visual cortex contra- and ipsilateral to the relevant stimulus side. That is, we analyzed effects in the contra- and ipsilateral hemisphere to lateralized target-stimuli. For all components, data were averaged across trials with right- and left-hand responses. Data of the early components P1 and N1 were subjected to repeated measures ANOVAs with the within-subject factors Condition (MS vs. CG) and Hemisphere (ipsi- vs. contralateral to the lateralized target stimulus). Data of target-evoked P3 were subjected to repeated measures ANOVAs with the within-subject factors Condition (MS vs. CG) and Electrode (C3, Cz, C4). The CNV was analyzed with a paired sample *t*-test comparing MS- and CG-trials. For visualization only, data were low-pass filtered with 15 Hz.

2.2.8 Time-Frequency Analysis

To study the inhibition related power changes in the alpha and beta band, single trial data were convolved with a complex Morlet wavelet as implemented in MATLAB (function cwt with parameter specification "cmor1–1.5"):

$$w(t) = (\pi f_b)^{-0.5} e^{-2\pi i f t_c} e^{-\frac{t^2}{f_b}}$$

where f_b = 1 was the bandwidth parameter and f_c = 1.5 was the wavelet center frequency (Teolis, 1998). Specifically, we computed and averaged for each subject changes in time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (1–40 Hz, linear increase) with respect to a pre-stimulus baseline (–250 ms to –50 ms prior to the stimulus). The selection of the analyzed alpha/mu (9–14 Hz) and beta (15–25 Hz) frequencies was based on visual inspection of the data and previous literature (Krämer et al., 2011; Solbakk et al., 2014). In order to reduce the number of statistical comparisons and to increase signal-to-noise ratio, we clustered the electrodes into regions of interest: Left prefrontal (F3, F5, FC3, FC5), right prefrontal (F4, F6, FC4, FC6), left central

(C3, C5, CP3, CP5), right central (C4, C6, CP4, CP6), left parieto-occipital (P5, P7, PO3, PO7) and right parieto-occipital (P6, P8, PO4, PO8) based on a previous study (Krämer et al., 2013). Effects over prefrontal, sensorimotor and occipital electrodes were analyzed differently. For motor related (sensorimotor mu and beta) and attention-related (occipital alpha) effects, data of trials requiring a left hand response were flipped along the midline (for a similar approach see e.g., Fogelson et al. (2009)). In the motor- and visual networks, lateralized activity could be expected as unimanual responses were given and lateralized stimuli were presented. Data was flipped along the midline to average across responses with the right/left hand and over lateralized presented stimuli. We were thereby able to analyze effects in the hemispheres contra- and ipsilateral to the respective response hand or visual stimulus. For prefrontal effects (beta over prefrontal electrodes) data was not flipped, because we did not expect these effects to be lateralized dependent on the side of motor actions or visual stimuli. That is, we compared data of left and right hemisphere. For all effects, data of trials with right- and left-hand responses were averaged. Then mean time-frequency power in a given time-window (see below) was subjected to repeated measures ANOVAs with the within-subject factors Condition (MS vs. CG) and Hemisphere (ipsi- vs. contralateral or left- vs. right). As measurement window for effects before target onset we chose 700–1100 ms because the cue-related activity was distant and target-onset (1100 ms) was closest. For target-related effects we investigated the window between 200 and 500 ms. For stopping-related effects of beta power over prefrontal electrodes similar time-windows have been reported before (Swann et al., 2009; Swann et al., 2011) and this timeframe encloses the period when participants enacted or inhibited their motor response after having processed the cue-stimulus. To account for multiple comparisons that were performed for each individual condition difference, we applied corrected *p*-values using the Bonferroni method (see “Results” section).

As a measure for proactive inhibition in the cue-target interval, we contrasted trials in which the later motor response might (MS) or might not have to be inhibited (CG). To assess how proactive inhibition modulated response execution after target signals, we compared trials following cues that signaled that responses might (No Stop) or might not have to be stopped (Frequent Go; see Swann et al. (2012); Swann et al. (2013)). Finally, to assess the correlates of reactive inhibition, we contrasted trials in which the response actually had to be inhibited (Stop) with matched go-trials still requiring a response (Rare Go).

2.3 Results

2.3.1 Behavioral Results

Participants were faster in Frequent- and Rare Go- compared to No Stop-trials (Figure 2.1; Frequent Go- (392 ± 103 ms) vs. No Stop- (463 ± 79 ms) trials: $t_{21} = 8.0$, $p < 0.001$; Rare Go- (404 ± 105 ms) vs. No Stop-trials: $t_{21} = 4.4$, $p < 0.001$). Subjects responded more accurately in No Stop- (98.0%) than Frequent Go-trials (95.1%; $t_{21} = 2.1$, $p = 0.044$), due to a higher rate of premature errors (button presses before the triangle had appeared) in Frequent Go-trials ($t_{21} = 2.4$, $p = 0.027$). Also, in Rare Go-trials more premature errors than in Stop-trials were committed ($t_{21} = 2.2$, $p = 0.037$).

2.3.2 EEG Results

As we performed several analyses in the time-frequency domain, we used Bonferroni corrected *p*-values, separately for effects taking place before and after target stimuli. In the cue-target interval, we conducted four comparisons (alpha at occipital regions, mu/beta at sensorimotor regions and beta at prefrontal regions) which results in a corrected *p*-value of 0.0125. For target-related effects six comparisons were conducted (beta at prefrontal regions for frequent and rare-trials and mu/beta at sensorimotor regions for frequent and

rare-trials). This results in a corrected *p*-value of 0.0083. For main findings of this study see Table 2.1.

2.3.2.1 Visual Attention Effects

2.3.2.1.1 Occipital Alpha

To investigate the role of visual attention in proactive motor control, we examined condition differences in alpha power over occipital sites in the cue-target interval. After cue-onset in both Maybe Stop- and Certain Go-trials, alpha decreased until about 400 ms and then increased again. Whereas alpha in CG-trials increased towards the baseline level, this rebound was dampened in MS-trials resulting in reduced alpha power (Figure 2.2A). We subjected mean alpha power between 700 ms and 1100 ms to repeated measures ANOVAs with the factors Condition (MS, CG) and Hemisphere (contra-, vs. ipsilateral to the upcoming, possibly lateralized target stimulus). Alpha power was lower in MS- compared to CG-trials ($F_{(1,21)} = 22.5$, $p < 0.001$). Also, alpha activity was lower in the hemisphere contralateral to the upcoming, possibly lateralized stimulus, compared to ipsilateral ($F_{(1,21)} = 19.9$, $p < 0.001$), but the two factors did not interact ($F_{(1,21)} = 1.4$, $p = 0.245$).

2.3.2.1.2 CNV

The CNV, measured in the cue-target interval, had a typical central topography, with a maximum at Cz and increasing towards the target (Figure 2.2B). We subjected the AUC between 1000 ms and 1100 ms to a paired sample t-test comparing MS- and CG-trials. The CNV was larger in MS-trials compared to CG-trials ($t_{21} = 2.5$, $p = 0.021$).

2.3.2.1.3 Target-Related P1/N1

To assess attention related effects on early visual target processing, we looked at the P1/N1 complex to the target stimuli. P1 peaked between 90–130 ms and N1 around 150–200 ms. Around the time of their maxima, both components were centered at PO7 and PO8 (Figure 2.2C). We subjected the AUC between 50–150 ms (P1) and 100–250 ms (N1) to ANOVAs with the factors Hemisphere (ipsi-, vs. contralateral to the target stimulus) and Condition (frequent trials: No Stop vs. Frequent Go, rare trials: Stop vs. Rare Go).

The N1 elicited by centrally presented stimuli was larger in No Stop- than Frequent Go-trials ($F_{(1,21)} = 11.7$, $p = 0.003$). The P1 did not differ between No Stop- and Frequent Go-trials ($F_{(1,21)} = 1.2$, $p = 0.288$). In trials with lateralized target-stimuli (Stop vs. Rare Go), neither N1 nor P1 showed a difference for the factor Condition (N1: $F_{(1,21)} = 0.7$, $p = 0.422$; P1: $F_{(1,21)} = 0.3$, $p = 0.611$).

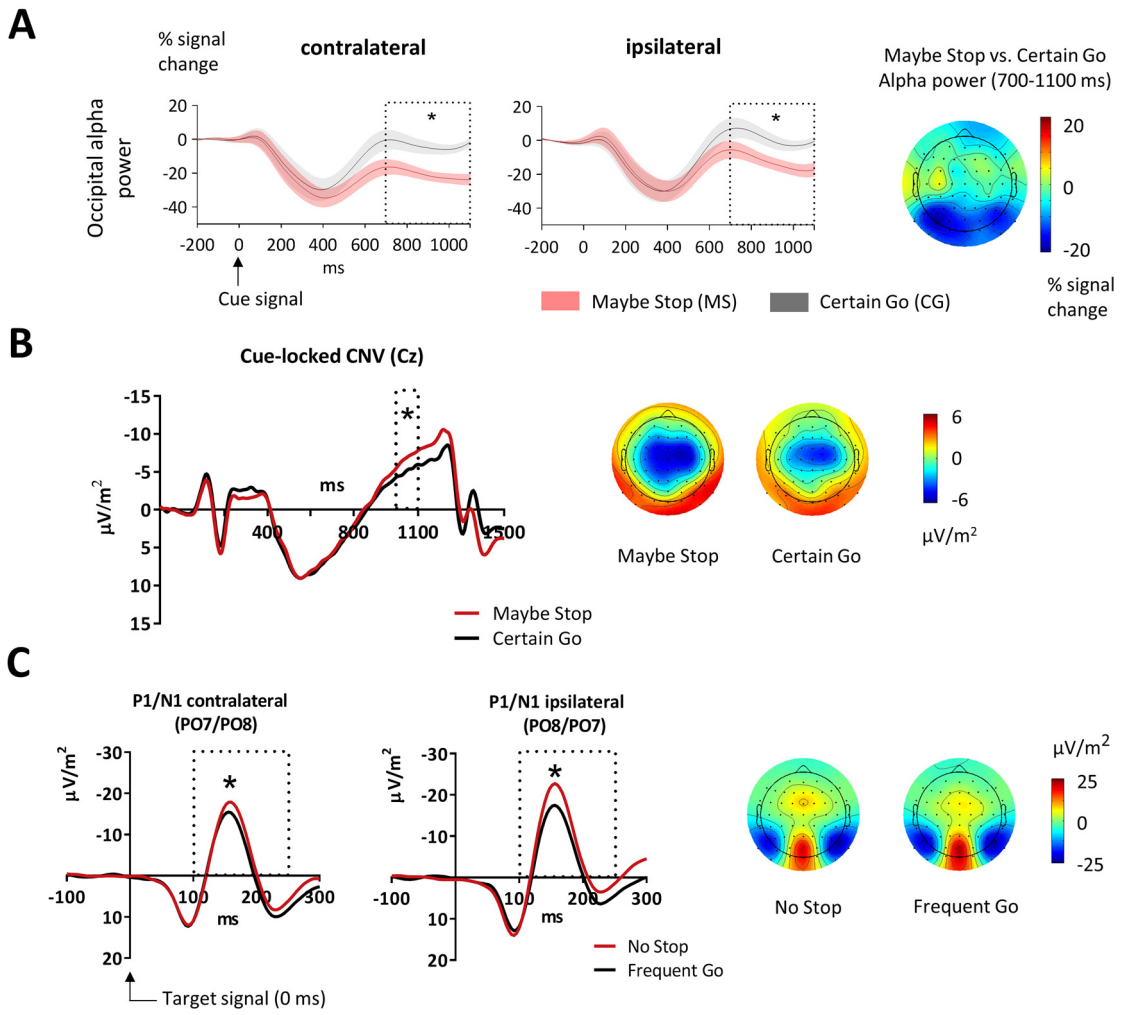


FIGURE 2.2 | Effects of attentional gating. (A) Alpha (9–14 Hz) power in the cue-target interval for the Maybe Stop (red) and the Certain Go condition (black) at occipital clusters. The analyzed time-window (700–1100 ms) is displayed as dotted box. The cue appeared at 0 ms and the target stimulus at 1100 ms. Alpha power was lower in MS- than CG-trials both contralateral and ipsilateral to the upcoming, possibly lateralized target. The SEM is displayed as shaded area. The topographic plot to the right shows the scalp distribution of the alpha band as difference between Maybe Stop- and Certain Go-trials. (B) Contingent negative variation (CNV) in the cue-target interval, measured at Cz. Displayed are MS- (red) and CG-trials (black). In the analyzed time-window (1000–1100 ms, dotted box) the CNV was increased in MS- compared to CG-trials. The target stimulus appeared at 1100 ms. The topographic plots display mean activity between 1000 ms and 1100 ms. (C) Target-evoked P1/N1 at sites contra- and ipsilateral to the visual stimuli. In the analyzed time-window (100–250 ms, dotted box) N1 was increased for No Stop than Frequent Go-trials. The topographies display mean activity between 130–170 ms. Here 0 ms indicates time of target-onset. Significant effects are stressed with asterisks.

2.3.2.2 Sensorimotor Effects

First, we were interested in the modulation of mu and beta activity over the sensorimotor cortex in preparation of the upcoming motor action (Figure 2.3A). That is, in the cue-target interval mean mu and beta power between 700 ms and 1100 ms was subjected to an ANOVA with the factors Condition (MS vs. CG) and Hemisphere (contra-, and ipsilateral to the upcoming motor response). In the beta band, power in the hemisphere ipsilateral to the relevant response hand was lower in MS- compared to CG-trials (Condition x Hemisphere: $F_{(1,21)} = 11.6$, $p = 0.003$; Condition at the ipsilateral hemisphere: $t_{21} = -4.3$, $p < 0.001$; Condition at the contralateral hemisphere: $t_{21} = -0.2$, $p = 0.871$). Beta power was also found to be generally reduced in the contralateral relative to the ipsilateral hemisphere (Hemisphere: $F_{(1,21)} = 13.7$, $p = 0.001$). In the mu band there was no difference between MS- and CG-trials ($F_{(1,21)} = 1.0$, $p = 0.319$). However, mu was lower on the contralateral than on the ipsilateral side ($F_{(1,21)} = 11.8$, $p = 0.002$).

Next, we tested how sensorimotor mu and beta power were modulated by proactive and reactive motor control in the timeframe after target signals appeared (Figure 2.3B). Therefore we subjected target-related mean mu/beta power around the time of response execution (200–500 ms) to ANOVAs with the factors Condition (frequent trials: No Stop vs. Frequent Go, rare trials: Stop vs. Rare Go) and Hemisphere (ipsi- vs. contralateral to the motor response). In rare trials (Stop vs. Rare Go), sensorimotor beta power was higher in Stop- than Rare Go-trials ($F_{(1,21)} = 20.5$, $p < 0.001$) and also activity in the mu band tended to be higher in Stop- than Rare Go-trials ($F_{(1,21)} = 3.6$, $p = 0.072$). Comparing frequent trials (No Stop vs. Frequent Go), sensorimotor mu power was higher in No Stop- than in Frequent Go-trials ($F_{(1,21)} = 12.2$, $p = 0.002$), but there were no condition differences in the beta band ($F_{(1,21)} = 0.0$, $p = 0.972$).

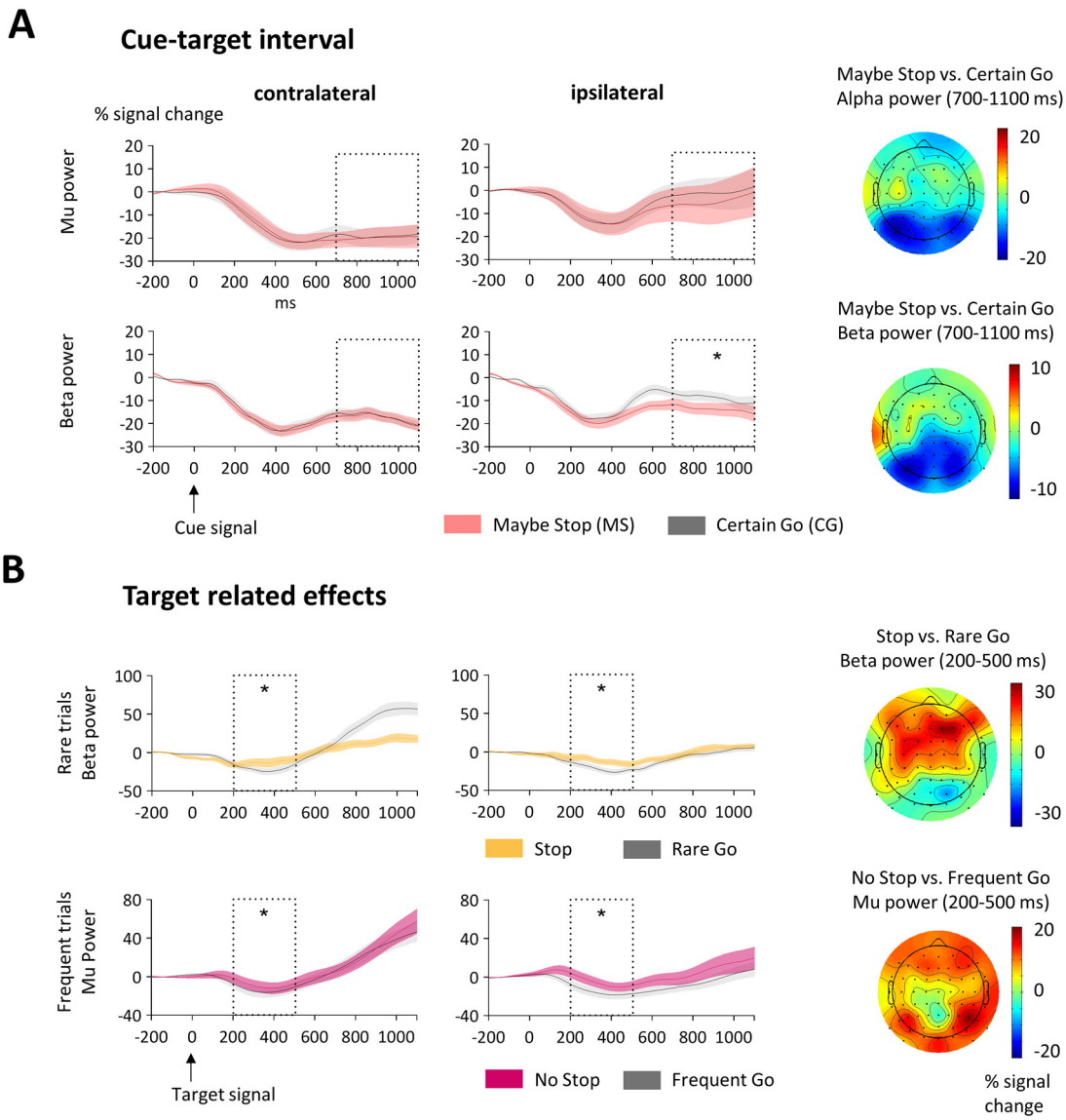


FIGURE 2.3 | Sensorimotor activity. (A) Activity in the cue-target interval. Here mu (9–14 Hz; upper row) and beta (15–25 Hz; lower row) power at sensorimotor clusters contralateral and ipsilateral to the standard motor response is displayed. The analyzed time-window (700–1100 ms) is indicated as dotted box and the SEM is shown as shaded area. The cue appeared at 0 ms and the target stimulus at 1100 ms. Mu was lower on the contralateral than on the ipsilateral side but did not differ between MS- and CG-trials. Beta decreased in MS-trials on the ipsilateral side only. The topographic plots to the right show the scalp distribution of the alpha and beta bands as differences between MS- and CG-trials. (B) Target-related effects of sensorimotor mu and beta. The analyzed time-window (200–500 ms) is indicated as dotted box. Here 0 ms indicates time of target-onset. Upper row: Beta power was higher in Stop- than Rare Go-trials at both sensorimotor clusters contralateral and ipsilateral to the motor response. Lower row: Mu power was higher in No Stop- than Frequent Go-trials at contralateral and ipsilateral sensorimotor clusters. The topographic plots to the right show the scalp distribution of the alpha and beta bands as differences between Stop- and Rare Go-, or respective No Stop- and Frequent Go-trials. Significant effects are stressed with asterisks.

2.3.2.3 Prefrontal Activity and P3

2.3.2.3.1 Prefrontal Activity

First, we analyzed whether beta power over prefrontal electrodes was modulated in the cue-target interval. We therefore subjected mean beta power at prefrontal sites between 700 ms and 1100 ms to an ANOVA with the factors Condition (MS vs. CG) and Hemisphere (left vs. right). Prefrontal beta did not differ between conditions ($F_{(1,21)}$ = 0.2, p = 0.643). This can also be assessed from the topographic map shown in Figure 2.3A which shows no differential beta power over prefrontal sites (lower topographic plot).

To test for a modulation of beta power after target signals, we subjected mean beta power over prefrontal electrodes between 200 ms and 500 ms to repeated measures ANOVAs with the factors Condition (MS vs. CG) and Hemisphere (left vs. right; Figure 2.4). This was done separately for rare (Stop- vs. Rare Go-) and frequent (No Stop- vs. Frequent Go-) trials. Beta power over prefrontal electrodes was higher in Stop- than Rare Go-trials ($F_{(1,20)}$ = 8.9, p = 0.007). Note that one participant showed extreme beta power compared to other subjects (>10 SD above mean value) and therefore was removed from the statistics regarding this comparison. Proactive beta power was also increased in No Stop- compared to Frequent Go-trials ($F_{(1,21)}$ = 10.2, p = 0.004). The effect did not differ between hemispheres in either rare or frequent trials (Condition x Hemisphere for rare trials: $F_{(1,20)}$ = 0.1, p = 0.772 and for frequent trials: $F_{(1,21)}$ = 0.3, p = 0.571).

To test whether after target signals the effect of Condition on beta differed between frequent and rare trials, we computed an ANOVA including the factors Frequency (rare, frequent), Condition (MS, CG) and Hemisphere. Beta power was higher in rare than frequent trials ($F_{(1,20)}$ = 12.2, p = 0.002) and the two types of trials differed in the MS condition but not in the CG condition (Frequency x Condition: $F_{(1,20)}$ = 5.5, p = 0.03; Frequency for MS: $F_{(1,20)}$ = 9.2, p = 0.007; Frequency for CG: $F_{(1,20)}$ = 0.2, p = 0.641), reflecting an increased beta response in Stop- relative to No Stop-trials but no difference between

Rare Go- and Frequent Go-trials. Please note that we did not specifically control for frontal muscular artifacts. Thus these might have affected our data. Consider however, that muscular artifacts should not be condition specific and therefore unlikely contribute to reported effects and very similar results have been obtained in a study using electrocorticography (ECoG; Swann et al. (2009)).

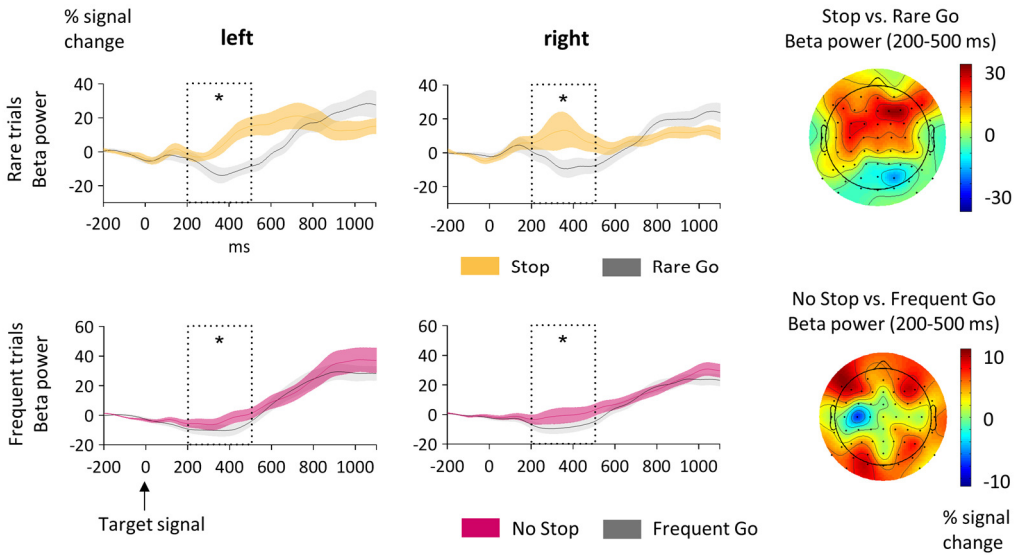


FIGURE 2.4 | Target related prefrontal activity. Here beta (15–25 Hz) power at left and right prefrontal clusters is displayed. The analyzed time-window (200–500 ms) is indicated as dotted box and the SEM is shown as shaded area. Beta was higher in Stop- than Rare Go-(upper row) and in No Stop- than Frequent Go-trials (lower row). The topographic plots to the right show the scalp distribution of the alpha and beta bands as differences between Stop- and Rare Go- or respective No Stop- and Frequent Go-trials. Significant effects are stressed with asterisks.

2.3.2.3.2 P3

Finally, we investigated the target-evoked P3. The P3 in frequent trials (No Stop, Frequent Go) was maximal around 400 ms and, in contrast to the typically reported central maximum, it showed two lateralized maxima at C3 and C4 (Figure 2.5). The P3 in rare trials (Stop, Rare Go) however, had a more central maximum. In both frequent and rare trials, we verified the maximum over central electrodes by testing three clusters of electrodes (F3, Fz, F4—C3, Cz, C4—P3, Pz, P4), revealing that it was larger over central than prefrontal and parietal sites (Site: $F_{(1,21)} = 15.3$, $p < 0.001$). The P3 elicited by frequent stimuli was larger in

No Stop- compared to Frequent Go-trials ($F_{(1,21)}$ = 11.4, p = 0.003). This effect was larger over C3 and C4 than Cz (Condition × Electrode: $F_{(1,21)}$ = 6.6, p = 0.004; Condition at C3: t_{21} = 3.5, p = 0.002; Condition at C4: t_{21} = 4.5, p < 0.001; Condition at Cz: t_{21} = 1.2, p = 0.260).

The P3 in rare trials had a less focused topography than in frequent trials. It was larger in Stop- compared to Rare Go-trials ($F_{(1,21)}$ = 20.7, p < 0.001). Here, this effect was larger over Cz than C3 and C4 (Condition x Electrode: $F_{(1,21)}$ = 5.0, p = 0.012; Condition at Cz: t_{21} = 4.3, p < 0.001; Condition at C3: t_{21} = 3.6, p = 0.002; Condition at C4: t_{21} = 2.1, p = 0.047). Thus, the target-evoked P3 was increased when participants had anticipated a possible stop in the cue-target interval (MS) before, compared to CG-trials, both for rare and frequent signals. To test whether this effect was identical for rare and frequent stimuli, over all tested electrodes (C3, Cz, C4) and whether there was a specific effect of stopping, we also computed an ANOVA including the factors Condition (MS vs. CG), Frequency (rare trials vs. frequent trials) and Electrode (C3, Cz, C4). The P3 was larger in trials where in the cue-target interval participants had anticipated a possible stop (MS) than in CG-trials ($F_{(1,21)}$ = 19.8, p < 0.001) and larger in rare compared to frequent trials ($F_{(1,21)}$ = 20.1, p < 0.001). An interaction of the factors Condition, Frequency and Electrode showed that the effect of Condition in frequent trials was largest over C3 and C4 whereas in rare trials it was largest over Cz (Condition x Frequency x Electrode: $F_{(1,21)}$ = 13.2, p < 0.001).

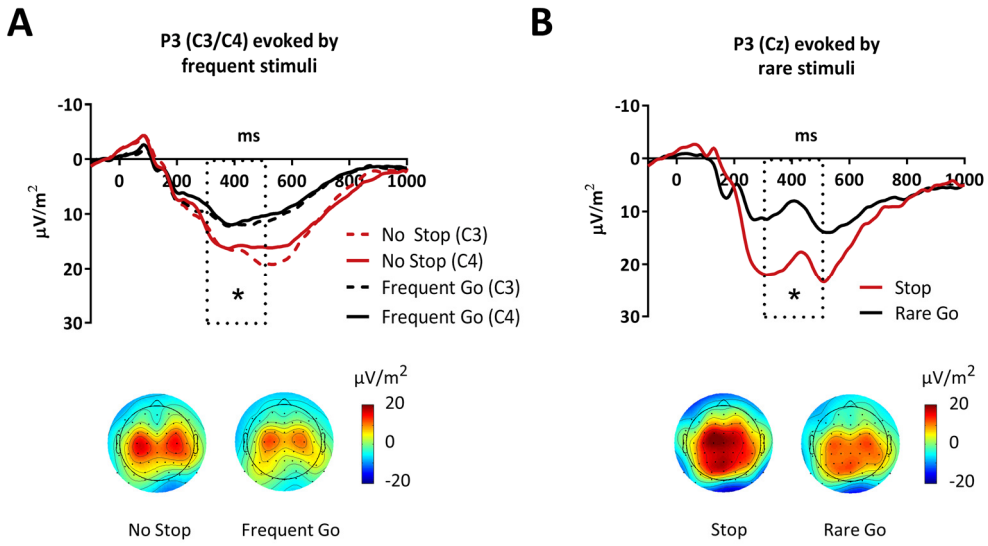


FIGURE 2.5 | P3 evoked by frequent and rare target-stimuli. The analyzed time-window (300–500 ms) is shown as dotted box. The topographies display mean activity between 300 ms and 500 ms in the different conditions. (A) P3 evoked by frequent stimuli was increased in No Stop- compared to Frequent Go-trials at both C3 and C4. (B) P3 evoked by rare stimuli was increased in Stop- compared to Rare Go-trials at Cz. Significant effects are stressed with asterisks.

	Proactive	**Reactive**
Attention		
Occipital alpha	↓	
N1/P1		↑
Proactive motor control led to increased attention in the Maybe Stop condition where informative target stimuli were anticipated and presented.		
Sensorimotor effects		
Mu	Before target onset: - After target onset: ↑	(↑)
Beta	Before target onset: ↓ IL side After target onset: -	↑
Before target onset, only beta was modulated by proactive inhibition but not mu. After target signals, mu and not beta was increased for proactive inhibition. Both mu and beta increased for reactive inhibition.		
Prefrontal effects		
Prefrontal beta	Before target onset: - After target onset: ↑	↑
Proactive and reactive motor inhibition were modulated by increased prefrontal control. Prefrontal activity for proactive inhibition occurred only after target onset but not before. Prefrontal areas were thus activated transiently rather than in a sustained way.		

TABLE 2.1 | Summary of main findings. IL = ipsilateral, ↓ = decrease, ↑ = increase, - = no effect.

2.4 Discussion

We investigated the temporal dynamics of proactive and reactive motor inhibition in a cued go/nogo task. During the cue-target interval, when participants prepared to either respond to the target or to possibly inhibit the motor response in case of MS-trials, proactive motor inhibition was associated with decreased occipital alpha power reflecting increased visual attention. Further supporting the implication of attention in proactive motor control, the CNV was found to be increased during this time and the target-evoked N1 was enhanced. Moreover, sensorimotor beta power ipsilateral to the prepared response hand was decreased in MS-trials. After the target, proactive and reactive motor control were reflected in increased beta power over prefrontal electrodes and in an increase of P3. Our results emphasize the importance of attention for proactive motor control and demonstrate that proactive inhibition modulates ipsilateral sensorimotor activity. Prefrontal control, as reflected in beta activity, was found to be employed in a phasic manner after target onset only, but not during the preparatory cue-target interval (see main findings in Table 2.1).

As predicted by the DMC theory, proactive motor inhibition was associated with increased attention and a modulation of sensorimotor and prefrontal activity. However prefrontal activity was not elicited in a sustained manner before target onset, but only transiently after target signals. This is against the predictions of the DMC, but dovetails recent findings in other motor inhibition paradigms (Swann et al., 2012; Swann et al., 2013; Zandbelt et al., 2013b; Vink et al., 2015). In the following, we will first discuss behavioral results and then refer to results pertaining to the different aspects of proactive and reactive control implied in the DMC model, namely visual attention, prefrontal control and sensorimotor activity.

2.4.1 Behavioral Data

In No Stop-trials, when participants were prepared to withhold their motor response, they slowed down in comparison to Frequent Go- and Rare Go-trials when stopping was not required. This slowing is in line with previous work (Verbruggen and Logan, 2008; Jahfari et al., 2012; Zandbelt et al., 2013b; Vink et al., 2015). Moreover, participants committed more premature errors during the CG than during in the MS condition. Together, behavioral data show that the paradigm was successful in eliciting proactive inhibition, leading to slower responses when stopping was anticipated.

2.4.2 Visual Attentional Gating

In the interval between cue and target, oscillatory alpha power over the occipital cortex showed a stronger reduction in MS than in CG-trials. Alpha activity over occipital sites has been interpreted as a gating mechanism, meaning that an increase in alpha reflects a suppression whereas a decrease facilitates processing of incoming visual input (Romei et al., 2010; Foxe and Snyder, 2011; Zumer et al., 2014). We thus believe that the decrease of alpha activity prior to target onset reflects enhanced allocation of attentional resources since in MS-trials the location of the upcoming target was of task relevance whereas in CG-trials this was not the case. Increased visual attention in the MS compared to the CG condition should result in enhanced processing of target stimuli in No Stop- and Stop-trials, measurable as increased N1 (Luck et al., 2000). This is exactly what we found as in No Stop-trials, the visual N1 was greater than in Frequent Go-trials. This was not observed for rare signals (Stop vs. Rare Go) though, but as these stimuli were also less frequent, the higher saliency might have led already to an increase. Our results support previous research showing the relevance of attentional processes in proactive inhibition. A recent behavioral study stressed that proactive (and reactive) motor control strongly rely on attentional and perceptual processes (Verbruggen et al., 2014). Lavallee et al. (2014)

observed increased delta power over posterior electrodes during proactive control, presumably reflecting activity of a posterior attentional network. Finally, our results dovetail with those of Schevernels et al. (2016), who reported a higher N1 to task-relevant go-targets compared to task-irrelevant nogo-targets.

Further evidence for the implication of attentional networks in proactive motor control was given by the CNV. The late CNV is thought to be a neural correlate of anticipatory attention towards the upcoming stimulus and of motor preparation (Tecce, 1972; Brunia and van Boxtel, 2001). In agreement with this, the late CNV is presumably comprised of at least two slow waves, namely a stimulus-preceding negativity (SPN) and a movement preceding negativity (MPN; Brunia (1988)). The larger CNV in the MS compared to the CG condition can be explained with stronger need for attentional resources and higher expectancy of relevant information (Fuentemilla et al., 2013). However, it cannot be ruled out that also increased preparatory motor processes caused or contributed to this effect.

2.4.3 Sensorimotor Activity

In the cue-target interval, we expected oscillations in the sensorimotor cortex as index of motor preparation to be influenced by proactive motor inhibition. Over sensorimotor electrodes, we observed a stronger decrease of mu power contra- than ipsilateral to the response hand. This is in line with findings that mu decreases in anticipation of movements (Babiloni et al., 2004; Kajihara et al., 2015; Tzagarakis et al., 2015) and that the decrease is most prominent over the contralateral hemisphere of the expected movement (Neuper et al., 2006). However, we did not find differences in mu between MS- and CG-trials. On the other hand, we observed sensorimotor beta in the ipsilateral hemisphere to be lower in MS- compared to CG-trials, whereas no differences were found over contralateral sites. A possible, yet speculative explanation is that a relative increase in beta oscillations over the ipsilateral motor cortex could facilitate response activation in the contralateral cortex via

interhemispheric connections. This might be dampened when expecting a nogo-signal, leading to a reduced lateralization of sensorimotor beta. A study using transcranial magnetic stimulation (TMS) points in this direction, showing that the left premotor cortex is involved in withholding and releasing a preselected movement generated by the right motor cortex (Kroeger et al., 2010). Future studies could directly test this hypothesis by combining double-pulse TMS protocols with EEG.

After target-onset, mu activity decreased more in trials of the CG condition compared to the MS condition. Since the observed mu decrease was maximal around the time of button press and response times in CG-trials were considerably faster than in MS-trials, this effect fits with a role of mu for gating functions of the sensorimotor cortex (for review see Cheyne (2013)). Proactive inhibition thus resulted in a modulation of target-evoked response preparation. With respect to actual stopping of motor output, we observed lower beta power in trials where subjects pressed a button compared to trials in which they inhibited motor behavior. Such a movement related beta decrease has been observed in numerous studies (Neuper et al., 2006; Zaepffel et al., 2013), mostly centered on the sensorimotor cortex with a contralateral predominance (Salmelin and Hari, 1994; Taniguchi et al., 2000). A relative increase of sensorimotor beta has also previously been reported for stop-trials in a stop-signal task (Krämer et al., 2011), which is in line with the observed beta increase when participants inhibited the motor output.

2.4.4 Dynamics of Prefrontal Activity

Reactive motor inhibition has previously been hypothesized to be driven by beta-oscillations in a frontal-basal-ganglia network (Aron, 2011). However, less is known about the role of prefrontal beta oscillations in proactive motor inhibition. With the present study, we show that prefrontal beta power is increased during the proactive and reactive implementation of response inhibition, that is, after the target, but not while preparing to

stop during the cue-target interval. This dovetails with two recent fMRI-studies which compared cue-target and target-interval and reported the rIFG to be activated after, but not before the target (Zandbelt et al., 2013b; Vink et al., 2015). Also in two ECoG-studies, gamma activity over prefrontal regions was higher after target-onset only, but not in the cue-target interval (Swann et al., 2012; Swann et al., 2013). Together, these results and our findings speak for a specific time-course of activity in prefrontal regions during proactive motor control. According to the DMC theory sustained activation of prefrontal regions can be expected for proactive control. Our data do not support this prediction, since no correlates of sustained PFC activity were detected before appearance of the target. Only during actual response execution or inhibition, PFC activity was observed. Taking prefrontal beta as correlate of cognitive control, our data suggest that activity in perceptual and sensorimotor regions is biased without sustained input from PFC. The PFC rather transiently exerts control once response conflicts occur and predominant responses have to withhold.

Interestingly, prefrontal beta power was not only increased in Stop-trials, meaning during actual response cancellation. Beta power was also higher in No Stop-trials, in which participants had been prepared to stop the response, in comparison to Frequent Go-trials, in which the action could be executed in a rather automatic fashion. Prefrontal beta thus does not simply signal an action to be canceled, as previously hypothesized (Swann et al., 2009). It more likely acts as a break, possibly to prevent automatic behavior or to slow down responses (Aron et al., 2014a). Finally, prefrontal beta is not the only measure to investigate prefrontal processes with EEG, just recently prefrontal ERPs (pN, pP) being in association with motor inhibition have been reported (Berchicci et al., 2016; Di Russo et al., 2016). It might be that these reflect similar processes as prefrontal beta and this could be tested in future studies.

The most-studied ERP component of response inhibition is the stop-P3 (Eimer, 1993; Kopp et al., 1996; Bokura et al., 2001; Huster et al., 2013). P3 has been linked to cognitive control (Pires et al., 2014) and suggested to stem from PFC (Wessel and Aron, 2015). In the present study, we observed a higher P3 as correlate of both proactive and reactive motor inhibition. Interestingly, the P3 topographies in frequent and rare trials were different (Figure 2.5). In frequent trials, the enhanced P3 in No Stop- relative to Frequent Go-trials was centered on bilateral motor cortex, whereas the P3 effect in rare trials showed a broader, more central and posterior topography. The P3 effect in frequent trials might reflect proactive inhibitory influence directly on the premotor or motor cortex. The broader, more central P3 in rare trials could reflect reactive engagement of the preSMA (Albert et al., 2013). These effects however, have to be interpreted considering that we applied Laplace transformation (Kayser and Tenke, 2015). This method reduces the blurring effects of volume conduction on EEG data and increases spatial resolution (Burle et al., 2015). It enhances focal while reducing broad effects and minimizes the contribution of sources localized deep in the brain (Luck, 2014). Thus, claims about the topography and specific sources of the P3 effects, as well as comparisons with previous P3 findings have to be taken cautiously. Alternatively, the increased P3 in Rare Go-trials might reflect an enhanced motor preparation as the go-P3 has been proposed to be superimposed by motor-related potentials (Verleger et al., 2006). The observed P3 effects parallel the target-evoked prefrontal beta findings. For both P3 and beta power, trials where subjects had prepared to stop beforehand (MS) showed an enhanced amplitude relative to trials where they did not have to (CG). This suggests that during the implementation of inhibitory motor control, similar mechanisms play a role both when actually canceling the motor output as in Stop-trials and when transiently braking the motor execution to allow for more controlled response selection as in No Stop-trials.

2.4.5 Conclusion

Our results shed light on the temporal dynamics of activity during proactive and reactive motor inhibition, including more generic (attention, cognitive control) and specific mechanisms (sensorimotor activity). As predicted by the DMC framework, activity in prefrontal, sensorimotor and visuoperceptual brain regions was modulated by proactive control. Prefrontal regions however, did not show sustained activity before target signals but only were activated transiently after target onset. Being prepared to stop resulted in enhanced attention for relevant visual signals, which was reflected in reduced occipital alpha power, an enhanced CNV and an increased target-evoked visual N1. At the same time, proactive motor control modulated activity in the sensorimotor cortex, particularly over ipsilateral sites. More precisely, if cues indicated that no nogo-signal was to be expected, beta power was enhanced over ipsilateral motor cortex, presumably facilitating response execution. When stopping was anticipated this facilitation was reduced, but no modulation of activity in the contralateral motor cortex was found. Finally, target-related actual implementation of response inhibition was associated with an enhanced P3 and increased prefrontal beta power. Both effects were observed also when participants were prepared to stop but eventually had to respond, which indicates that the same mechanisms are involved during response preparation when actually slowing down or when completely inhibiting response execution. However, these mechanisms were different from visuoperceptual and sensorimotor processes engaged proactively during the cue-target interval.

3 Effects of Lesions to the Prefrontal Cortex or Basal Ganglia on Proactive and Reactive Motor Inhibition

3.1 Introduction

Motor inhibition is a central executive function, which can be seen for instance when a pedestrian has to stop his ongoing movement due to a car suddenly driving over the street. Most studies investigating cognitive functions focused on healthy subjects in order to understand fundamental neural processing. On the contrary, one of the first insights into human brain were obtained in individuals with specific brain lesions (Broca, 1861; Wernicke, 1874) and still significant knowledge can be obtained from patient studies. Importantly, in neurological or psychiatric patients impairments of motor control can be observed. For instance patients with Parkinson's disease (PD) or patients with lesions to the prefrontal cortex (PFC) show significant deficits in motor inhibition (Picton et al., 2007; Obeso et al., 2011). In this study, we investigated the role of the basal ganglia (BG) and lateral PFC in proactive and reactive motor inhibition, studying patients with lesions to the first or latter.

Motor inhibition, probably the best studied aspect of motor control, is thought to be subserved by a network comprising the right inferior frontal cortex (IFC), pre-supplementary motor area (pre-SMA) and basal ganglia (Verbruggen and Logan, 2008; Schall and Godlove, 2012; Aron et al., 2014a). Extensive research linking the PFC to motor inhibition is based on results from functional imaging (Rubia et al., 2001; Wager et al., 2005; Aron et al., 2007), cognitive electrophysiology (Liotti et al., 2005; Ramautar et al., 2006; Schmajuk et al., 2006), lesion studies (Leimkuhler and Mesulam, 1985; Aron et al., 2003; Picton et al., 2007; Swick et al., 2008; van Dijk et al., 2008; Krämer et al., 2013) and brain stimulation (Chambers et al., 2006; Wessel et al., 2013). Similarly, there is convincing evidence for a substantial role of the basal ganglia in inhibitory motor control. This is stemming from studies using electrophysiology (Swann et al., 2011; Ray et al., 2012; Alegre

et al., 2013), functional imaging (Zandbelt and Vink, 2010; Leunissen et al., 2016), deep brain stimulation (Hershey et al., 2010), single cell recordings (Benis et al., 2016) and optogenetics (Freeze et al., 2013).

Conceptually, two variants of inhibitory motor control can be distinguished, reactive and proactive control (Aron, 2011). Reactive motor inhibition refers to a process when a prepotent movement has to be withheld or stopped in reaction to an external signal. Proactive motor inhibition however, describes preparatory processes facilitating motor inhibition which might be required later. Whereas reactive inhibition has been thoroughly studied in the past, proactive inhibition is a newer concept, introducing the element of endogenous preparation into theories of motor control. Importantly, the concept of proactive inhibition might bear more ecological validity, since neurological and psychiatric patients may have especially problems in proactive processes (Aron, 2011).

A substantial body of research speaks for a central role of oscillations, specifically alpha/mu and beta in motor control. Sensorimotor beta decreases when motor actions are prepared and executed (Pfurtscheller et al., 1997; Neuper et al., 2006), with this decrease being stronger in the contralateral hemisphere to the expected action (Babiloni et al., 2004; Kajihara et al., 2015). After the motor response is executed, beta increases again. A similar pattern can be observed for sensorimotor mu (Neuper et al., 2006). Mu seems to be relevant to motor inhibition as in a go/nogo task prestimulus sensorimotor alpha was predictive of errors in being increased before subjects failed to successfully withhold a button press (Mazaheri et al., 2009). Previous response inhibition studies (Krämer et al., 2011; Picazio et al., 2014) have shown that sensorimotor beta is relatively increased during reactive motor inhibition. In recordings of intracranial electrodes in epileptic patients, a similar increase of beta power was observed over prefrontal electrodes (Swann et al., 2009; Swann et al., 2012; Wessel et al., 2013). One study with EEG recordings in Parkinson patients on/off deep-brain stimulation (DBS) suggested a dependency of the frontal beta effect on

subcortical nodes (Swann et al., 2011). These observations led to the hypothesis of a cortico-basal ganglia network mediated by beta activity underlying motor inhibition (Aron, 2011).

Generally, lesion studies are a promising approach as they offer causational rather than mere correlational insights into the role of specific brain areas in distinct cognitive processes. Few studies investigated underlying neural oscillations of motor inhibition in patients with lesion to PFC or BG. Following failed inhibitions, patients with lesions to the orbitofrontal cortex (OFC) displayed an increased central beta response (Solbakk et al., 2014). In a stop-signal task (SST), lateral PFC patients showed a weaker decrease of sensorimotor beta compared to controls, while performing a motor action (Krämer et al., 2013). This smaller decrease was present around the timeframe of response execution and over the lesioned hemisphere only. This data speaks for altered sensorimotor processing in patients with lesions to the PFC. Mentioned studies however, focused on oscillatory mechanisms of reactive motor inhibition. Few studies investigated oscillatory markers of proactive inhibition and to our knowledge preparatory motor inhibition has not yet been studied in patients with specific lesions to the BG or PFC. Given the role of PFC and BG in proactive inhibition (Aron et al., 2016), sensorimotor and prefrontal markers of preparatory processes can be expected to be altered in patients with lesions to the first or latter.

In a response inhibition context successful target detection is fundamental and here visual attention becomes critical. The PFC as part of a frontoparietal network is a central hub guiding attention (Rossi et al., 2009; Solbakk and Løvstad, 2014; Paneri and Gregoriou, 2017). When performing in a SST, patients with unilateral lesions to the PFC showed reduced parietal activity in response to stop-signals and increased activation of intact prefrontal areas, speaking for compensatory effects (Krämer et al., 2013). This underpins a role of lateral PFC regions in attentional monitoring in a setting of motor inhibition. There is fundamental evidence for alpha oscillations in attention (Hanslmayr et al., 2011;

Klimesch, 2012) and occipital alpha power was shown to be predictive of successful response inhibition (Mazaheri et al., 2009; Bengson et al., 2012). That is, in PFC patients altered occipital alpha oscillations are expected as sign of reduced visual attention towards relevant visual stimuli.

In a recent study, we investigated the temporal dynamics of proactive and reactive motor inhibition using electroencephalography (EEG) in a cued go/nogo-task (Liebrand et al., 2017). We found that activity over (i) frontal regions, exercising cognitive control, (ii) sensorimotor regions as final gate for motor actions and (iii) occipital regions engaged in visual attention, is modulated by proactive and reactive motor inhibition. During the cue-target interval, the anticipation of nogo-signals led to increased visual attention, reflected in reduced occipital alpha power, and to a modulation of sensorimotor cortex activity, reflected in reduced beta power ipsilateral to the relevant response hand. Increased prefrontal activity, indicated by higher frontal beta power, was observed after target presentation only, but not during the cue-target interval. The aim of the current study was to directly test the critical impact of basal ganglia and prefrontal nodes on response inhibition and associated cortical oscillatory markers. Therefore, patients with lesions to the PFC or basal ganglia performed in a slightly modified version of the above mentioned cued go/nogo-task.

We investigated (i) beta power over prefrontal regions related to cognitive control, (ii) sensorimotor mu/beta oscillations and the CNV, and (iii) occipital alpha power and P1/N1 reflecting visual attention. We expected patients with lesions to critical nodes of the stopping network (PFC, BG) to show deficits in proactive and reactive motor inhibition. We hypothesized both patients groups to behaviorally show diminished or absent proactive inhibition, reflected in reduced reaction time differences between trials calling for proactive inhibition and trials without. Both patient groups were anticipated to show increased error rates compared to controls when having to inhibit motor tendencies. In

PFC and BG patients we expected reduced sensorimotor effects of proactive control. Additionally, given the role of the PFC in a frontoparietal attentional network, PFC patients were hypothesized to show decreased proactive occipital alpha effects. Finally, for reactive effects in both patients groups, we expected reduced or absent modulation of prefrontal beta, reflecting impaired cognitive control.

3.2 Methods

3.2.1 Participants

Nine patients (39-63 years, mean: 53 years, 6 females) with focal unilateral prefrontal lesions due to tumor resection or stroke took part in the study (5 left hemisphere (LH), 4 RH). Five of those patients were recorded in Oslo, three in Berkeley and one in Lübeck. One other PFC patient had to be excluded due to excessive movement artefacts in EEG. Nine patients (37-67 years, mean: 58 years, 1 female) with focal unilateral lesions in the basal ganglia caused by stroke participated in the experiment (5 LH, 4 RH), all recorded in Lübeck. Data of another three basal ganglia patients had to be discarded due to poor behavioral performance, suggesting they did not understand the task instructions. Further characteristics of the two patient groups can be found in Table 3.1. Exclusion criteria for patients were a comorbid neurological/psychiatric disease or medication, non-correctable visual impairments, non-focal or secondary lesions and drug or alcohol abuse. Patients were included based on a structural MRI scan prior to the experiment. A neuroradiologist confirmed the lesion and that no other signs of pathology were present in the brain. The experiment took place at least 6 months after stroke or surgery.

Twenty-two healthy participants served as controls who were matched as close as possible to the patients in terms of age, sex and education (36-68 years, mean: 55 years, 8 females; Lübeck: n = 21, Oslo: n = 1). Another six controls had to be excluded from analyses due to extensive EEG artifacts (n = 4) or poor behavioral performance (n = 2). All controls were

by self-report free of neurological or psychiatric disorders. All participants reported normal or corrected to normal vision. The study was performed in agreement with the Declaration of Helsinki. All subjects gave informed consent. The study was approved by the University of California, Berkeley Committee for Protection of Human Subjects and the Department of Veterans Affairs Northern California Health Care System Human Research Protection Program, by the Norwegian Regional Committee for Medical Research Ethics, Region South and by the Ethics Committee of the University of Lübeck. Patients and controls received monetary compensation for participation.

Subject	***Lesion etiology***	***Lesion side***	***Lesion size (cm^3)***	***Month since injury***
BG patients				
1	BGH	right	1.8	38
2	BGI	left	1.1	38
3	BGI	left	0.5	20
4	BGH	left	8.3	20
5	BGH	left	5.5	23
6	BGI	right	1.9	36
7	BGI	left	2.1	9
8	BGI	right	0.6	20
9	BGI	right	1.0	18
PFC patients				
1	Oligodendroglioma	right	111.4	198
2	Astrocytoma	left	0.8	115
3	Oligo-/astrocytoma	right	102.4	24
4	Cavernous haemangioma	right	15.1	130
5	Astrocytoma	right	29.2	10
6	Stroke of unknown cause	left	69.1	160
7	Stroke of unknown cause	left	34.0	Missing
8	Stroke of unknown cause	left	179.5	198
9	Intracerebral haemorrhage	left	14.8	16

TABLE 3.1 | Patient characteristics. Summary of lesion etiology, lesioned hemisphere, normalized lesion size and time since onset of injury in included BG and PFC patients. BGH = basal ganglia haemorrhage, BGI = basal ganglia infarction.

3.2.2 Lesion Reconstruction

Lesion reconstructions were based on structural MRIs obtained after study inclusion. Lesions were outlined by drawing manually on Fluid Attenuated Inversion Recovery (FLAIR) images of each participant's brain using the software ITK-Snap (Yushkevich et al., 2006) (www.itksnap.org) or MRIcron (Rorden et al., 2007) (http://people.cas.sc.edu/rorden/mricron/). T1- and T2-weighted images provided additional information to determine the borders of the lesions. The resulting lesion masks were transferred to normalized space using the Statistical Parametric Mapping software (SPM12: www.fil.ion.ucl.ac.uk/spm/). We followed two different procedures for normalization. For BG lesions, best results were obtained with the Clinical Toolbox for SPM (Rorden et al., 2012). For PFC lesion reconstructions, superior results were achieved using a procedure suggested by Ripollés et al. (2012). In PFC patients, T1 images were segmented and normalized at the same time using the "unified segmentation" approach. Then the normalization transformation was applied to FLAIR and lesion reconstruction images. Involved lesion volumes were calculated using MRIcron. Individual lesion reconstructions are shown in Figure 3.2 and 3.3. Overlay of lesion reconstructions of BG and PFC patients are presented in Figure 3.1C. Note that in the overlay left-sided lesions were flipped for visualization.

3.2.3 Design and Stimuli

The participants performed a cued go/nogo-task (see Figure 3.1A), very similar to the paradigm used in (Liebrand et al., 2017). A centrally presented square or circle served as cue, which indicated the probability of an upcoming nogo-stimulus (0% or 25%). The following target stimulus was a triangle. If the cue had been a square, the triangle was in 75% of the trials presented in the center of the screen and in 25% lateralized to the right side (5°). If the cue had been a circle, the triangle appeared in 75% of the trials in the center

of the screen and in 25% lateralized to the left side (5°). The probability of the two cues was 50% each. Participants had to press the right mouse button to targets following the square and the left button to targets following the circle. Before each block, participants were told to refrain from pressing the button either when the triangle appeared on the right side (Block: Stop right) or on the left side (Block: Stop left). This association of the cues with the probability of having to inhibit the response alternated from block to block.

This design thus results in two different trial conditions, which we refer to as Maybe Stop (MS) and Certain Go (CG; see Figure 3.1A). In the MS condition, the cue indicated that the participant might have to stop afterwards, whereas in a CG condition no stop was required in any case. In the MS condition participants had to stop in 25% of the trials (Stop-trials), but were instructed to press the button in the remaining 75% (No Stop-trials). In the CG condition, participants had to press the button both in response to central targets (75%, Frequent Go-trials) and to lateralized targets (25%, Rare Go-trials). For instance, if the current block was a *Stop-left* block and a circle was presented followed by a triangle on the left side, the response had to be withheld (MS condition, Stop-trial). If in the same block a square was presented followed by a triangle on the right side, the participant had to press the right button (CG condition, Rare Go-trial). In the following we refer to trials with 75% probability as frequent trials (No Stop and Frequent Go) and to those with 25% probability as rare trials (Stop, Rare Go).

Cue and target stimuli were presented for 100 ms. The target followed the cue after an inter-stimulus interval of 1000 ms. The time between two subsequent trials was jittered (1300 to 1600 ms). The experiment was divided into 6 blocks with 160 trials each, resulting in 960 trials. The to-be-stopped side of the first block was counterbalanced among participants. Throughout the whole experiment a fixation line was presented underneath the stimuli, which participants were instructed to fixate. Participants were told to respond as fast and accurate as possible and not to press the button until the triangle had appeared.

Patients used the hand ipsilateral to the lesions' side to avoid general motor slowing due to the lesion. Controls used the same hand as the patient whom they were matched to. Participants used their index and middle finger to perform the task. Before the start of the experiment the participants practiced the task in three short blocks with 16 trials each. This practice session could be repeated until the participant fully understood the instructions.

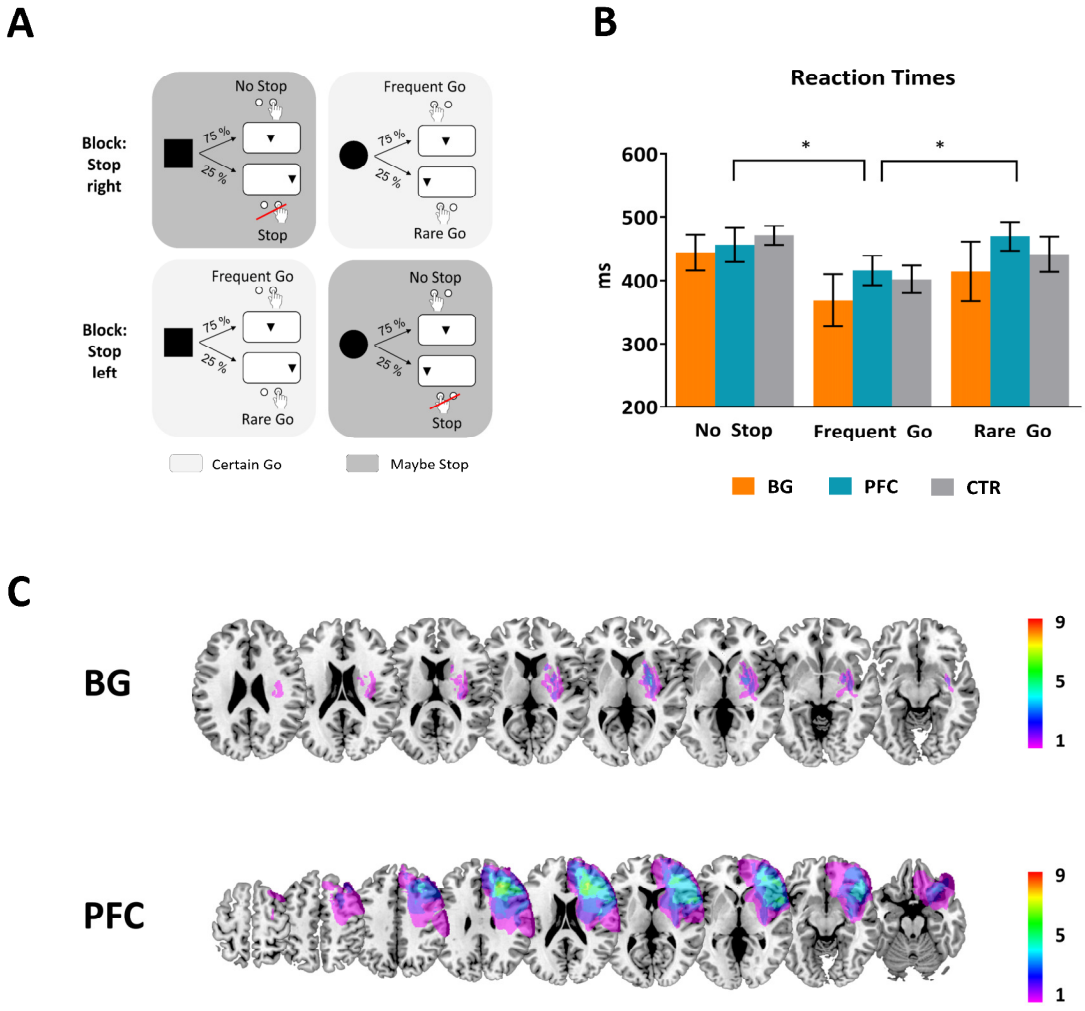


FIGURE 3.1 | Experimental design, behavioral results and lesion reconstruction. (A) Design of the cued go/nogo task. On the upper row a block is illustrated where subjects had to refrain from pressing the button when the target (triangle) appeared on the right side of the screen. Similarly, in the block displayed in the lower row a stop was required when the target appeared on the left side. In the **Maybe Stop condition** (dark gray) the subject was told by the cue (square, circle) that he might have had to stop later on, while in the **Certain Go condition** (light gray) he was informed by the cue that he always could press the button when the target appeared later. (B) Behavioral results showing mean reaction times in No Stop-, Frequent Go- and Rare Go-trials. As error bars the standard errors of the mean (SEM) are displayed. Patients and controls responded faster in Frequent Go- than No Stop- and Rare Go-trials. (C) Overlay of lesion reconstructions of BG and PFC patients. The color coding indicates the number of patients with damaged tissue in that area. Note that left-sided lesions were flipped.

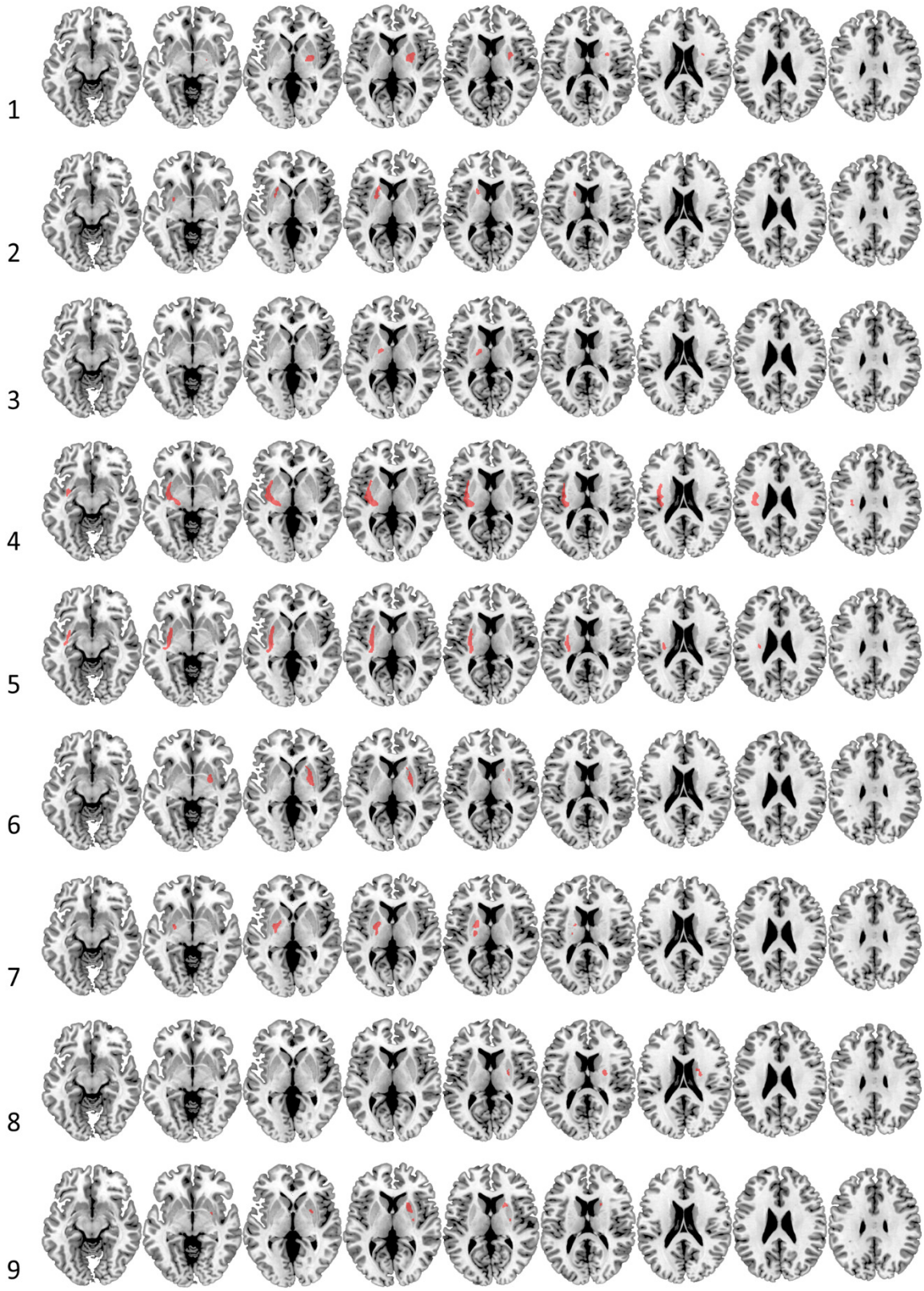


FIGURE 3.2 | Lesion reconstructions of BG patients. Displayed are reconstructions for individual patients, which are normalized into the Montreal Neurological Institute (MNI) space.

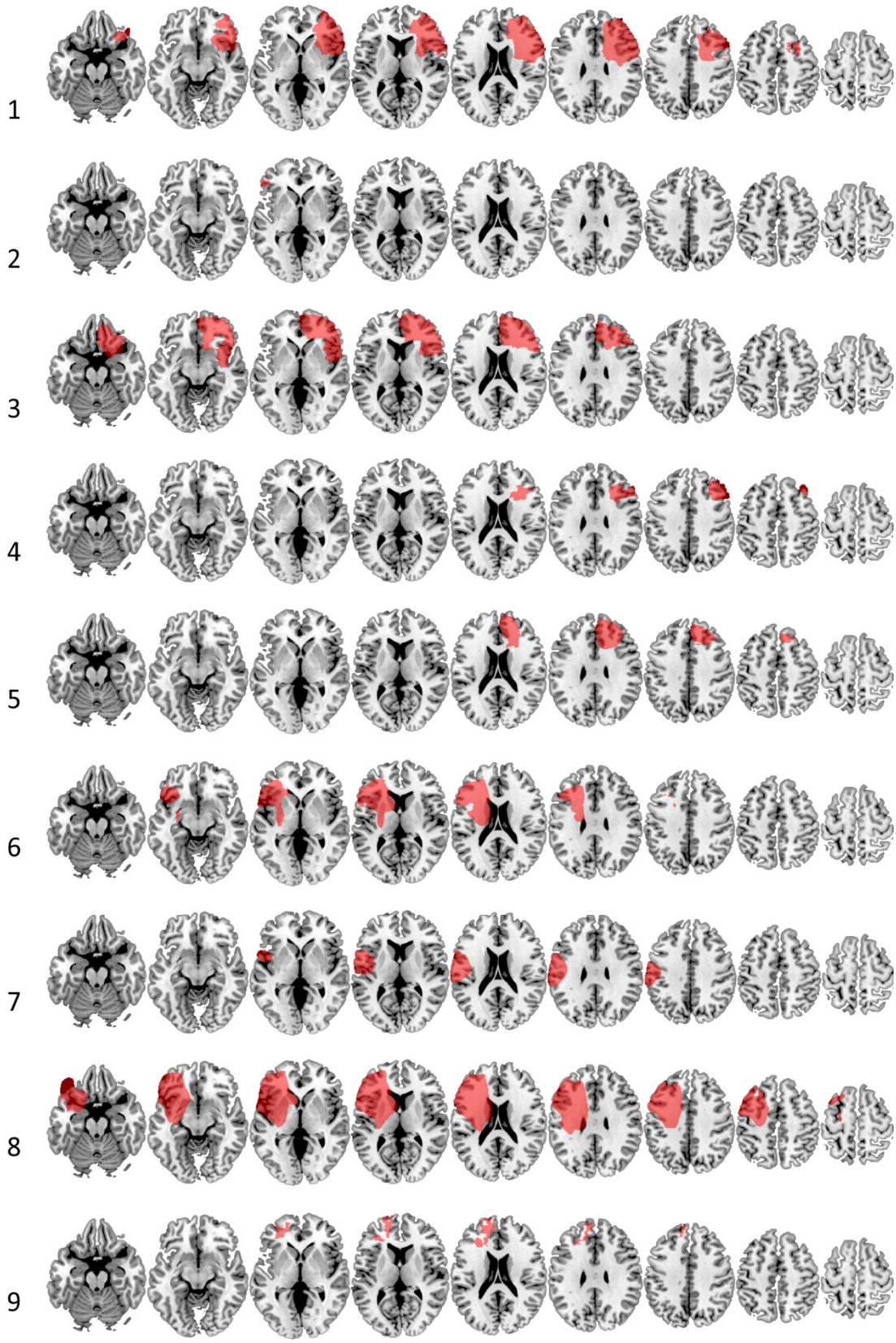


FIGURE 3.3 | Lesion reconstructions of PFC patients. Displayed are reconstructions for individual patients, which are normalized into the Montreal Neurological Institute (MNI) space.

3.2.4 Procedure

The experiment was controlled using the Presentation® software. Stimuli were presented on a screen, about 1 m away from the participant. Participants were sitting in a comfortable chair and in the middle and after each of the experimental blocks they had a short break of 20 s to relax. The total duration of the experiment was about 50 min.

3.2.5 EEG Recordings and Data Preprocessing

In Lübeck, the EEG was recorded with a 64-channel BrainAmp MR plus amplifier with a sampling rate of 250 Hz. Electrodes were placed according to an extension of the international 10–20 system (Nuwer et al., 1998). Vertical and horizontal eye movements (vertical electrooculogram (vEOG) and hEOG) were recorded. For vEOG we used an electrode placed below the right eye and a frontopolar electrode and for hEOG two electrodes located on the outer canthus of each eye. The ground was placed at Fpz and the EEG was recorded against a reference electrode placed on the right earlobe. In Oslo and Berkeley, the EEG was recorded with a 64 + 8 channel BioSemi Active-Two amplifier, with a sampling rate of 1024 Hz in Oslo and 256 Hz in Berkeley. The hEOG was recorded as in Lübeck and for the vEOG one electrode was placed below and one above the right eye. In Oslo and Berkeley the ground and reference were placed at two locations close to Pz.

3.2.6 General Analysis and Relevant Contrasts

Since there were neither age, nor years of education differences between PFC and BG patients ($p > 0.1$ in all comparisons), we compared the results of both patient groups to the combined group of 22 controls in one ANOVA (see Voytek and Knight (2010) for a similar approach).

As a measure for proactive inhibition in the cue-target interval, we contrasted trials in which the later motor response might (MS) or might not have to be inhibited (CG). To assess how proactive inhibition modulated response execution after target signals, we

compared trials following cues that signaled that responses might (No Stop) or might not have to be stopped (Frequent Go; see Swann et al., 2012, 2013). Finally, to assess the correlates of reactive inhibition, we contrasted trials in which the response actually had to be inhibited (Stop) with matched go-trials still requiring a response (Rare Go).

3.2.7 Behavioral Data Analyses

Mean reaction times, failed inhibitions, commission, omission and premature error rates (button presses before the target stimulus had appeared) were computed for each subject and submitted to mixed-design ANOVAs with the within-subject factor Condition (depending on the comparison) and the between-subject factor Group (prefrontal lesion patients: PFC, basal ganglia lesion patients: BG, and controls: CTR). The behavioral measure of proactive inhibition was the reaction time difference between No Stop- compared to Frequent Go- and Rare Go-trials (Liebrand et al., 2017). To assess whether individual patient's behavior differed from the control group, we used a (two-tailed) t-test as recommended by Crawford and Garthwaite (2012) with the formula:

$$t_{n-1} = \frac{x^* - \bar{x}}{s\sqrt{\frac{n+1}{n}}}$$

with x^* being the individual's score, n the control group size, x the mean and s the standard deviance of the control group. We assessed whether reaction times and accuracy differed for ipsi- and contralesional target stimuli. Finally, we computed whether reaction times or accuracy correlated with lesion size.

3.2.8 EEG Data Analyses

EEG data analysis was performed with EEGLAB (Delorme and Makeig, 2004), ERPLAB (Lopez-Calderon and Luck, 2014) and custom written MATLAB (Natick, MA) scripts. EEG data were re-referenced offline to the average of the signal from the two earlobe electrodes.

The data were high-pass filtered with 0.5 Hz (butterworth filter, 2nd order) and subsequently low-pass filtered with 40 Hz (butterworth filter, 6th order). Data from Oslo was down sampled to 256 Hz. The data were segmented into epochs for the different conditions. Epochs included 1000 ms before and 2000 ms after the stimulus. The baseline was defined as the 100 ms preceding the stimulus. An Independent Components Analysis (ICA), as implemented in EEGLAB (Infomax extended), was performed on the epoched data including all conditions. Independent components accounting for blink artifacts and horizontal eye movements were identified and removed from the data (Jung et al., 2000). Trials affected by other artifacts caused e.g. by muscle tension were rejected from further analysis with a threshold for rejection of ±80 μV. Noisy channels identified by visual inspection and artefact rejection thresholds were interpolated (mean 1.5 channels per subject). If more than 30% of the data of one participant were rejected, this subject was excluded from analysis (one PFC patient, four controls). Current source density interpolation of the data was estimated through Laplacian computation based on a spherical spline interpolation (with a spline order of 4) (Kayser and Tenke, 2006) using a toolbox for MATLAB (Kayser, 2009). We took advantage of the Laplace transformation, as it accentuates local effects while filtering out distant effects due to volume conduction, which increases the signal-to-noise ratio, especially in combination with higher density recordings (≥ 64 electrodes) (Babiloni et al., 1995).

3.2.8.1 Event-Related Potentials (ERPs)

We analyzed the amplitude of the CNV in the cue-target interval and the cue- and target-related P1 and N1. As measure of the amplitude we chose the area under the curve (AUC) in a given time-window, zeroing negative values in positive waveforms and vice versa. Analyzed time-windows and selection of electrodes for the different components were based on visual inspection of the data and on a previous study (Liebrand et al., 2017) as follows: P1 (50-150 ms), N1 (100-250 ms), CNV (1000-1100 ms). P1 and N1 were measured

at PO7 and PO8 and the CNV at Cz and FCz. In order to enable a comparison of activity in the lesioned and the non-lesioned hemisphere, data of patients with a lesion in the LH were flipped along the midline (for a similar approach see e.g., Fogelson et al. (2009)). Data of the cue-evoked P1 and N1 were subjected to mixed-design ANOVAs with the within-subject factors Condition (Maybe Stop vs. Certain Go), Hemisphere (ipsi- vs. contralesional) and the between-subject factor Group (BG, PFC, CTR). P1 and N1 evoked by frequent target stimuli was subjected to an ANOVA with the within-subject factors Condition (No Stop vs. Frequent Go), Hemisphere (ipsi- vs. contralesional) and the between-subject factor Group. For rare target stimuli, which were presented lateralized to the right or left side, the ANOVA included the within-subject factors Condition (Stop vs. Rare Go), Hemisphere (ipsi- vs. contralesional), Stimulus side (ipsi- vs. contralesional) and the between-subject factor Group. The CNV was analyzed with an ANOVA including the within-subject factors Condition (MS vs. CG), Electrode (FCz, Cz) and the between-subject factor Group. For visualization only, data were low-pass filtered with 15 Hz.

3.2.8.2 Time-Frequency Analysis

To study the inhibition related power changes in the alpha (9-14 Hz) and beta band (15-25 Hz), single trial data were convolved with a complex Morlet wavelet as implemented in MATLAB (function cwt with parameter specification 'cmor1-1.5'):

$$w(t) = (\pi f_b)^{-0.5} e^{-2\pi i f t_c} e^{-\frac{t^2}{f_b}}$$

where $f_b = 1$ was the bandwidth parameter and $f_c = 1.5$ was the wavelet center frequency (Teolis, 1998). Specifically, we computed and averaged for each subject, changes in time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (1-40 Hz, linear increase). Data was computed as percent power change with respect to a pre-stimulus baseline (-250 to -50 ms prior to the stimulus). The selection of the analyzed alpha/mu (9-14 Hz) and beta (15-25 Hz) frequencies was based on previous

literature (Krämer et al., 2011; Solbakk and Løvstad, 2014; Liebrand et al., 2017). In order to reduce the number of statistical comparisons and to increase the signal-to-noise ratio, we clustered the electrodes into regions of interest: Left prefrontal (F3, F5, FC3, FC5), right prefrontal (F4, F6, FC4, FC6), left central (C3, C5, CP3, CP5) and right central (C4, C6, CP4, CP6), based on previous studies (Krämer et al., 2013; Liebrand et al., 2017). Similar to ERP data, activity of patients with lesions in LH was flipped along the midline. Since the performing hand also depended on the lesion side, we also accounted for sensorimotor activity with this procedure. Contralesional corresponds thus directly to the contralateral hemisphere (in relation to the responding hand) and ipsilesional corresponds to the ipsilateral hemisphere. Mean time-frequency power in a given time-window (see below) was subjected to mixed-design ANOVAs. Time windows for analysis were based on our previous study (Liebrand et al., 2017). As measurement window for effects before target onset we chose 700–1100 ms when the cue-related activity was distant and target-onset (1100 ms) was closest. For target-related effects, we investigated the window between 200 and 500 ms, focusing on the period when participants were executing the motor response.

For sensorimotor effects between cue and target, mean mu and beta activity over sensorimotor clusters (700-1100 ms) was subjected to ANOVAs with the within-subject factors Condition (MS vs. CG), Hemisphere (contra- vs. ipsilateral to the upcoming motor response) and the between-subject factor Group (BG, PFC, CTR). For attention related effects between cue and target, we subjected mean alpha power over occipital clusters (700-1100 ms) to an ANOVA with within-subject factors Condition (MS vs. CG), Stimulus (contra- vs. ipsilesional side of upcoming possibly lateralized target stimulus) and Hemisphere (contra- vs. ipsilesional) and the between-subject factor Group. To investigate prefrontal activity preceding target onset we subjected mean beta power at prefrontal sites (700-1100 ms) to an ANOVA with the within-subject factors Condition (MS vs. CG), Hemisphere (contra- vs. ipsilesional) and the between-subject factor Group. To test for a

modulation of beta power after target signals, we subjected mean beta power over prefrontal electrodes (200-500 ms) to ANOVAs with the factors Condition, Hemisphere (contra- vs. ipsilesional) and the between-subject factor Group. As Conditions rare (Stop- vs. Rare Go-) and frequent (No Stop- vs. Frequent Go-) trials were separately analyzed.

3.3 Results

In order to assess whether BG and PFC patients can be directly statically compared with one healthy control group, we tested for differences between groups in terms of age, and years of education. BG and PFC patients did not differ from the control group including all matched control participants in terms of these two criteria (BG vs. all controls: age: $t_{29} = 0.8$, $p = 0.425$; education: $t_{29} = 0.5$, $p = 0.643$; PFC vs. all controls: age: $t_{29} = -0.8$, $p = 0.434$; education: $t_{29} = 0.2$, $p = 0.850$; PFC vs. BSG: age: $t_{16} = 1.3$, $p = 0.205$; education: $t_{16} = 0.2$, $p = 0.862$).

3.3.1 Behavioral Results

Participants were faster in Frequent Go- (398±99 ms) compared to Rare Go- (441±119 ms) and No Stop-trials (461±75 ms) (Figure 3.1B; Condition: $F_{2,74} = 19.2$, $p < 0.001$; Frequent Go- vs. No Stop-trials: $F_{1,37} = 44.2$, $p < 0.001$; Frequent Go- vs. Rare Go-trials: $F_{1,37} = 37.8$, $p < 0.001$; No Stop- vs. Rare Go-trials: $F_{1,37} = 1.3$, $p = 0.261$). Importantly, there was no effect of Group, meaning that patients did not differ from controls in terms of reaction times (Group: $F_{2,74} = 0.4$, $p = 0.663$; Group x Condition: $F_{4,148} = 1.1$, $p = 0.347$). Additionally, we computed if participants individually showed significantly different behavior to the control group. Compared to controls, no BG-patient (all $t > -1.4$, $p > 0.178$), nor any PFC-patient (all $t > -1.3$, $p > 0.211$) showed a significant reaction time slowing in Frequent Go- in contrast to No Stop-trials. This speaks for intact proactive inhibitory control. Our results indicate that patients and controls were able to perform the task successfully.

We also assessed in patients whether reaction times differed if target stimuli were presented on the ipsi- or contralesional side. In Rare Go-trials reaction times were similar for ipsi- (440±125 ms) and contralesional (442±122 ms) stimuli and did not differ between patient groups (Laterality: $F_{1,37} = 0.0$, $p = 0.892$; Group: $F_{2,74} = 0.5$, $p = 0.634$; Group x Laterality: $F_{2,74} = 0.1$, $p = 0.945$). Finally, reaction times collapsed over all trials did not correlate with normalized lesion size, in neither patient group (BG: $r = 0.2$, $p = 0.339$; PFC: $r = 0.3$, $p = 0.214$).

Patients did not differ from controls in the percentage of failed inhibitions (Group: $F_{2,74} = 1.3$, $p = 0.273$). This was also true, when comparing single patients to the overall control group. No BG patient (all $t < 1.3$, $p > 0.204$) and only two PFC patients (all $t < 2.8$, $p > 0.010$) showed an increased rate of failed inhibitions compared to controls. Regarding commission errors, subjects were as accurate in the Certain Go as in the Maybe Stop condition (Condition: $F_{1,37} = 1.9$, $p = 0.180$; Group: $F_{2,74} = 1.9$, $p = 0.168$; Group x Condition: $F_{2,74} = 0.5$, $p = 0.630$). Subjects omitted more trials in the Certain Go than the Maybe Stop condition (Condition: $F_{1,37} = 11.1$, $p = 0.002$; Group: $F_{2,74} = 1.4$, $p = 0.249$; Group x Condition: $F_{2,74} = 1.7$, $p = 0.196$). Subjects committed more premature errors in Certain Go- than Maybe Stop-trials with no difference between groups (Condition: $F_{1,37} = 16.0$, $p < 0.001$; Group: $F_{2,74} = 0.7$, $p = 0.516$; Group x Condition: $F_{2,74} = 1.8$, $p = 0.183$). In BG- and PFC-patients accuracy did not differ between ipsi- and contralesional target stimuli (Laterality: $F_{1,37} = 0.0$, $p = 0.844$; Group: $F_{2,74} = 1.4$, $p = 0.258$; Group x Laterality: $F_{2,74} = 0.1$, $p = 0.768$). In both patient groups, overall hit rate did not correlate with normalized lesion size (BG: $r = 0.2$, $p = 0.282$; PFC: $r = 0.0$, $p = 0.472$).

3.3.2 EEG Results

The EEG was recorded with different systems and amplifiers at Lübeck (BrainAmp MR plus) and Oslo/Berkeley (BioSemi Active-Two). To ensure that this did not affect our

results, we compared baseline corrected broadband (1-40 Hz) and alpha/beta power between the two sites. There was no difference in oscillatory power (Broadband power: $t_{38} = -0.7$, $p = 0.459$; alpha power: $t_{38} = -1.0$, $p = 0.330$; beta power: $t_{38} = -1.6$, $p = 0.109$).

3.3.2.1 Sensorimotor Effects

First, we were interested in the modulation of mu and beta activity over the sensorimotor cortex in preparation of the upcoming motor action (Figure 3.4). Mean mu and beta power between 700 ms and 1100 ms during the cue-target interval was subjected to an ANOVA with the within-subject factors Condition (MS vs. CG), Hemisphere (contra- and ipsilateral to the upcoming motor response) and the between-subject factor Group (BG, PFC, CTR). Across all groups, mu power tended to be decreased in Maybe Stop- compared to Certain Go-trials (Condition: $F_{1,37} = 3.7$, $p = 0.061$; Group: $F_{2,74} = 0.4$, $p = 0.690$; Group x Condition: $F_{2,74} = 0.5$, $p = 0.620$). In PFC patients only, mu was decreased on the contra- compared to the ipsilateral side (Group x Hemisphere: $F_{2,74} = 4.8$, $p = 0.014$; Hemisphere in PFC: $F_{1,8} = 12.0$, $p = 0.009$, Hemisphere in BG: $F_{1,8} = 1.6$, $p = 0.243$, Hemisphere in CTR: $F_{1,21} = 3.0$, $p = 0.098$). This effect of Hemisphere did not interact with Condition (Group x Hemisphere x Condition: $F_{2,74} = 0.3$, $p = 0.714$).

In PFC patients and controls, beta power was decreased on the contra- compared to the ipsilateral side (Group x Hemisphere: $F_{2,74} = 5.3$, $p = 0.009$; Hemisphere in PFC: $F_{1,8} = 21.1$, $p = 0.002$, Hemisphere in CTR: $F_{1,21} = 7.2$, $p = 0.014$, Hemisphere in BG: $F_{1,8} = 0.2$, $p = 0.651$). When comparing the beta effect only between PFC patients and controls, it was increased for patients (Group x Hemisphere: $F_{1,29} = 7.8$, $p = 0.009$). Generally, there was no effect of condition (Condition: $F_{1,37} = 0.0$, $p = 0.854$; Condition x Hemisphere: $F_{1,37} = 0.5$, $p = 0.464$; Group x Hemisphere x Condition: $F_{2,74} = 0.0$, $p = 0.979$).

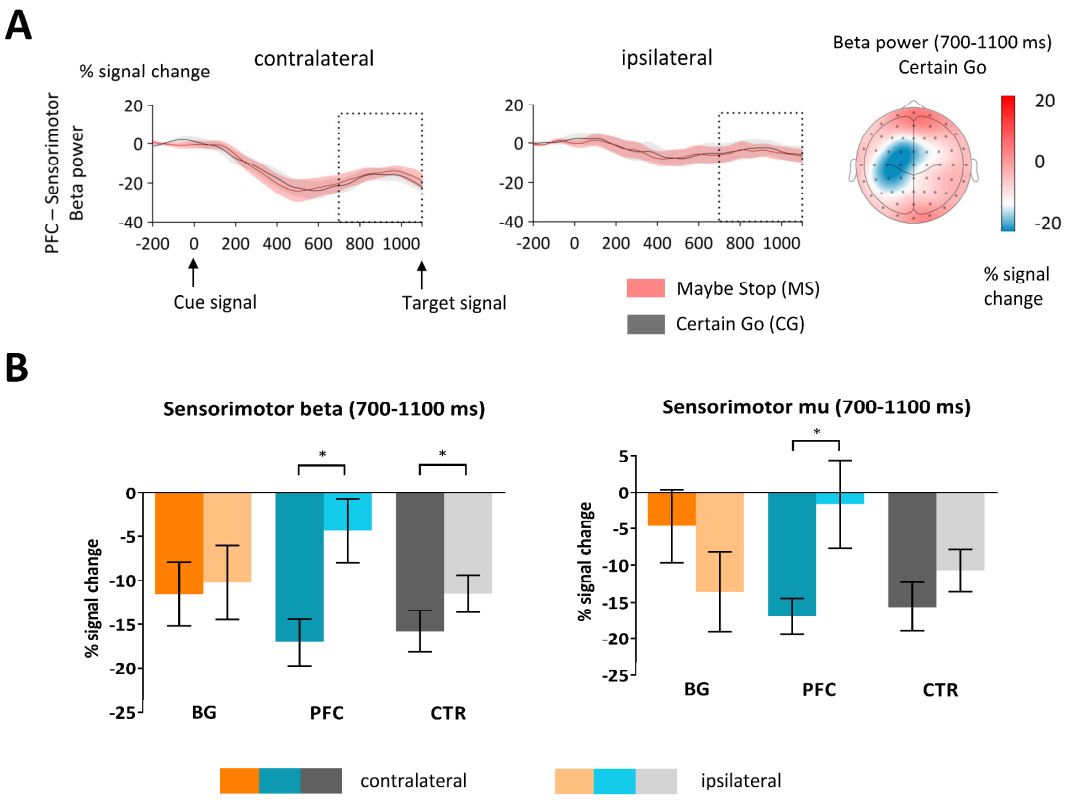


FIGURE 3.4 | Proactive sensorimotor activity. (A) Activity in the cue-target interval in PFC patients. Here beta (15-25 Hz) power at sensorimotor clusters contra- and ipsilateral to the standard motor response is displayed. The analyzed time-window (700-1100 ms) is indicated as dotted box and the SEM is shown as shaded area. The cue appeared at 0 ms and the target stimulus at 1100 ms. In PFC patients beta power was lower on the contra- than on the ipsilateral side but did not differ between Maybe Stop- and Certain Go-trials. The topographic plot to the right show the scalp distribution of the beta band in the Certain Go condition. (B) Mean mu and beta activity (700-1100 ms) in the cue-target interval in all three groups. Displayed is activity at the contra- and ipsilateral side to the upcoming standard motor response. As error bars the SEM are displayed. In the beta band PFC patients and controls showed increased activity on the contra- compared to the ipsilateral side. In the mu band this effect was present in PFC patients only.

3.3.2.2 Visual Attention Effects

3.3.2.2.1 Occipital Alpha

To investigate the role of visual attention in proactive motor control, we examined condition differences in alpha power over occipital sites in the cue-target interval. After cue-onset in both Maybe Stop- and Certain Go-trials, alpha decreased until about 400 ms and then increased again. Whereas alpha in CG-trials increased towards the baseline level, this rebound was dampened in MS-trials resulting in reduced alpha power (Figure 3.5A).

We subjected mean alpha power between 700 ms and 1100 ms to a repeated measures ANOVA with within-subject factors Condition (MS, CG), Stimulus (contra-, vs. ipsilesional side of upcoming possibly lateralized target stimulus) and Hemisphere (contra- vs. ipsilesional) and the between-subject factor Group. In general, alpha power was reduced in MS- compared to CG-trials (Figure 3.5B; $F_{1,37} = 35.1$, $p < 0.001$) with no difference between groups (Group: $F_{2,74} = 2.2$, $p = 0.128$; Group x Condition: $F_{2,74} = 0.6$, $p = 0.562$). In individual group comparisons, alpha power differed between groups. Alpha power was increased in PFC patients compared to controls (PFC vs. CTR: $F_{1,29} = 4.2$, $p = 0.049$; PFC vs. BSG: $F_{1,16} = 0.9$, $p = 0.358$; BSG vs. CTR: $F_{1,29} = 0.9$, $p = 0.361$). Finally the factors Stimulus and Hemisphere interacted ($F_{1,37} = 25.0$, $p < 0.001$). In all three groups, for ipsilesional target stimuli alpha decreased more in the contra- than the ipsilesional hemisphere ($F_{1,37} = 8.3$, $p = 0.006$) and for contralesional target stimuli more in the ipsi- than contralesional hemisphere ($F_{1,37} = 9.1$, $p = 0.005$). This effect did not differ between groups (Group x Stimulus x Hemisphere: $F_{2,74} = 0.1$, $p = 0.896$).

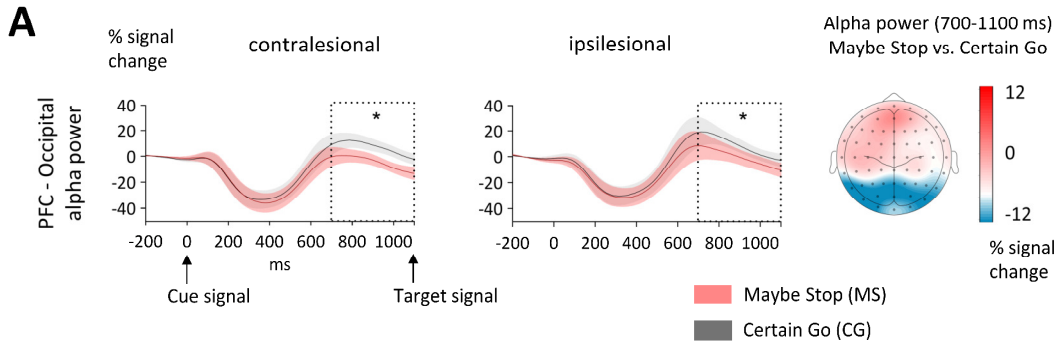
3.3.2.2.2 Cue- and Target-Related P1/N1

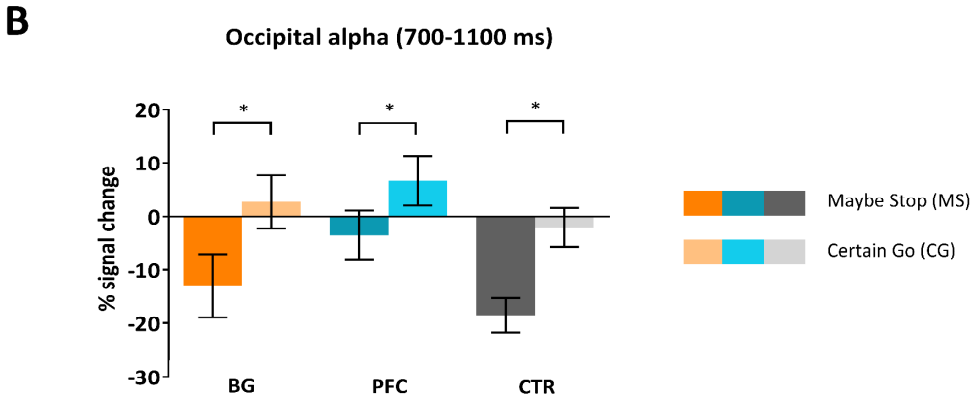
To assess attention related effects on early visual target processing, we looked at the P1/N1 complex to cue and target stimuli. Both components were centered at PO7 and PO8 (Figure 3.5D). We subjected the AUC between 50–150 ms (P1) and 100–250 ms (N1) to ANOVAs. For the cue-evoked P1 this ANOVA included the within-subject factors Hemisphere (ipsi- vs. contralesional), Condition (Maybe Stop vs. Certain Go) and the between-subject factor Group. The factors Group and Hemisphere showed an interaction (Figure 3.5C). While PFC patients tended to have an increased P1 over the contra- compared to the ipsilesional hemisphere, BG patients tended to show the opposite effect (Group x Hemisphere: $F_{2,74} = 3.8$, $p = 0.032$, Hemisphere for PFC: $F_{1,8} = 2.2$, $p = 0.180$, Hemisphere for BG: $F_{1,8} = 2.5$, $p = 0.155$, Hemisphere for CTR: $F_{1,21} = 0.6$, $p = 0.458$). One single PFC patient showed the exact opposite pattern to all other PFC patients with an increased P1 on the

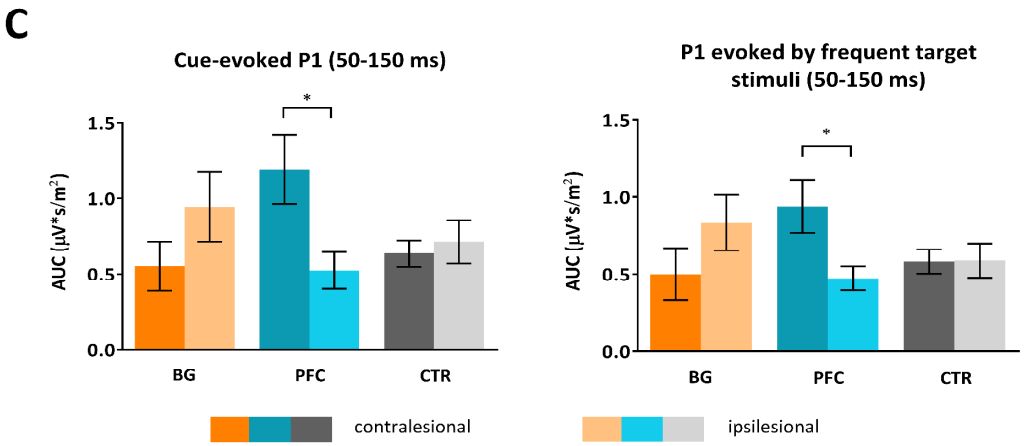
ipsilesional side. When excluding this subject, the effect of Hemisphere increased considerably (Hemisphere for PFC: $F_{1,7} = 8.9$, $p = 0.02$). There was no effect of Condition ($F_{1,37} = 0.1$, $p = 0.796$). There were no effects regarding the cue-evoked N1.

To test for effects of proactive control on target-related stimulus processing, we measured the P1 and N1 to frequent targets. The ANOVA consisted of the within-subject factors Hemisphere (ipsi- vs. contralesional), Condition (No Stop vs. Frequent Go) and the between-subject factor Group. Again, there was an interaction of Group and Hemisphere, with a tendency towards an increased P1 on the contra- compared to the ipsilesional side in PFC patients, and an opposite effect in BG patients (Figure 3.5C; Hemisphere x Group: $F_{2,74} = 3.6$, $p = 0.036$; Hemisphere for PFC: $F_{1,8} = 2.3$, $p = 0.168$, Hemisphere for BG: $F_{1,8} = 2.0$, $p = 0.194$, Hemisphere for CTR: $F_{1,21} = 0.0$, $p = 0.934$). The above mentioned PFC patient again showed an opposite pattern and when excluding it, the effect became clearer (Hemisphere for PFC: $F_{1,7} = 8.4$, $p = 0.023$). There was no effect of Condition for P1 ($F_{1,37} = 0.0$, $p = 0.900$). Across all subjects, the N1 was increased in No Stop- compared to Frequent Go-trials (Condition: $F_{1,37} = 18.0$, $p < 0.001$), with no difference between groups (Condition x Group: $F_{2,74} = 0.6$, $p = 0.536$; see Figure 3.5D for data of PFC patients, data not displayed for BG patients and controls).

To test for effects of reactive control on early visual processing, the P1/N1 evoked in rare trials was measured. The ANOVA consisted of the within-subject factors Hemisphere (ipsi- vs. contralesional), Stimulus (ipsi- vs. contralesional), Condition (Stop vs. Rare Go) and the between-subject factor Group. There was no effect for P1. The N1 was increased in the hemisphere contralateral to the lateralized presented stimulus with no difference between groups (Stimulus x Hemisphere: $F_{1,37} = 38.1$, $p < 0.001$, Stimulus x Hemisphere x Group: $F_{2,74} = 0.5$, $p = 0.638$; data not displayed). There was no effect of Condition, neither for P1 ($F_{1,37} = 0.0$, $p = 0.896$) nor for N1 ($F_{1,37} = 2.3$, $p = 0.141$).


A
% signal change
contralesional
ipsilesional
Alpha power (700-1100 ms)
Maybe Stop vs. Certain Go
PFC - Occipital alpha power
40
20
0
-20
-40
-200 0 200 400 600 800 1000
ms
*
Cue signal
Target signal
12
0
-12
% signal change
Maybe Stop (MS)
Certain Go (CG)


B
Occipital alpha (700-1100 ms)
% signal change
20
10
0
-10
-20
-30
*
BG
PFC
CTR
Maybe Stop (MS)
Certain Go (CG)


C
Cue-evoked P1 (50-150 ms)
P1 evoked by frequent target stimuli (50-150 ms)
AUC [µV*s/m²]
1.5
1.0
0.5
0.0
*
BG
PFC
CTR
contralesional
ipsilesional

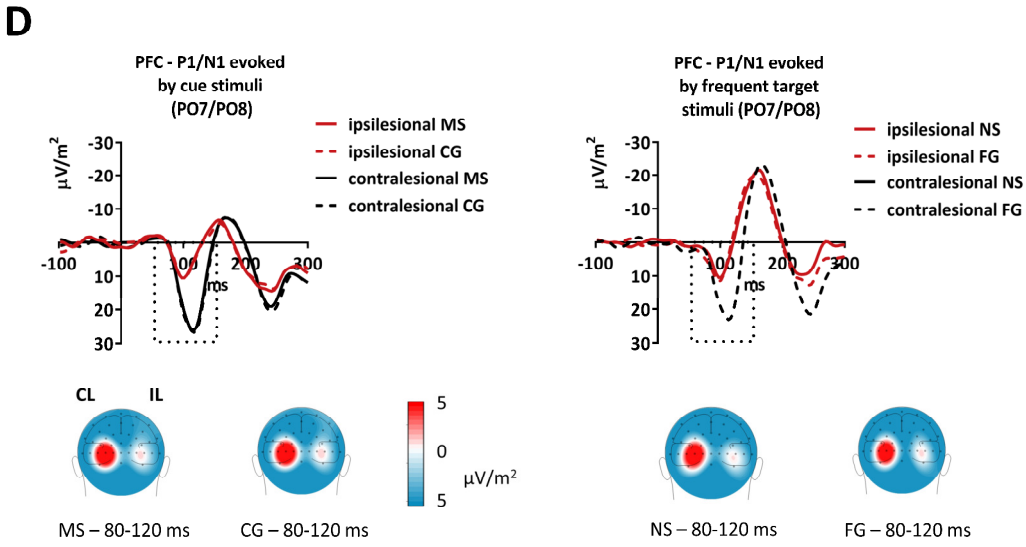

D
PFC - P1/N1 evoked by cue stimuli (PO7/PO8)
PFC - P1/N1 evoked by frequent target stimuli (PO7/PO8)
µV/m²
-30
-20
-10
10
20
30
-100
100
200
300
ms
ipsilesional MS
ipsilesional CG
contralesional MS
contralesional CG
ipsilesional NS
ipsilesional FG
contralesional NS
contralesional FG
CL
IL
5
0
5
µV/m²
MS – 80-120 ms
CG – 80-120 ms
NS – 80-120 ms
FG – 80-120 ms

FIGURE 3.5 | Effects of attentional modulation. (A) Alpha (9-14 Hz) power in PFC patients in the cue-target interval for the Maybe Stop (red) and Certain Go condition (black) at occipital clusters. The analyzed time-window (700-1100 ms) is displayed as dotted box. The cue appeared at 0 ms and the target stimulus at 1100 ms. Alpha power was decreased in Maybe Stop- than Certain Go-trials at both the contra- and ipsilesional side to the upcoming, possibly lateralized target. The SEM is displayed as shaded area. The topographic plot to the right shows the scalp distribution of the alpha band as difference between Maybe Stop- and Certain Go-trials. (B) Mean occipital alpha power between 700-1100 ms for all three groups. As error bars the SEM are displayed. In both controls and patients alpha power was decreased in MS- compared to CG-trials. (C) Area under the curve (AUC) of the cue-evoked and the target-evoked P1 (50-150 ms). In PFC patients only, P1 was increased on the contra- compared to the ipsilesional side. Data is displayed without the single PFC-patient, which was excluded from statistical analysis. (D) Timecourse of the cue-P1 and the P1 evoked by frequent target stimuli (NS = No Stop, FG = Frequent Go) in PFC patients. Again, the P1 was increased on the contra- compared to the ipsilesional side. In the topographic plots below mean activity between 80-120 ms after cue- or target-onset is shown.

3.3.2.2.3 CNV

The CNV, measured in the cue-target interval, had its maximum at FCz/Cz (Figure 3.6) and increased towards the target in all three groups. We subjected the AUC between 1000 ms and 1100 ms to an ANOVA with the within-subject factors Condition (MS vs. CG) and Electrode (FCz, Cz) and the between-subject factor Group. Only in controls, but not in patients an increased CNV in MS compared to CG was observed (Condition for CTR: $F_{1,21} = 14.0$, $p = 0.001$, Condition for BG: $F_{1,8} = 0.2$, $p = 0.703$, Condition for PFC: $F_{1,8} = 0.4$, $p = 0.552$). The interaction with the factor Group was not significant though (Condition x Group: $F_{2,74} = 2.0$, $p = 0.144$). There was no main effect of Group ($F_{1,37} = 1.6$, $p = 0.206$).

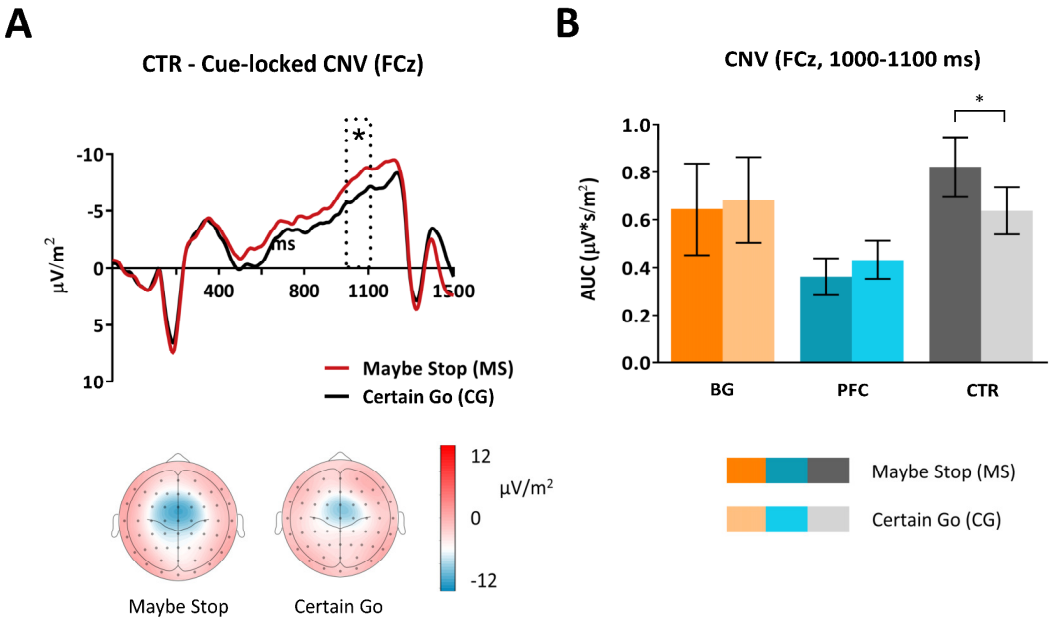


FIGURE 3.6 |Contingent negative variation. (A) CNV in the cue-target interval in control subjects (CTR). In the analyzed time interval the CNV was increased in Maybe Stop- (MS) compared to Certain Go- (CG) trials. The topographic plots below display mean activity between 1000 and 1100 ms. (B) Area under the curve (AUC) of the CNV between 1000 and 1100 ms at FCz. As error bars the SEM are displayed. Only healthy controls but not patients showed an increased CNV in MS compared to CG.

3.3.2.3 Prefrontal Activity

First, we analyzed whether beta power over prefrontal electrodes was modulated in the cue-target interval. We therefore subjected mean beta power at prefrontal sites between 700 ms and 1100 ms to an ANOVA with the within-subject factors Condition (MS vs. CG), Hemisphere (contra- vs. ipsilesional) and the between-subject factor Group. Prefrontal beta only tended to be increased in the CG compared to the MS condition, with no difference between groups regarding this effect (Condition: $F_{1,37} = 3.5$, $p = 0.069$; Group: $F_{1,37} = 1.6$, $p = 0.208$; Condition x Group: $F_{2,74} = 0.8$, $p = 0.445$; data not shown).

To test for a modulation of beta power after target signals, we subjected mean beta power over prefrontal electrodes between 200 ms and 500 ms to repeated measures ANOVAs with the factors Condition, Hemisphere (contra- vs. ipsilesional) and the between-subject factor

Group (Figure 3.7). This was done separately for rare (Stop- vs. Rare Go-) and frequent (No Stop- vs. Frequent Go) trials. Beta power over prefrontal electrodes was higher in Stop- than Rare Go-trials ($F_{1,36}$ = 7.3, p = 0.011), with no difference between groups (Group x Condition: $F_{2,72}$ = 0.6, p = 0.530). Note that one BG patient showed extreme beta power compared to other subjects (> 5 SD above mean value in one condition) and therefore was removed from the statistics regarding this comparison. Reactive beta power was also increased in No Stop- compared to Frequent Go-trials ($F_{1,37}$ = 8.2, p = 0.007). The effect did not differ between groups (Group x Critical: $F_{2,74}$ = 1.4, p = 0.251). In No Stop- and Frequent Go-trials prefrontal beta was increased in BG compared to controls and tended to be increased compared to PFC patients (Group: $F_{2,74}$ = 3.1, p = 0.058; BG vs. CTR: $F_{1,29}$ = 6.0, p = 0.021; BG vs. PFC: $F_{1,16}$ = 4.3, p = 0.055; CTR vs. PFC: $F_{1,29}$ = 0.1, p = 0.711).

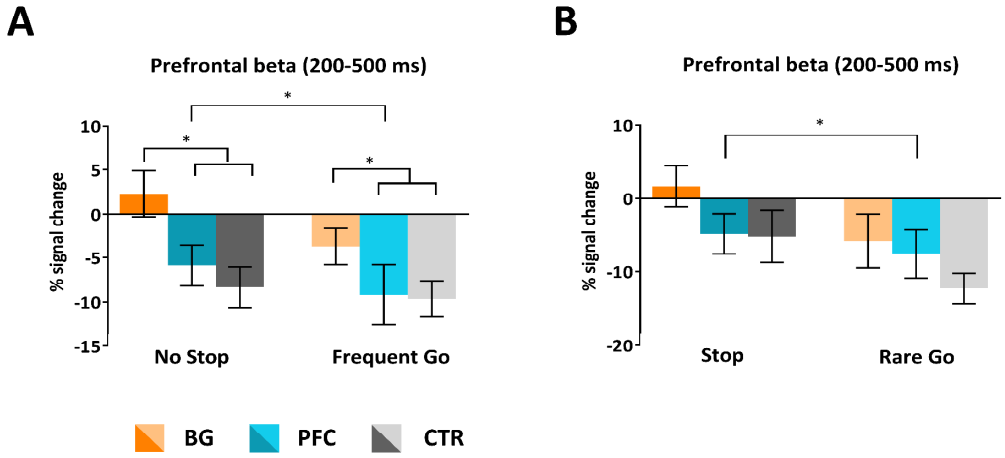


FIGURE 3.7 |Target related prefrontal activity. Mean prefrontal beta power (200-500 ms) in all three groups. As error bars the SEM are displayed. (A) Here, activity in frequent trials is shown. In patients and controls beta power was increased when they prepared to inhibit the button press (No Stop) compared to trials where a certain motor action could be anticipated (Frequent Go). Also, beta power was increased in BG compared to PFC patients and controls. (B) Here, activity in rare trials is displayed. Prefrontal beta power both in controls and patients was increased when the motor action had to be inhibited (Stop) compared to when a button press was realized (Rare Go). Data is displayed without the single BG patient, which showed extreme beta power.

3.4 Discussion

We aimed to investigate the critical importance of prefrontal and basal ganglia nodes for proactive and reactive motor inhibition. To this end, patients with lesions to the BG or lateral PFC performed in a cued go/nogo task. We expected patients to show impairments in proactive and reactive motor inhibition, both reflected on the behavioral and neural level. Importantly, we did not find differences between patients and controls in behavior, indexed by comparable reaction times and accuracy. In line with behavioral findings, apart from the CNV, patients did not show altered prefrontal, sensorimotor or occipital activity related to experimental manipulation of proactive or reactive inhibition. Our results speak for a preserved ability in both patient groups to employ preparatory and reactive inhibitory processes. We suggest that an insufficiently challenging paradigm and statistical power, sufficient only to detect strong effects, hindered to find causal influence on inhibitory processing as hypothesized.

In contrast to control subjects, BG patients did not show a modulation of the CNV when anticipating stopping, nor pre-movement lateralization of sensorimotor beta. This speaks for altered processes of sensorimotor preparation. In PFC patients, modulation of the CNV was similarly absent but sensorimotor lateralization was increased. Furthermore, occipital alpha power in the cue-target interval was increased and the contralesional P1 was enhanced. These findings indicate irregular attentional/visual processing, possibly compensated by a more stable sensorimotor representation. Our data show reorganization of activity in visual and sensorimotor regions following BG and PFC lesions, however not directly related to motor inhibition.

3.4.1 Behavioral Results

Patients were able to engage in proactive motor inhibition, as reflected in preserved reaction time slowing movement when cancellation was anticipated. Moreover, compared

to controls, patients did not show an increased rate of failed inhibitions, which would speak for an impairment in reactive motor inhibition. Neither in reaction times (RT) nor in accuracy, any differences between contra- and ipsilesional target stimuli were found, indicating an intact ability to shift attention to both hemifields. In contrast to our findings, previous studies investigating patients with lateral PFC lesions in go/nogo tasks reported an increased rate of errors in nogo-trials speaking for deficient reactive inhibition (Swick et al., 2008; Krämer et al., 2013). These contradictory results might be explained by lesion etiology as most lesions in these studies were due to stroke (Swick et al.: 12/12, Krämer et al.: 9/14), in contrast to the present sample, where more than half of the lesions were due to tumor resection (5/9). It might be that slowly growing tumors leave more time for functional reorganization and compensation of affected brain structures than a sudden stroke. Similarly to our results, in a study employing a go/nogo delayed response task in lateral PFC patients, no differences in go- or nogo-accuracy were found for patients compared to controls (Funderud et al., 2012). Here, lesion etiology was tumor resection in all cases. However, in contrast to our task, inhibitory effort was limited as auditory cues signaled reliably whether to inhibit a manual response to an upcoming visual target signal. Alternatively, PFC patients might display deficits in switching between task modalities. In both studies of Swick et al. (2008) and Krämer et al. (2013) alternating blocks of high and low probability of nogo-signals were presented, whereas nogo-signal probability was kept constant in the present paradigm. Support for this idea comes from studies showing PFC activation in task switching (Braver et al., 2003; Yeung et al., 2006) and data linking PFC lesions to deficits in task switching (Aron et al., 2004a).

One study reported impaired reactive behavioral stopping in BG lesion patients in a SST (Rieger et al., 2003). Deficient inhibition was indexed by prolonged stop-signal reaction time (SRTT), with no differences in error rates between patients and controls. In a go/nogo task patients with lesions to the BG only showed a trend towards an increased rate of failed

inhibitions (Thoma et al., 2008). These together with our results suggest that the cued go/nogo paradigm might not have been challenging enough for patients to detect impaired inhibitory performance. This idea is supported by normal RTs and RT variability in PFC patients, while commonly longer RTs and increased variability is reported in groups of patients with lesions to lateral PFC (Chao and Knight, 1998; Stuss et al., 2003; Barcelo and Knight, 2007; Funderud et al., 2013; Krämer et al., 2013). The SST for instance, might be more sensitive to detect behavioral deficits in patients, as it is more challenging, adjusting to individual task performance.

To our knowledge this is the first study to investigate effects of BG or PFC lesions on proactive inhibition. As, unlike hypothesized, we did not find effects of both patients groups on reactive inhibition, it does not seem clear whether null findings on preparatory stopping can be attributed to preserved ability for proactive inhibition. Our data stands against the idea of a prefrontal-basal ganglia network underlying preparation for inhibition (Aron, 2011). It is also not in line with findings which link PFC lesions to prolonged reaction times in a proactive visual detection task (Alivisatos and Milner, 1989) and BG lesions to reduced ERP components of motor preparation (Feve et al., 1994). It might be that abovementioned aspects as task design or lesion etiology in PFC patients, prevented to detect causal effects of basal ganglia or prefrontal nodes on proactive inhibitory processes.

3.4.2 CNV, Attention and Occipital Alpha Oscillations

In a previous experiment, we found an increased contingent negative variation (CNV) in trials calling for proactive of inhibition (Maybe Stop) compared to trials without (Certain Go). Here we replicate this effect in control subjects. Importantly no such modulation was observed for BG and PFC patients. The CNV is the most prominent component implicated in preparatory processes and both attentional and sensorimotor processes have been

attributed to it (Tecce, 1972; Brunia and van Boxtel, 2001). Our results thus speak for an aberrant attentional and/or motor preparation in patients. In line with our findings, previous work linked both basal ganglia and the PFC to generation of the CNV. Using intracranial recordings in the basal ganglia, these nuclei have been implicated in generating a CNV-like preparatory potential (Bareš and Rektor, 2001; Purzner et al., 2007), with the CNV amplitude at the scalp level being reduced in patients with PD (Amabile et al., 1986; Pulvermüller et al., 1996; Ikeda et al., 1997). Also, reduced differentiation between go- and nogo-CNV in patients with lesions to the lateral PFC has been reported and interpreted as a deficit in preparatory attention (Funderud et al., 2013). In another study, a reduced late CNV was observed in patients with lesions to the dorsolateral PFC (Rosahl and Knight, 1995) and seen in a context of the PFC in sustaining distributed neural activity during delay periods. Our results indicate altered preparation for a critical motor response in BG and PFC patients. However, whether attentional or motor preparation are underlying absent CNV differentiation cannot be directly inferred by the current study.

In a previous study, we found occipital alpha to be reduced in trials calling for proactive inhibition, speaking for an increased engagement of visual attention. Here, we replicate this effect in controls and patients, speaking for an intact attentional modulation in both patient groups. Whereas we expected this finding for BG patients, we did not for PFC patients, as PFC lesions have been associated with attentional deficits (Solbakk and Løvstad, 2014; Szczepanski and Knight, 2014). When performing in a SST, patients with unilateral lesions to the PFC showed reduced parietal activity in response to stop-signals and increased activation of intact prefrontal areas, speaking for limited attentional capacity and compensatory effects over the intact hemisphere (Krämer et al., 2013). An explanation for intact attentional modulation in the present study might be that the cued go/nogo-task was visually not challenging enough. The SST in contrast, stresses visual attention more,

as the delay between go- and stop-signal is dynamically adjusted to individual task performance.

In PFC patients, compared to controls and BG patients, we observed (i) a general increase in occipital alpha and (ii) an increased cue- and frequent target-P1 on the contra- compared to the ipsilesional side. This speaks for generally altered visual processing in patients and compensatory activity on the contralesional side. These findings are in line with a top-down role of the PFC in modulation of occipital visual activity (Paneri and Gregoriou, 2017). Importantly, occipital alpha and P1 were altered irrespective of the experimental manipulation and thus attentional modulation was preserved in PFC patients.

3.4.3 Sensorimotor Activity

In controls and both patient groups, no difference in sensorimotor beta between Certain Go- and Maybe Stop-trials was found, opposite to results of our preceding study. Previously, we observed a beta decrease in MS- compared to CG-trials on the ipsilateral side and interpreted this as impediment of motor processes. The fact that this modulation was not replicated in control subjects speaks for an age-related effect. Inhibitory control is a cognitive function which is known to decline with age (Gazzaley and D'esposito, 2007; Anguera and Gazzaley, 2012), often explained by prefrontal deficits (Kramer et al., 1994; Coxon et al., 2012). For instance longer SSRTs have been observed in elderly, speaking for slowing of inhibitory processes (Williams et al., 1999; Bedard et al., 2002; Coxon et al., 2012). However, also motor regions seem to be affected as in elderly sensorimotor alpha has been reported to be decreased during sustained inhibition (Bönstrup et al., 2015). Moreover, in a go/nogo task older subjects showed a smaller decrease of sensorimotor beta during preparation and execution of movements and increased mu following response inhibition (Schmiedt-Fehr et al., 2016). In sum, we interpret absent modulation of proactive

sensorimotor beta in patients as an effect related to age rather than to specific dysfunction of BG or PFC nodes in motor inhibition.

Previous studies found a reduction of mu/beta when planning an upcoming movement, with this decrease being more prominent over the contralateral side to the expected movement (Babiloni et al., 1995; Kajihara et al., 2015; Liebrand et al., 2017; Liebrand et al., in revision). Here, in the beta band this effect was replicated for aged controls. In patients with lesions to the basal ganglia, this lateralization of mu/beta in preparation to the upcoming movement was absent. When performing in a reaching task, the opposite finding was observed in PD patients, with present beta lateralization in patients, but not controls (Meziane et al., 2015). Absent lateralization in controls was explained by task difficulty, as more bilateral activation has been associated with task complexity (Kilavik et al., 2013). In another electrocorticography (ECoG) study dystonia patients with unilateral electrodes over primary motor cortex, showed reduced desynchronization of movement-related beta (Crowell et al., 2012). Finally, when executing a movement, PD patients exhibited an increased activation in bilateral motor cortex, as measured with fMRI (Sabatini et al., 2000; Haslinger et al., 2001). These findings do not point in a specific direction, but indicate aberrant sensorimotor activation when patients with BG dysfunction perform motor actions. Our results speak for similarly altered sensorimotor activity when preparing for upcoming responses.

In PFC patients, we observed a markedly stronger decrease on the contra- compared to the ipsilateral side for both the mu and the beta band. The mu effect was not present in control subjects and the beta modulation was increased compared to that of controls. To our knowledge, no previous PFC lesion study examined proactive sensorimotor mu/beta. Only the Bereitschaftspotential (BP) has been investigated as another neurophysiological correlate of motor preparation. The BP is a preparatory potential which precedes self-initiated movements (Kornhuber and Deecke, 1965). Both increased and decreased BP have

been reported in patients with PFC lesions. Stroke patients displayed a decreased BP (Singh and Knight, 1990) and chronic traumatic brain injury (TBI) patients showed an enhanced BP compared to control subjects (Wiese et al., 2004). Data of TBI patients was interpreted in terms of increased activity of the lateral premotor cortex during movement preparation and discussed as a correlate of a more challenging motor preparation. The present result of increased sensorimotor lateralization might similarly reflect more arduous motor preparation. Alternatively, it could represent a compensatory mechanism, with impairment of the PFC being compensated by a more stable sensorimotor representation. The fact that a functional mechanism (the lateralization) is increased rather than mere mu/beta power speaks for such a compensation. Moreover, we found altered processing in occipital visual areas. Visual effects are possibly linked to PFC top-down control, which might be compensated by sensorimotor mechanisms. Compensatory effects have been reported in PFC lesion patients before, as for instance in the domain of attention the contralesional seemed to take over functions of the ipsilesional hemisphere (Krämer et al., 2013). Summing up, absent sensorimotor lateralization in BG patients speaks for altered motor preparation and increased lateralization in PFC patients suggests compensatory reorganization of the sensorimotor network.

3.4.4 Prefrontal Cognitive Control

There is overwhelming evidence for the importance of prefrontal nodes in cognitive control (Miller, 2000) and motor control (Aron et al., 2014a). In previous studies, we found that prefrontal beta increased when (i) having to adapt a motor action and (ii) when an adaptation had been anticipated but did not have to be realized (Liebrand et al., 2017; Liebrand et al., in revision). We interpreted these findings as increased cognitive control when motor behavior might have and has to be adapted. Here, we replicated these results in control subjects and in both patient groups. This suggests intact modulation of cognitive

control in BG and PFC patients. This stands in contrast to previous findings of impaired cognitive control in patients with lesions to the PFC. In a large voxel-based lesion mapping study (n = 344), across several paradigms lesions in PFC were associated with behavioral deficits in cognitive control, with anterior cingulate cortex (ACC) and dorsolateral PFC as key regions (Gläscher et al., 2012). More specifically in a context of motor inhibition, when performing in a SST patients with lesions to the lateral PFC displayed increased activity over intact prefrontal areas, indexed by enhanced N2 (Krämer et al., 2013). As suggested above, the cued go/nogo task might not have been challenging enough to reveal deficient neural processing in patients. Alternatively, null findings might be attributable to differences in lesion etiology as aforementioned. Another explanation for findings of preserved modulation of beta over prefrontal regions could be that beta oscillations, unlike ERPs, are not sensitive enough to detect aberrant processing in PFC. High frequency oscillations are more susceptible to noise than those of lower frequencies (Muthukumaraswamy, 2013). Especially frontal muscle artefacts might have influenced prefrontal beta. However, the finding of increased prefrontal beta in BG but not PFC patients speaks against this argument.

Results of preserved modulation of prefrontal beta in BG patients are not consistent with a fundamental role of the basal ganglia in models of cognitive control, as posited for instance by the prefrontal-basal ganglia working memory (PBWM) model (O'Reilly and Frank, 2006). In line with this model, patients with dysfunctional BG seem to display impaired cognitive control, as deficits in task switching have been reported in PD (Cameron et al., 2010; Kehagia et al., 2014). Since we recorded scalp EEG, our data cannot speak about activity at the subcortical level of the basal ganglia. The observed modulation of beta over prefrontal regions might suggest intact processing within PFC regions. However, BG patients showed increased prefrontal beta power in frequent trials compared to PFC patients and controls. This could reflect a more effortful recruitment of cognitive

control, as prefrontal beta power has been linked to the amount of cognitive control needed in a given condition (Liebrand et al., in revision). This finding however, was not present when BG patients actually had to inhibit motor actions (Stop and Rare Go) and therefore has to be interpreted with caution.

3.4.5 Limitations

Here, regarding correlates of motor inhibition, we did not find differences between patients and controls and, with exception of the CNV, also not on the neural level. Null findings are generally difficult to interpret, it might be that low statistical power prevented to find group differences. This is a general problem in lesion studies with small sample sizes. However, other studies reported effects of impaired inhibitory capacity in patients groups with comparable size (e.g. Swick et al., 2008; Krämer et al., 2013). Since lesions were already in a chronic state and reorganization of lesioned brain networks is an established phenomenon (Weiller et al., 1992; Witte, 1998; Bütefisch, 2004), it might be that patients adopted compensatory strategies to cope with lesion-associated deficits. Also, compensatory mechanisms have been suggested in several lesion studies (Duffau et al., 2003; Thiel et al., 2006; Krämer et al., 2013). However, we did not find clear indications for compensatory effects related to inhibitory processes. An important limitation of our study is that lesions in the present sample were distributed throughout the entire lateral PFC and BG with all existing substructures. In contrast, both reactive and proactive inhibition have been associated with specific PFC and BG regions. Thus, results might lack of specificity, being not able to pinpoint certain functions to distinct anatomical regions. A solution to this challenge is voxel-based lesion-symptom mapping (Bates et al., 2003), which comes with the price of a big sample size. Future studies investigating response inhibition in lesion patients might take advantage of this technique.

3.4.6 Conclusions

In summary, this study does not provide evidence for a critical role of basal ganglia and prefrontal cortex in both reactive and proactive response inhibition. This is surprising as overwhelming evidence points to implication of BG and PFC in processes of action inhibition (Aron, 2011; Ridderinkhof et al., 2011; Aron et al., 2016). On the behavioral level, patients showed intact markers of preparatory and reactive cancellation of actions. Apart from the CNV, no differential neural processing related to inhibitory processes was found. We suggest that our experimental task did not challenge patients enough to reveal impaired inhibitory performance. Other factors as lesion etiology, distributed lesions and low statistical power might similarly have contributed to null effects.

However, general sensorimotor preparation seems to be affected by BG lesions, as suggested by absent CNV differentiation and sensorimotor mu/beta lateralization in patients. In PFC patients we found altered effects of sensorimotor preparation, reflected in an increased sensorimotor lateralization. Absent CNV modulation, increased occipital alpha and an enhanced contralesional P1 indicate altered visual processing. We suggest that changes in the visual/attentional network are compensated by a more stable sensorimotor presentation. In sum, our data speak for functional reorganization of sensorimotor and visual networks following brain lesions to the BG and PFC.

4 Ready for Change: Oscillatory Mechanisms of Proactive Motor Control [2]

4.1 Introduction

"Change is inevitable. Change is constant." (Benjamin Disraeli, 1867).

A key human feature is the ability to adapt to an ever-changing environment. This capability requires cognitive control, namely the ability to flexibly change or cancel preexisting action plans. Situations differ though in the likelihood of relevant changes to happen, for instance when driving on a street having right of way or when approaching traffic lights which might change. This study concentrates on motor control, one aspect of cognitive control. Most motor control studies focused on the neural response after changes occur, i.e. so-called reactive motor control. Even more important might be, though, how we prepare for upcoming changes in terms of biasing perceptual processes or motor preparation, which is termed proactive motor control. Here, we studied proactive motor control using electroencephalography (EEG) in a cued reaction time task.

The dual mechanisms of control (DMC) framework by Braver states that cognitive control can be employed in a proactive or in a reactive way, depending on current costs and benefits of the respective processes (Braver et al., 2008; Braver, 2012). It hypothesizes that proactive control is based on prefrontal activity, attention and modulation of activity in a motor network. Perceptual and action systems are thought to be biased in a goal-driven manner. In a recent study using EEG in a cued go/nogo paradigm, we investigated the interplay of prefrontal cognitive control, visual attention and sensorimotor activity mediating proactive motor inhibition (Liebrand et al., 2017). We contrasted trials in which

[2] This chapter corresponds largely to: Liebrand, M., Kristek, J., Tzvi, E., & Krämer, U. M (2018). Ready for Change: Oscillatory Mechanisms of Proactive Motor Control. *Plos One*, *13*(5), e0196855. UMK and I conceived the study. I designed the paradigm, performed the experiments, analyzed the data and wrote the manuscript.

a cue signaled that an upcoming motor action might have to be inhibited with others where no cancellation was necessary. During the cue-target interval, we found that the anticipation of nogo-signals led to increased visual attention, reflected in reduced occipital alpha power, and to a modulation of sensorimotor cortex activity, reflected in reduced beta power ipsilateral to the relevant response hand. Prefrontal activity, indicated by increased beta power, was observed only after target presentation, but not during the cue-target interval. We interpreted the increase in prefrontal beta power as enhanced cognitive control. In the present study, we focused on sensorimotor and prefrontal mechanisms, given their principal role in motor inhibition. Attentional effects were replicated, but did not provide novel insights into stopping processes and thus are not reported to prevent overextensive results.

Prefrontal cortex and specifically prefrontal beta oscillations have previously been implicated in proactive and reactive motor inhibition (Chikazoe et al., 2009; Aron, 2011). Studies investigating reactive inhibition reported increased prefrontal beta power when subjects had to inhibit a motor response (Alegre et al., 2004; Swann et al., 2009). Together with evidence of basal ganglia dependent changes in cortical beta oscillations (Swann et al., 2011; Ray et al., 2012; Alegre et al., 2013), these observations led to the hypothesis of an inhibition-related cortico-basal ganglia network mediated by beta activity (Aron, 2011). For proactive motor inhibition a similar prefrontal mechanism seems to be relevant as in reactive control. For instance, beta power over right dorsolateral prefrontal cortex (dlPFC) increased before successfully inhibiting a saccade (Hwang et al., 2014). Two studies using a modified stop signal task (SST) in a small group of epileptic patients found evidence for right inferior frontal cortex (IFC) and dorsolateral prefrontal cortex (PFC) to be implicated in proactive inhibition, there indicated by increased gamma (and not beta) power over those regions (Swann et al., 2012; Swann et al., 2013). Importantly, in these two studies prefrontal regions were activated only after, but not before target signals. Even though

counterintuitive, proactive effects can take place after appearance of target-signals. Specifically, having anticipated a possible inhibition modulated target-related processing but not preparatory activity. This, along with our previous finding of target-related prefrontal beta activity suggests that prefrontal beta activity provides a phasic control signal in response to the target. Prefrontal beta seems to play less of a role in a sustained way during the preparatory period between cue and target.

Over sensorimotor cortex, both mu and beta power decrease during movement preparation (Pfurtscheller et al., 1997; Neuper et al., 2006) with a stronger decrease contralateral to the expected action (Babiloni et al., 2004; Kajihara et al., 2015). In general, beta power has been linked to motor cortex excitability, as measured by transcranial magnetic stimulation (TMS) and motor evoked potentials (MEP) (Mäki and Ilmoniemi, 2010). In a recent study, Tzagarakis et al. (2015) investigated motor preparation in terms of directional uncertainty of an upcoming movement. In the task, the direction in which a joystick had to be pulled was cued to be at a specific location or within a range of 90° or 180°. The authors investigated beta power over sensorimotor cortex in the interval between cue and target. They found that the greater the directional certainty of a movement, the lower the beta power, and thus concluded that beta power reflects the level of motor preparation. In another study, in which a wrist extension was signaled by sounds, the pre-movement decrease of central beta power was similarly interpreted to reflect preparation of movements (Alegre et al., 2004). Our finding of a stronger beta power decrease ipsilateral to the relevant response hand when anticipating an inhibition (Liebrand et al., 2017) supports the significance of beta in motor planning. Moreover, it suggests that the activation of the ipsilateral motor cortex or activity differences between ipsi- and contralateral motor cortex are important for motor preparation. Also sensorimotor mu power, and not beta alone, seems to be relevant for proactive motor control. Prestimulus mu has been shown to be elevated before commission errors in a go-nogo task, indicating

that these errors might result from decreased motor cortex excitability already before target presentation (Mazaheri et al., 2009).

Prefrontal and sensorimotor cortex can be assumed to form a network, probably involving the basal ganglia (Aron, 2011), mediating inhibitory motor control. This asks for a network approach to characterize neural dynamics and connectivity changes related to proactive motor control. A putative marker for information flow within neural networks is phase-coupling (Fries, 2005). During recent years, phase synchrony has increasingly attracted attention as a measure of both local computations (Singer and Gray, 1995) and largescale integration (Fries, 2005), subserving cognitive functions as attention (Sadaghiani et al., 2012), motor control (van Wijk et al., 2012; Krämer et al., 2013) or memory (Fell and Axmacher, 2011). It has been shown that interhemispheric fronto-frontal and intrahemispheric fronto-central theta and alpha phase coupling is increased when motor output has to be inhibited (Shibata et al., 1997; 1998; Ruiz et al., 2009). Moreover, alpha coupling is aberrant in patients with movement disorders, such as musician's dystonia (Ruiz et al., 2009) and Parkinson's disease (Silberstein et al., 2005), but also Tourette's syndrome (Serrien et al., 2005). Also, prestimulus alpha coupling seems to have an impact on behavior, as interhemispheric coupling correlated negatively with reaction times in a go-nogo-task (Vecchio et al., 2014).

To sum up, converging evidence from invasive and noninvasive EEG-studies speaks for specific modulations of sensorimotor mu/beta and prefrontal beta oscillations when pro- or reactively inhibiting motor output. Critically, most studies on proactive and reactive motor control focused on motor inhibition using variants of the classical go/nogo and stop-signal tasks. In these studies a prepotent standard motor action has to be cancelled when nogo- or stop-signals appear. This has its limitations though, since everyday life rarely calls for the complete suppression of actions but rather behavioral adjustments and execution of alternative actions (for review see Böcker et al. (2013)). Often one action has

to be inhibited (e.g. pushing the gas pedal), while another action is executed at the same time (e.g. pushing the brake). This can be studied with change-stop tasks (Logan, 1994), as for instance the change-signal paradigm (Brown and Braver, 2005; Krämer et al., 2011). In those tasks, in change-trials a frequent motor action has to be inhibited and replaced with an alternative motor response. However, there is sparse knowledge about the neural network dynamics underlying the preparation to change.

Extending our previous results, we were interested in what role sensorimotor mu and beta play in preparing to switch actions and as to whether the inhibition-related prefrontal beta effects generalize to action change. We developed a cued go-nogo-change task, in which cues indicated that participants might have to inhibit the standard go response (button press with one hand), might have to switch to a different response (button press with the other hand) or have to give the standard response with certainty.

Based on the DMC framework, above-mentioned findings and our previous study, we focused on oscillatory activity (mu/beta) over sensorimotor and prefrontal regions and on network interactions. For the cue-target interval, when preparing to possibly inhibit or change one's action, we expected a decrease of ipsilateral mu/beta replicating and extending our previous study. We hypothesized prefrontal beta to increase after target presentation, both if the standard action had to be inhibited or changed. As increased alpha phase coupling between prefrontal and central sites has been observed when actually inhibiting a motor response (Ruiz et al., 2009), we expected similarly increased connectivity when preparing to adapt one's action.

4.2 Methods

4.2.1 Subjects

Twenty-eight participants took part in the study. One participant was excluded due to mixed-handedness and five participants had to be excluded due to extensive EEG artifacts

(further explanation given below). All of the remaining 22 participants (20-32 years, mean: 24.8 years, 15 women) were right-handed and by self-report free of neurological or psychiatric disorders. The participants had normal or corrected to normal vision. They gave informed consent and received money (8€/h) or course credit for participation. The study was performed in agreement with the Declaration of Helsinki and had been approved by the ethics committee of the University of Lübeck.

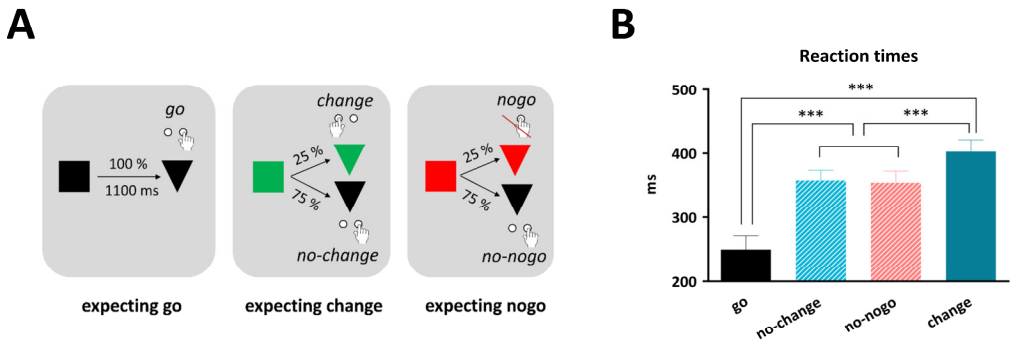


FIGURE 4.1 | Design and behavioral results. (A) Design of the cued go-nogo-change task. In expecting go-trials, the cue (black square) was always followed by a black triangle, indicating a right button press. In expecting change-trials, the cue (green square) was followed in 75% by a black triangle, indicating a right button press and in 25% by a green triangle, indicating a left button press. In expecting nogo-trials, the cue (red square) was followed in 75% by a black triangle, indicating a right button press and in 25% by a red triangle, indicating no button press. In the second half of the experiment, the matching of the response buttons was reversed (meaning expecting go-trials required a left button press etc.). (B) Reaction times. Mean reaction times in ms in go-, no-change-, no-nogo- and change-trials. As error bars the standard error of the mean (SEM) is depicted. Participants responded faster in go- than no-change-/no-nogo- than change-trials. Significant effects are indicated with asterisks (* for ≤ 0.05, ** for ≤ 0.01, *** for ≤ 0.001).

4.2.2 Design and Stimuli

The participants performed in a cued go-nogo-change-task (Figure 4.1A). The experiment included three different conditions: expecting go (EG), expecting change (EC), and expecting nogo (EN). Each condition occurred with the same probability (33%). In all trials, a cue (square) appeared first, indicating the condition, followed by a target (triangle) which signaled the action to be performed. In expecting go-trials, a black square appeared first, which was always followed by a black triangle. The participants were instructed to press the right button with their right index finger once the triangle had appeared (go condition).

Expecting change-trials began with a green square, followed either by a black or a green triangle. If the green square was followed by a black triangle (75% of the expecting change-trials), the participant had to press the right button (no-change condition). Once the green square was followed by a green triangle (25% of the expecting change-trials), the participant was supposed to press the left button with the left index finger (change condition). Expecting nogo-trials started with a red square, followed either by a black or a red triangle. In case the red square was followed by a black triangle (75% of the expecting nogo-trials), the participant had to press the right button (no-nogo condition). Once the red square was followed by a red triangle (25% of the expecting nogo-trials), the participant was supposed to refrain from pressing any button (nogo condition). In no-change- and no-nogo-trials, participants thus were prepared to cancel or change the motor response, but had to execute the standard action finally. In nogo- and change-trials, participants actually had to switch their standard behavior to an alternative action or to no action. Our choice for a low percentage of nogo-trials is in line with a recent study, suggesting that fast-paced go/nogo tasks with low share of nogo-trials are best suited to capture activity actually related to motor inhibition (Wessel, 2018).

The cue (square) was presented for 100 ms. After an inter-stimulus interval of 1 s, the target (triangle) followed, which was also shown for 100 ms. The time between two subsequent trials was jittered (1.3 to 1.6 s). The experiment was divided into 6 blocks with 160 trials each, resulting in 960 trials. After half of the experiment (3 blocks), the assignment of the response hands was switched, meaning that participants were instructed to press the left button according to the black triangle and the right button in reaction to the green triangle (left handed blocks, LHB). The assignments of response hands of the first and second half were counterbalanced among participants. Half of the participants started with three blocks in which right handed actions were standard (right handed blocks, RHB), the other half with three blocks, in which left handed actions were standard (LHB). Before the start

of the experiment, the participants practiced the task in two short blocks with 12 trials each, using both hands as standard actions. Throughout the whole experiment, a line was presented underneath the stimuli, which participants were instructed to fixate. Participants were told to respond as fast and accurately as possible and not to press the button until the triangle had appeared.

4.2.3 Procedure

The experiment was controlled using the Presentation® software (Version 14.5). Stimuli were presented on a 17" screen, about 1 m away from the participant. Participants were sitting in a comfortable chair. In the middle and at the end of each block they had a short break of 20 s to relax. The total duration of the experiment was about 50 min.

4.2.4 EEG Recordings and Data Preprocessing

The EEG was recorded with a 64-channel BrainAmp MR plus amplifier with a sampling rate of 250 Hz, resolution of 0.1 μV and a 0.1-250 Hz pass band. Electrodes were placed according to an extension of the international 10–20 system (Nuwer et al., 1998). Vertical and horizontal eye movements (vEOG and hEOG) were recorded, the former using an electrode placed below the right eye and a frontopolar electrode, the latter using electrodes located on the outer canthus of each eye. The EEG was recorded against a reference electrode placed on the right earlobe.

4.2.5 Behavioral Data Analyses

Mean reaction times, hit rates and premature responses were computed for each subject and submitted to repeated measures ANOVAs with the within-subject factor Condition (go, no-change, change, no-nogo) and to subsequent paired-sample t-tests.

4.2.6 EEG Data Analyses

EEG data analysis was performed with EEGLAB (Delorme and Makeig, 2004) and custom written MATLAB (Natick, MA) scripts. EEG data were re-referenced offline to the average of the signal from the two earlobe electrodes. The data were high-pass filtered with 0.5 Hz in addition to a notch filter of 50 Hz. The data were segmented into epochs for the different conditions. Epochs included 1 s before and 2 s after the stimulus. The baseline was defined as the 100 ms preceding the stimulus. An Independent Components Analysis (ICA) as implemented in EEGLAB (Infomax extended), was performed on the segmented data including all conditions. Independent components accounting for blink artifacts and horizontal eye movements were visually identified and removed from the data (mean 2.7, range: 1-4 per subject) (Jung et al., 2000). Additionally, trials affected by other artifacts caused e.g. by muscle tension were rejected from further analysis using an amplitude threshold rejection of ±80 μV. If more than 30% of the data of one participant were rejected, this subject was excluded from analysis (five subjects). Current source density interpolation of the data was estimated through a spatial Laplacian transform based on a spherical spline interpolation (using a spline order of 4) (Kayser and Tenke, 2006) using a current density toolbox for MATLAB (Kayser, 2009). We took advantage of the Laplace transformation, as it improves the spatial resolution of EEG, especially in combination with high density recordings (≥ 64 electrodes) (Babiloni et al., 1995).

4.2.6.1 Time-Frequency Analysis

To study the inhibition related power changes in the alpha (9-14 Hz) and beta band (15-25 Hz), single trial data were convolved with a complex Morlet wavelet as implemented in MATLAB (function cwt with parameter specification ‘cmor1-1.5’):

$$w(t) = (\pi f_b)^{-0.5} e^{-2\pi i f t_c} e^{-\frac{t^2}{f_b}}$$

Where $f_b = 1$ was the bandwidth parameter and $f_c = 1.5$ was the wavelet center frequency (Teolis, 1998). Specifically, we computed and averaged for each subject, changes in time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (1-40 Hz, linear increase) with respect to a pre-stimulus baseline (-250 to -50 ms prior to the stimulus). The selection of the analyzed alpha/mu (9-14 Hz) and beta (15-25 Hz) frequencies was based on visual inspection of the data and previous literature (Krämer et al., 2011; Solbakk et al., 2014; Liebrand et al., 2017). In order to reduce the number of statistical comparisons and to increase the signal-to-noise ratio, we clustered the electrodes into regions of interest: Left prefrontal (F3, F5, FC3, FC5), right prefrontal (F4, F6, FC4, FC6), left central (C3, C5, CP3, CP5) and right central (C4, C6, CP4, CP6), based on previous studies (Krämer et al., 2013; Liebrand et al., 2017) .

Effects over prefrontal and sensorimotor electrodes were analyzed differently. For motor related effects (sensorimotor mu and beta) data of left handed blocks (LHB) were flipped along the midline. This allowed for analysis of effects dependent on the side (contra- vs. ipsilateral) relative to the response hand. For prefrontal effects (beta power) no lateralization relative to the response hand was expected. Thus data were not flipped and we compared data over left and right hemisphere. For all effects, trials of RHB and LHB blocks were averaged.

4.2.6.1.1 Analysis of the Cue-Target Interval

For analysis of the cue-target interval, we subjected mean power of 100-ms intervals between 200 and 1100 ms to paired-sample t-tests comparing conditions separately for the contralateral and ipsilateral or right and left hemisphere. Intervals with length of 100 ms were chosen as a balance between providing fair temporal resolution on the one hand while not ending up with a large number of statistical tests on the other hand. We only considered effects after 200 ms to exclude the time where subjects visually processed and

evaluated the cue before they were able to prepare for the later button press. We accounted for multiple comparisons with the false discovery rate (FDR) method using a q-value of 0.05 (Benjamini and Hochberg, 1995).

4.2.6.1.2 Analysis of Target-Related Effects

For effects following the target stimulus (prefrontal beta) mean time-frequency power in the time-window between 200-500 ms was subjected to repeated measures ANOVAs with the within-subject factors Condition (see results) and Hemisphere (left- vs. right). The time-window was based on a previous study (Liebrand et al., 2017), focusing on the period when participants were executing the motor response. For all statistical effects involving more than two degrees of freedom, the Greenhouse–Geisser correction was applied to correct for possible violations of the sphericity assumption (Greenhouse and Geisser, 1959). We report the uncorrected degrees of freedom and the corrected probabilities.

4.2.6.1.3 Phase-Coupling Analysis

Additionally, we analyzed phase-coupling between electrodes as a measure of neural connectivity. We computed the phase relation between electrodes as phase-locking value (PLV) following Lachaux et al. (1999):

$$\mathrm{PLV}_{e1e2} = \frac{1}{N}\left|\sum \exp(i[\phi_{e1} - \phi_{e2}])\right|$$

with N being the number of time trials and ϕ_{e1} and ϕ_{e2} being the instantaneous phase of electrodes 1 and 2. The instantaneous phase was calculated via the Hilbert transform. We were interested in phase coupling in the cue-target interval and investigated the alpha (9-14 Hz) band, as this has been linked to top-down processing (von Stein et al., 2000; Sadaghiani et al., 2012) and inter-regional connectivity in motor control studies (Shibata et al., 1997; 1998; Ruiz et al., 2009). We analyzed the time-window directly preceding the target (900-1100 ms) to capture preparatory connectivity and exclude stimulus-driven

effects. We investigated sensorimotor alpha coupling and computed the PLV for electrodes C3 and C4 with all other electrodes. As the PLV values were not normally distributed, condition effects were evaluated with the Wilcoxon signed rank test and corrected for multiple comparisons with the FDR method.

4.2.6.1.4 Relevant Contrasts in the Analysis

As measure for proactive inhibition in the cue-target interval, we contrasted trials in which the later motor response might have to be changed/inhibited (expecting change/nogo) to trials which did not require an adaptation (expecting go). To assess how proactive inhibition modulated response execution after target signals, we compared trials in which participants were prepared to execute the standard motor response (go-trials) with trials in which participants were prepared to switch to an alternative motor plan but finally had to give the standard response (no-change- and no-nogo-trials; for this account also see Swann et al. (2012); Swann et al. (2013)). To assess correlates of reactive inhibition, we contrasted trials in which the response actually had to be changed/inhibited (change-/nogo-trials) with trials in which the standard response was given (no-change-/no-nogo-trials). For a brief summary of the contrasts used in this study see Table 4.1.

Cue-target interval	
expecting change vs. expecting go	Preparation to change a standard motor response
expecting nogo vs. expecting go	Preparation to inhibit a standard motor response
expecting change vs. expecting nogo	Differential activity between preparing to change or inhibit a standard motor response
Target-related effects	
No-change/no-nogo vs. go	Preparation to change/inhibit a standard motor response (after target signals but proactive)
No-change/no-nogo vs. nogo/change	Implementation of a change or inhibition of a standard motor response (reactive)

TABLE 4.1 | Overview of utilized contrasts in the study. The first three contrasts reflect proactive effects taking place in the cue-target interval. The latter two contrasts reflect effects taking place after target onset. Thereby the upper contrast reflects a proactive effect and the lower a reactive effect.

4.3 Results

4.3.1 Behavioral Results

Reaction times differed between conditions ($F_{3,63}$ = 119.5, $p < 0.001$). Participants were faster in go-trials (250±100 ms) than in no-change-trials (358±76 ms; t_{21} = 11.3, $p < 0.001$), no-nogo-trials (354±84 ms; t_{21} = 12.1, $p < 0.001$) and change-trials (403±88 ms; t_{21} = 14.2, $p < 0.001$) (Figure 4.1B). Furthermore, they were faster in no-change- compared to change-trials (t_{21} = 5.4, $p < 0.001$) and faster in no-nogo- than in change-trials (t_{21} = 6.5, $p < 0.001$). There was no difference between no-change- and no-nogo-trials (t_{21} = 0.9, $p = 0.382$).

Accuracy was nearly at ceiling in no-change- (98%) and no-nogo- (99%) trials. It was reduced in change- (91%), go- (90%) and nogo- (87%) trials. Premature errors (button presses before the target stimulus) were committed more often in the expecting go (EG) condition (9.8%) than in expecting change (EC)- (0.45%) and expecting nogo (ES)- (0.34%) trials ($F_{4,84}$ = 24.8, $p < 0.001$; EG vs. EC: t_{21} = 5.0, $p < 0.001$, EG vs. ES: t_{21} = 5.0, $p < 0.001$, EC vs. ES: t_{21} = 0.8, $p = 0.432$). There were more choice errors and omissions in change- vs. go-trials (choice errors: t_{21} = 4.3, $p < 0.001$; omissions: t_{21} = 2.4, $p = 0.025$). Participants failed to inhibit in 13% of nogo-trials.

4.3.2 Results of the Cue-Target Interval

4.3.2.1 Mu and Beta Power over Sensorimotor Cortex

To investigate the role of the sensorimotor cortex in proactive motor control, we analyzed mu (alpha) (9-14 Hz) and beta (15-25 Hz) activity over central sites. We subjected mean mu/beta power of 100-ms intervals between 200 and 1100 ms to paired-sample t-tests comparing different conditions separately for the contralateral and ipsilateral sensorimotor cortex to the standard motor response. Correction for multiple comparisons was applied using the FDR method. Mu was centered above bilateral motor cortex and differed between the three conditions and both sensorimotor clusters (Figure 4.2C). Over

the contralateral motor cortex mu decreased in all three conditions constantly over the whole cue-target interval towards movement onset (Figure 4.2A). In an early time-interval after cue-onset, contralateral mu decreased more in expecting go- (EG) than expecting nogo- (ES) trials (200-700 ms; all $t_{21} < -2.7$, $p < 0.01$) and more in EG than expecting change (EC) (300-700 ms: all $t_{21} < -2.7$, $p < 0.01$) while there was no difference between EC and EN (all $t_{21} < 0.9$, $p > 0.39$). Over the ipsilateral motor cortex mu increased in the EG condition, remained around baseline-level in EN-trials and decreased in EC-trials. In an interval starting well before target-onset and lasting until movement onset, ipsilateral mu decreased more in EC- than EG-trials (400-1100 ms; all $t_{21} < -2.5$, $p < 0.02$) and EN- than EG-trials (500-1100 ms; all $t_{21} < -2.7$, $p < 0.01$). Mu also decreased more in EC than EN (600-1100 ms; all $t_{21} < -3.1$, $p < 0.01$).

Beta activity over the sensorimotor cortex showed generally comparable effects to the pattern in the mu band (Figure 4.2). Over the contralateral sensorimotor cortex, beta decreased more in EG- than EN-trials (200-700 ms, 1000-1100 ms; all $t_{21} < -2.4$, $p < 0.03$), whereas there was no difference between EC- and EG-trials (all $t_{21} < 2.5$, $p > 0.02$) nor between EC- and EN-trials (all $t_{21} < 2.7$, $p > 0.01$). Over the ipsilateral sensorimotor cortex, beta decreased more in EC than EG (400-1100 ms; all $t_{21} < -3.2$, $p < 0.005$) and more in EC than EN (400-1100 ms; all $t_{21} < -2.8$, $p < 0.01$). There was no difference between EG and EN (all $t_{21} < 2.9$, $p > 0.008$).

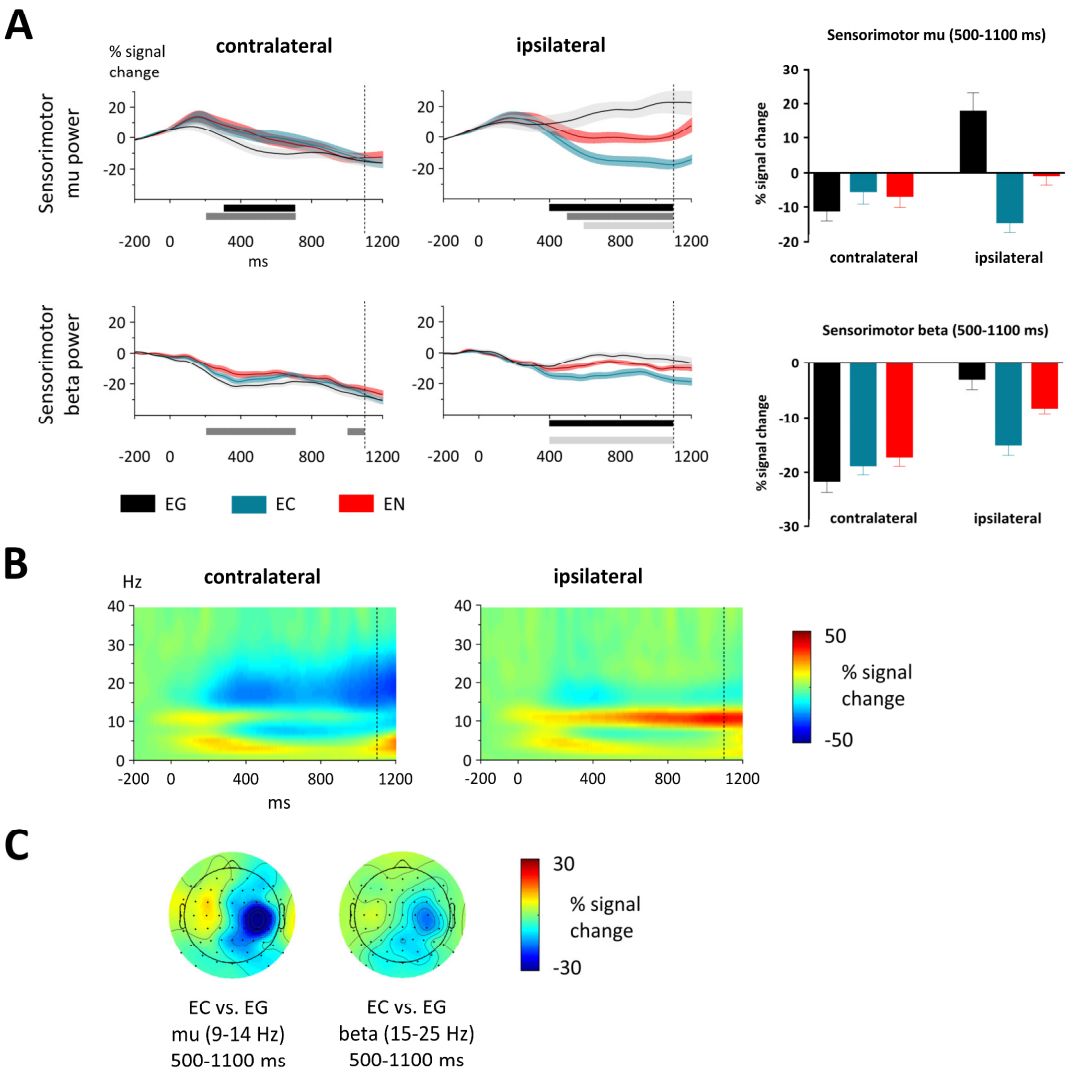


FIGURE 4.2 | **Sensorimotor effects in the cue-target interval.** (A) On the left timecourses of mu (9-14 Hz) and beta (15-25 Hz) power at contralateral and ipsilateral sensorimotor clusters in relation to the standard motor response are displayed. The modulation of mu power was strongest over the ipsilateral hemisphere. Between 500-1100 ms mu increased in expecting go (EG), was around baseline in expecting nogo (EN) and decreased clearly in expecting change (EC). As shaded area around the mean, the SEM is displayed. Target onset was at 1100 ms (dotted line). Horizontal bars under the time axis highlight time-windows with significant differences between conditions. Black bars highlight windows where EG & EC significantly differed, dark grey bars where EG & EN differed and light grey bars where EN & EC differed. To the right bar graphs show mean mu/beta power between 500-1100 ms at contralateral and ipsilateral sensorimotor sites. As error bars the SEM is depicted. Significant differences are stressed with asterisks. (B) Time-frequency plots of activity in the EG condition at contra- and ipsilateral sensorimotor clusters. (C) The topographic plots show the scalp distribution of the mean signal change (500-1100 ms) as differences between EC and EG. All data in this figure is flipped along the midline.

4.3.2.2 Beta Power over Prefrontal Cortex

Mean beta power in prefrontal clusters in the right and left hemisphere between 200 and 1100 ms in intervals of 100 ms was subjected to paired-sample t-tests comparing different conditions (FDR correction was applied). Over prefrontal electrode sites, we found decreased beta power in EC- than EG-trials in the right hemisphere (500-700, 900-1000 ms: all $t_{21} > 2.8$, $p < 0.01$). There was no difference between EN- and EG-trials (all $t_{21} < 2.6$, $p > 0.02$), nor between EC- and EN-trials (all $t_{21} < 2.3$, $p > 0.03$).

4.3.2.3 Fronto-Central Alpha Phase-Coupling

We computed phase synchrony in the alpha (9-14 Hz) band for connections from bilateral motor sites to all other electrodes. We analyzed the time-window between 900-1100 ms, when target onset was closest and cue-related effects were most distant. We observed decreased synchrony in EC- than EG-trials (Figure 4.3) from ipsilateral motor cortex to prefrontal and central sites mostly in the ipsilateral hemisphere (8 connections; all $z > 2.8$, $p < 0.045$). One connection showed decreased coupling EC- compared to EN-trials (ipsilateral motor cortex to F5/F6; $z = 3.5$, $p < 0.001$). There was no effect for the contralateral side. No differences between EN- and EG-trials were found.

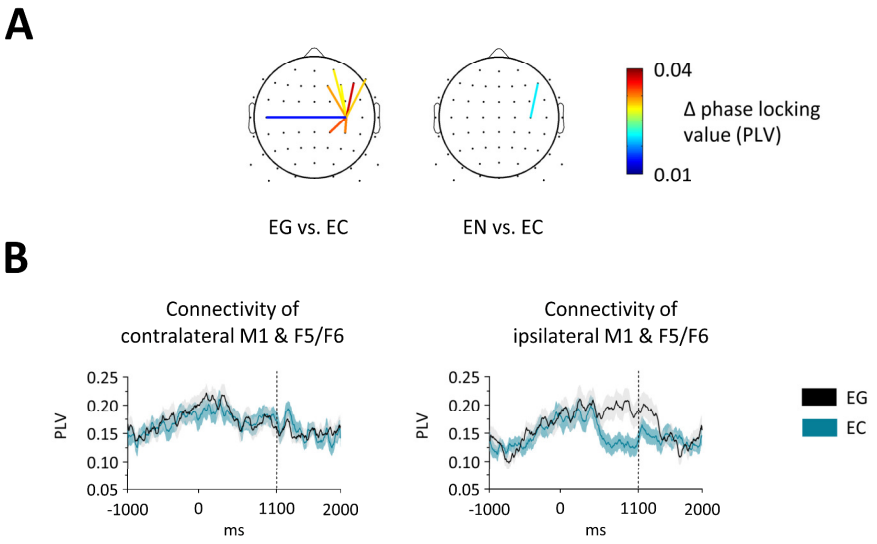


FIGURE 4.3 | Alpha coupling effects. (A) Alpha coupling between 900-1100 ms is shown. Displayed connections show significantly increased coupling from ipsilateral motor cortex to corresponding electrodes for EG- compared to EC-trials and for EN- compared to EC-trials. (B) Exemplary time-courses of the PLV. On the left, synchrony between contralateral motor cortex and a same-side prefrontal electrode (F5/F6) and on the right synchrony between ipsilateral motor cortex and a same-side prefrontal electrode (F5/F6) is displayed. Note that there was a significant difference for connectivity to ipsilateral but not to contralateral M1.

4.3.3 Target-Related Results

4.3.3.1 Beta Power over Prefrontal Cortex

As there is evidence for prefrontal regions to be implicated in proactive and reactive motor control after target signals, we were interested in the modulation of prefrontal beta power when implementing the change or inhibition. We subjected mean prefrontal beta activity between 200 and 500 ms to ANOVAs with the factors Condition and Hemisphere (left, right). One participant showed extreme beta power compared to other subjects (> 10 SD above mean value) in change-, nogo- and no-change-trials and therefore was removed from the statistics which are reported below.

First, we were interested in whether the context of being prepared to change or inhibit a standard motor action modulates beta power over prefrontal electrodes, even if that possibility is not realized (proactive changing/inhibition after target signals). Therefore we compared trials in which participants were cued to possibly adapt their behavior, but executed the standard response (no-change-, no-nogo-trials) with go-trials (Figure 4.4A, first row). Prefrontal beta was increased in no-change- and no-nogo- compared to go-trials (Condition: $F_{2,40} = 9.2$, $p = 0.002$; no-change vs. go: $F_{1,20} = 11.4$, $p = 0.003$; no-nogo vs. go: $F_{1,20} = 17.5$, $p < 0.001$; no-change vs. no-nogo: $F_{1,20} = 1.0$, $p = 0.318$). Second, we tested if prefrontal beta increases, when the standard response has to be changed or inhibited (reactive changing/inhibition) (Figure 4.4A, second row). Beta power was higher, when participants actually had to update their response (change/nogo), in comparison to trials where they did not have to update (no-change/no-nogo) ($F_{1,20} = 9.7$, $p = 0.005$) and in

comparison to go-trials (Condition: $F_{2,40} = 9.0$, $p = 0.001$; change vs. go: $F_{1,20} = 21.5$, $p < 0.001$; nogo vs. go: $F_{1,20} = 10.4$, $p = 0.004$; change vs. nogo: $F_{1,20} = 0.2$, $p = 0.632$). As prefrontal activity has been associated with motor slowing (Wessel et al., 2013; Aron et al., 2014a), we were interested if prefrontal beta power was correlated with reaction times. However, neither beta power nor beta power differences between conditions correlated significantly with reaction times or reaction time differences.

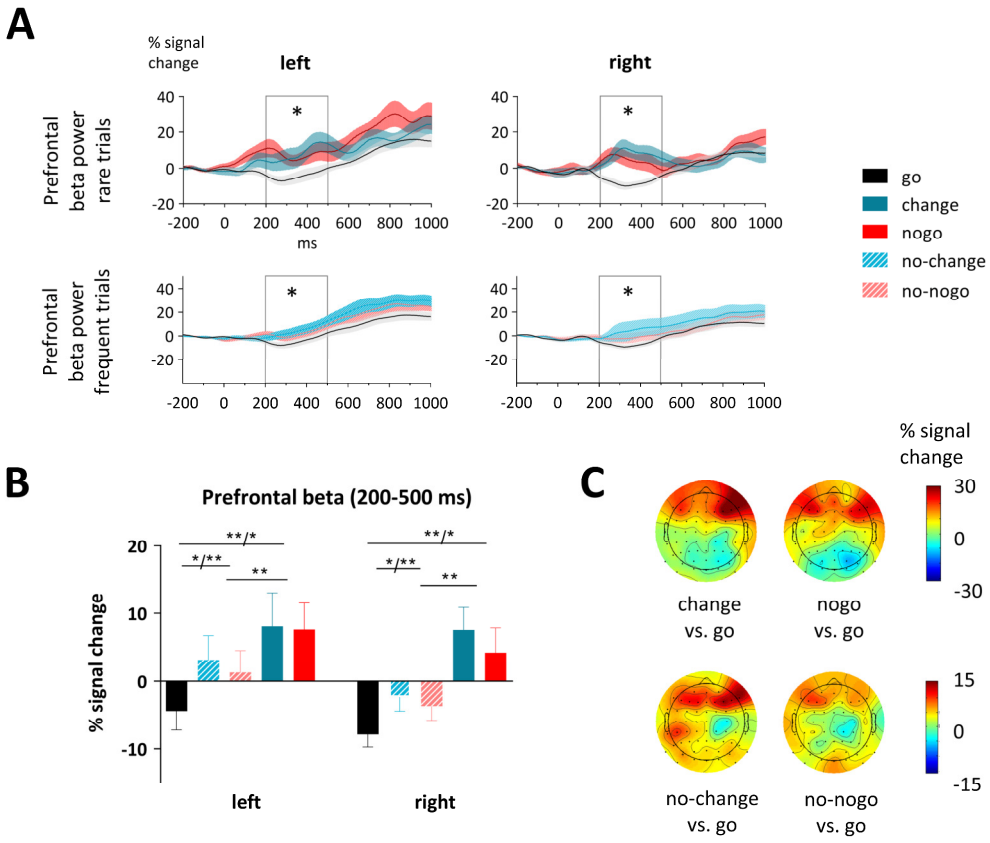


FIGURE 4.4 | Target-evoked prefrontal beta power (15-25 Hz). (A) Timecourse of beta power at left and right prefrontal clusters. As shaded area the SEM is displayed and the time-window we analyzed (200-500 ms) is marked with a grey box. Significant differences are indicated with asterisks. (B) At both left and right prefrontal clusters beta power was higher in change- and nogo- than no-change-/no-nogo-trials and lowest in go-trials. As error bars the SEM is depicted. (C) Topographic plots show the scalp distribution of the mean signal change (200-500 ms) in the beta band as difference between conditions.

4.4 Discussion

We investigated the oscillatory mechanisms associated with proactive motor control in a cued go-nogo-change task. In the paradigm, cues signaled participants to possibly change or inhibit a subsequent standard motor action. We found that in the cue-target interval, sensorimotor mu and beta activity differentiated a possible upcoming change from an inhibition and from a standard motor action. This modulation was strongest for sensorimotor mu ipsilateral to the hand of the standard button press. Activity in the mu band was consistent with a role of mu to selectively inhibit/disinhibit relevant neural populations (for reviews see Klimesch et al. (2007); Jensen and Mazaheri (2010)) in preparation for upcoming behavior. During preparation to change, the ipsilateral motor cortex seems to be decoupled from prefrontal control. This was suggested by decreased alpha phase-coupling from ipsilateral prefrontal to motor cortex when participants anticipated the change. When implementing an action adaptation, beta power over prefrontal regions increased, speaking for a phasic increase of cognitive control when actually needed.

4.4.1 Behavioral Effects

In trials, in which participants were prepared to withhold or change their motor response (no-nogo-, no-change-), they slowed down in comparison to go-trials where inhibition was not required. This proactive slowing is in line with several other studies (Verbruggen and Logan, 2008; Jahfari et al., 2012; Zandbelt et al., 2013b; Vink et al., 2015; Liebrand et al., 2017) and facilitates action inhibition or changing when needed. Participants slowed down most when they actually had to change their motor action to an alternative response (Rangel-Gomez et al., 2015). In sum, behavioral results show that participants prepared for upcoming inhibition or change of motor actions, and our experiment therefore successfully elicited proactive motor control.

4.4.2 Sensorimotor Activity

As the motor cortex is the final gate of motor control, it seems a likely target area to be modulated by a context in which proactive control is implemented. With this study, we provide evidence that ipsilateral sensorimotor mu and beta are modulated by the anticipation of motor adaptation and by uncertainty as to which motor action has to be performed. During the cue-target interval, mu power over the sensorimotor cortex contralateral to the standard performing hand decreased in all three conditions (expecting go/nogo/change). This is in line with previous studies which found mu to decrease in preparation of upcoming motor actions (Babiloni et al., 2004; Kajihara et al., 2015; Tzagarakis et al., 2015), possibly providing a sensory gating mechanism for motor preparation or anticipation of sensory input (Cheyne, 2013) and reflecting disinhibition of relevant neural populations (for reviews see Klimesch et al. (2007); Jensen and Mazaheri (2010)). This hypothesis is supported by results from a TMS study, in which MEPs were elicited more easily when mu power over cortical motor areas immediately before stimulation was low, and vice versa (Sauseng et al., 2009). The exact mechanism how mu suppression is implemented on a neural level still needs to be clarified. Some evidence points to involvement of the basal ganglia, as the degree of suppression has been linked to bradikinesia in PD patients and as the reduced ability to suppress mu in patients seems to recover with dopamine medication (Brown and Marsden, 1999; Wang et al., 1999). Also, it has been suggested that prefrontal cortex modulates mu activity downstream (Pineda, 2005). However, further studies are needed to delineate critical nodes causing mu suppression.

In a rather early time-window (300-700 ms), contralateral mu decreased to a greater degree when subjects prepared a standard motor action (expecting go) compared to preparing both the standard action and an infrequent action (expecting change) or to cancel the response (expecting nogo). This modulation seems to reflect the higher certainty the

standard motor action could be anticipated (100% in expecting go vs. 75% in expecting change/nogo), leading to a stronger disinhibition of neurons involved in movement preparation. Interestingly however, the strongest difference in mu between conditions was on the ipsilateral side. Here, mu increased when subjects prepared the standard motor action, decreased when they prepared to change and was around baseline level when they prepared to inhibit. Based on the above outlined idea of the inhibitory nature of alpha oscillations (Jensen and Mazaheri, 2010), the increase in expecting go-trials can be interpreted as inhibition of task-irrelevant areas, whereas the decrease in expecting change-trials might reflect the disinhibition of neural assemblies relevant for the possible upcoming change. If this was the case, mu power should be also increased in the expecting nogo condition, since similarly to the expecting go condition the ipsilateral motor cortex was irrelevant. However, this was not the case. A possible explanation is that ipsilateral mu plays an active role in motor preparation and inhibition via interhemispheric connections. Increased inhibition of the ipsilateral motor cortex in expecting go-trials might thereby facilitate action execution. Reduced inhibition as in expecting nogo-trials on the other hand would facilitate an inhibition of the contralateral side when the motor response has to be canceled later. Generally, interhemispheric inhibition seems to be important for motor control (Beaule et al., 2012; Genc et al., 2015). Our reasoning is supported by a TMS study, which showed that left premotor cortex is involved in withholding and releasing a preselected movement generated by the right motor cortex (Kroeger et al., 2010). The relevance of mu oscillations in the ipsilateral motor cortex for unimanual motor preparation and selection is further supported by a recent transcranial alternating current stimulation (tACS) study reporting reduced reaction times in a movement selection task when stimulating the ipsilateral hemisphere with 10 Hz (Brinkman et al., 2016). tACS is a very novel technique, thought to entrain local brain activity in an oscillatory manner, here in the alpha band, and thereby having an impact on

behavior (Herrmann et al., 2013). Still, the relationship between tACS and underlying neural oscillations remains to be established. Summarizing, our findings demonstrate that the action preparation context drives ipsilateral motor cortex activity reflected in a flexible modulation of mu oscillations.

Our findings of beta power resemble those in the mu band. Importantly, similar to mu, beta was strongly modulated over ipsilateral motor cortex. Over this side however, we did not find a differentiation between expecting go- and expecting nogo-trials. Our data therefore suggests that beta reflects movement preparation less specifically than mu. A recent study found contralateral beta but not mu to reflect the directional specificity of hand movement preparation (Tzagarakis et al., 2015). Also in our cued go-nogo task, we observed a modulation of beta power by proactive inhibition over the ipsilateral motor cortex (Liebrand et al., 2017). However, these two experiments differed from the present paradigm. In the former only right-handed movements were required and movement selection pertained to movement direction and not response hand as in the present study. The cued go-nogo task required frequent switches between response hands whereas response hand switches occurred in only about 8% of all trials in the current paradigm. Moreover, in another study, contralateral beta immediately before target signals was not found to be modulated by how much information about an upcoming action was presented by a preceding cue (Zaepffel et al., 2013). It thus remains controversial how beta reflects motor preparation and movement selection. Summarizing our sensorimotor results, the present data suggest that mu might be particularly relevant for movement selection involving both hemispheres and thus for interhemispheric connectivity.

4.4.3 Sensorimotor Coupling

Whereas changes in frequency-specific power at a specific region are thought to reflect local processing of information, phase coupling might represent connectivity across

regions (Fries, 2005). Specifically, alpha phase locking across regions is argued to reflect information transfer (Daume et al., 2016). Based on previous findings of reactive inhibition (Shibata et al., 1997; 1998; Ruiz et al., 2009), we hypothesized that alpha phase-coupling between prefrontal and motor cortex would be increased when subjects prepare to cancel or change actions. In contrast, we observed decreased coupling between ipsilateral prefrontal regions and the ipsilateral motor cortex when subjects prepared to change. First, this results speaks for different mechanisms taking place in proactive and reactive processes. Second, it suggests that preparing to change an action involves a relative decoupling of the ipsilateral motor cortex from prefrontal control. Also beta power over prefrontal regions decreased when subjects prepared to change, indicating diminished cognitive control. In line with this notion, connectivity in the alpha band has been linked to top-down processing (von Stein et al., 2000; Sadaghiani et al., 2012). A recent study reported alpha decoupling of fronto-central regions when inhibiting execution of a well-trained motor sequence and no such effect for inhibition of a novel sequence (Sauseng et al., 2013). Based on this finding, the authors suggested that alpha oscillations and decoupling might serve the context-dependent inhibition of motor memory. It has also been shown that alpha coupling between mesial frontocentral areas and the primary motor cortex is reduced when novel compared to memorized sequences of complex sequential finger movements have to be executed (Bönstrup et al., 2014). Our findings are in line with these studies, all demonstrating a link between motor memory and fronto-central coupling. Our data extends these studies in showing that alpha/mu decoupling might not only become relevant when implementing more complex movement sequences. Instead, mu decoupling was found already when participants had to prepare for a less automatized action.

4.4.4 Correlates of Prefrontal Control

When motor behavior needs to be adapted (e.g. changing or inhibiting it), the putative source of cognitive control modulating activity in sensorimotor regions is the PFC (Miller, 2000; Rae et al., 2015). A recent EEG study supports such a view, showing an increased negativity over PFC regions (pN), when deliberately deciding not to engage in a motor action (Bianco et al., 2017). Consistent with the notion of prefrontal beta as correlate of cognitive control (Buschman et al., 2012; Wessel et al., 2016b), target-related beta oscillations over prefrontal regions increased when participants had to change or cancel motor behavior. Moreover, beta increased, although to a lesser degree, when participants had been prepared to change or inhibit responses (no-change, no-nogo), but in the end did not have to. This finding suggests that prefrontal activity increases as a function of cognitive control, being higher when rare actions might have to be executed and highest when they actually have to be implemented. Importantly and in line with previous work (Swann et al., 2012; Swann et al., 2013; Zandbelt et al., 2013b; Vink et al., 2015; Liebrand et al., 2017), prefrontal activity increased only after target signals and not before. Moreover, as already discussed above, in the cue-target interval prefrontal beta power even decreased when participants prepared to change. In summary, this points to a twofold mechanism of cognitive control. Cognitive control is reduced to allow infrequent behavior to be prepared (Bönstrup et al., 2014) and increases during action adaptation, possibly to implement a break over motor response tendencies (Wessel et al., 2013; Aron et al., 2014a).

Our results provide evidence for prefrontal regions to be implicated in such motor braking, as corresponding to frontal beta, reaction times increased in no-change- and no-nogo- in contrast to go-trials and further increased when subjects had to change their motor action. However, we could not find any direct correlation between frontal beta and reaction times. Overall, this study adds to existing findings that frontal beta power increases not only when having to inhibit motor actions but also when implementing an infrequent action.

Thus, oscillatory dynamics (here in the beta band) can be regarded as a more generalized marker of top-down frontal cognitive control (Helfrich and Knight, 2016).

4.4.5 Conclusion

This study shows a task-specific modulation of sensorimotor mu/beta power in anticipation of motor action adaptation. Preparing to change or inhibit an upcoming action flexibly modulated mu power over the contralateral and especially over ipsilateral sensorimotor cortex. Moreover, alpha phase coupling between PFC and ipsilateral sensorimotor cortex was modulated proactively. This suggests that the ipsilateral motor cortex becomes decoupled from prefrontal regions when preparing to switch to an infrequent action. Prefrontal beta power increased when adapting one's actions reflecting a phasic increase of cognitive control. Overall, our results provide evidence for a crucial role of mu oscillations in ipsilateral motor cortex and a prefrontal-motor network when preparing for action adaptation.

5 General Discussion

The current thesis aimed to further our understanding of the neural networks underlying reactive and proactive inhibition. In three studies, I used EEG to investigate neural correlates of inhibitory behavior. The first study (Chapter 2) was targeted at delineating the time course of proactive and reactive cancellation of actions. Some work has been invested in exploring the underlying brain structures of proactive inhibition, but few studies attempted to disentangle preparation for and later implementation of inhibitory processes. Here, I took advantage of the high time resolution of EEG to study the temporal dynamics of both stopping modes in a cued go/nogo task. In a second study (Chapter 3), the specific importance of basal ganglia and prefrontal cortex on proactive and reactive inhibitory processes was tested using the cued go/nogo task established in Study I. Patients with lesions to one of these regions are of particular interest, since overwhelming evidence points to involvement of BG and PFC in motor inhibition. In contrast to most neuroscientific work, lesion studies offer the possibility to seek for causal rather than mere correlational evidence about cognitive processes. I was especially interested in preparatory processes, as to our knowledge no previous human lesion study investigated correlates of proactive motor inhibition. The third study (Chapter 4) was designed to move experimental investigations of inhibition closer to everyday life. In real life, the cancellation of actions rarely occurs without subsequent behavioral adjustment. I designed a novel paradigm where participants not only had to inhibit motor actions, but in some trials also had to switch to another non-standard response. I was specifically interested in oscillatory correlates of the preparation and actual implementation of stopping and switching to alternative behavior.

5.1 Summary of Findings from Healthy Subjects

In the first study, we investigated the temporal dynamics of cancelling a dominant motor response. We found that prefrontal, sensorimotor and occipital regions are involved in preparation for and later implementation of inhibitory signals. This shows that cognitive control, attentional mechanisms and sensorimotor processes are implicated in motor inhibition. Therefore, as evident from daily life, the pure inhibition of actions has to be regarded in interplay with related cognitive functions as attention and higher cognitive control.

In the third study, we confirmed our previous findings of the implication of prefrontal regions for anticipated and realized action cancellations. Moreover, PFC regions were similarly active when changing a standard motor response. Most importantly, this study shows that sensorimotor cortex acts as a gate, specifically preparing for upcoming actions and inhibitions. This result demonstrates an active role of the motor cortex in models of motor inhibition and motor control (for further discussion see below).

Generally, findings from the first study were replicated in elderly participants (Study II). Importantly, this validates our results and demonstrates them to be stable across different cohorts and age groups. Also, it shows that inhibitory performance is preserved with age. The proactive modulation of sensorimotor activity (beta power) observed in the first study was however not found in older subjects. This suggests that although general performance when inhibiting motor actions seemed to be intact, older subjects might rely on different neural mechanisms when implementing proactive inhibition. Still, effects of age on inhibitory processes were beyond the scope of the present thesis and we did not specifically compare different age groups.

5.2 Summary of Findings from Lesions to BG and PFC

Prefrontal cortex and basal ganglia are considered key structures in a network underlying motor inhibition. Evidence for the important role of these two regions is stemming from neuroimaging studies both in healthy subjects (Chambers et al., 2009; Aron, 2011; Ridderinkhof et al., 2011) and in patients with lesion to the BG (Rieger et al., 2003) and PFC (Aron et al., 2003; Picton et al., 2007; Swick et al., 2008; Krämer et al., 2013). Our data stands against these findings, as no differences between patients and controls on the behavioral and neural (with exception of the CNV) level were found. An important constraint of lesions studies is that they entail several limitations as low statistical power due to small sample size, heterogeneous lesion location or compensatory effects of impaired cognitive functions. One or several of these reasons might have contributed to observed null effects. We suggest that the main underlying reason for lack of differences between patients and controls is another, namely the experimental paradigm. Earlier studies reporting impaired stopping in patients either used the SST or faster paced go/nogo-tasks, which are likely more demanding than our paradigm. Therefore, our cued go/nogo task might not have been challenging enough for patients to reveal impaired motor inhibition. If this idea was true, results of our study would imply that simple forms of inhibition might be compensated in patients without fully intact BG and PFC. Compensation might be limited nevertheless, not extending to more demanding situations of motor inhibition. This however needs to be tested in future work.

5.3 Implications for Models of Proactive and Reactive Inhibition

Results of the studies detailed in this thesis have several implications on existing models on motor inhibition. First, our data strongly support the importance of alpha and beta oscillations in motor control and inhibition specifically. We showed that when preparing for and inhibiting motor actions, oscillations in the alpha and beta band are modulated at

multiple cortical sites. Present findings support the idea of a beta-driven cortico-basal ganglia network underlying inhibition. In all three studies, beta over prefrontal regions increased when an inhibition was prepared and further increased when the action actually had to be cancelled. These results support the hypothesis of PFC functioning as a "brake" (Aron et al., 2014a). This brake can be partially active, resulting in response slowing in proactive inhibitory contexts. Beyond that, the brake can be fully activated, leading to complete cancellation of motor actions. In situations of response conflict, meaning simultaneous activation of two or more motor responses, it has been proposed that the STN can but a pause on behavior (Aron et al., 2016), similar to the idea of a brake. This pause might reflect an increased decision threshold, representing further accumulation of upstream cortical evidence for a certain motor command. A network of PFC and STN has been proposed to underlie pausing when conflict arises, mediated by low-frequency oscillations (2-8 Hz). This concept of a pause in behavior might extend to proactive inhibition, a situation where conflict exists insofar as the upcoming motor action may be inhibited, but also may be not. In a condition, where motor actions might have to be cancelled, behavior similarly might be paused to prevent false responding in case of nogo-trials. Here, communication between PFC and basal ganglia, and thus abovementioned brake, might be realized by modulation of beta oscillations. This is, as increased beta accompanies situations of proactive slowing and further increases when actions actually have to be stopped. Additionally, our results demonstrate that alpha/mu also plays a significant role in motor inhibition. Alpha was modulated in a context of visual attention over occipital regions and in motor preparation over sensorimotor cortex.

Second, our studies question assumptions about the role of prefrontal regions in proactive inhibition. In all three studies we show that PFC regions, as reflected by prefrontal beta power, are modulated by proactive processes. However, no modulation was observed until the target signals appeared. Our data supports previous work suggesting that PFC nodes

are involved in proactive inhibition (Chikazoe et al., 2009; Jahfari et al., 2010). It however speaks against the idea that PFC regions are activated in advance of upcoming inhibitions (Chikazoe et al., 2009; Aron, 2011). Our data stands in contrast to these assumptions, as no differentiation between conditions was observed when anticipating stopping in the cue-target interval. PFC regions were differentially activated by preparation for stopping, but not before inhibition was actually implemented.

Third, Study III shows that in a more realistic context of motor inhibition, when cancelling one response and switching to another, similar mechanisms seem to be active as in simple stopping. Alike in a simple cancellation, oscillatory activity in prefrontal and sensorimotor regions was modulated. Thus, as suggested in Chapter 1, results from simple stopping seem to be generalizable to more complex situations of motor inhibition. The third study especially highlights the sensorimotor cortex in situations where several action alternatives are present.

This leads to the fourth point, namely that our studies underscore the importance of the sensorimotor cortex in frameworks of motor inhibition. In circuits of stopping much emphasis has been put on the right IFC (Aron et al., 2004b; Aron et al., 2014a), which together with pre-SMA and STN is thought be the critical hub for implementation of inhibition. The motor cortex is considered in such networks as final relay of inhibitory commands, but mostly is only mentioned in passing. Our results suggest it to be underestimated in its importance. In particular, Study III shows that sensorimotor cortex is involved in action preparation as a gate, selectively preparing for upcoming motor actions, inhibitions and changes. Motor cortex thus does not seem to be a passive recipient of upstream inhibitory signals, but is suggested to play much more of an active role in preparation of movements and upcoming cancellations of those. Such a view is supported by TMS studies showing an active involvement of M1 in both movement preparation (Duque et al., 2017) and inhibition (Stinear et al., 2009). For instance, one study stimulated

M1 using TMS, while subjects performed in an SST and recorded MEPs of the task relevant muscle. Here, the higher MEPs of the thumb muscle, and therefore activation of M1, the lower the probability of successfully inhibiting a motor response (van den Wildenberg et al., 2010a). These studies strengthen the role of M1 as active actor in proactive and reactive inhibitory processing.

Fifth, there is the question what we can learn from null results of data from patients about models of motor inhibition. Null results are generally problematic to interpret, as it cannot be inferred from them that there are no differences between groups or conditions. Lack of statistical power might just have prevented to find those differences. Thus, implications of these results on models of motor inhibition remain very limited. Our results show that (simple) proactive and reactive motor inhibition is still possible with lesions to important nodes in a network underlying this function. This suggests the network not to be static but dynamic, being able to compensate limited capacity and to react to disturbance within the system.

5.4 Strengths and Limitations

In three studies, we used EEG to measure neural activity. EEG has the critical advantage of being able to resolve neural processes on a very small time-scale. This allows to study temporal events of specific cognitive processes. As one major aim of this thesis was to disentangle preparation for from actual implementation of inhibition, time resolution was of critical importance in this work. Furthermore, EEG offers the possibility to study oscillatory dynamics of cognitive processes. This was of crucial relevance, as our work was built on the assumption that inhibition is based on a beta-driven network and further that we specifically were interested in oscillatory correlates of motor inhibition. The high resolution of EEG in the time-domain is contrasted by its limited spatial resolution. With EEG recordings, only insight about activity at the cortical level can be gained, leaving no

possibility to explore subcortical processes. Even resolution of cortical regions is limited, especially as no methods for source reconstruction were used, being inferior to fMRI for instance. Still, EEG recordings allow statements about broader regional activity as for instance processing at prefrontal, sensorimotor or occipital regions and that is what we aimed for.

In all three studies, response inhibition was induced and quantified by a cued go/nogo task. Go/nogo tasks are widely employed to investigate motor inhibition in healthy subjects and in clinical populations. The SST in contrary, offers the possibility to quantify the internal latency of the stop-process (SSRT) and is more demanding than go/nogo tasks. The latter might have been a critical benefit in the second study, where we did not find impaired inhibitory performance in subjects with lesion to BG or PFC. In patients a balance has to be found between paradigms, which can be performed on the one hand, and still are challenging enough to reveal impaired behavioral and neural processes. Given null results of Study II, our choice for a relatively simple go/nogo task might have been too conservative.

In the introduction, I discussed ecological validity in paradigms of motor inhibition. I concluded that standard paradigms tapping into motor inhibition lack of certain aspects present in real life, as complex stopping signals, behavioral adjustment, preparation for and partial stopping. The third study was specifically designed to overcome some of these limitations. However, the experimental setup of our study is still far away from motor inhibition in real life. Future studies might move experimental design closer to everyday life, using novel scenarios such as simulations of traffic situations. Another possibility is to study stopping of kicking, throwing or other gross movements, taking advantage of wireless EEG (Debener et al., 2012) or novel wearable magnetencephalography (MEG) (Boto et al., 2018) systems in the near future.

5.5 Future Directions

Several questions arise from the results of the studies included in this thesis. The most important is why patients with BG and PFC lesions showed an intact ability to perform in our motor inhibition paradigm. As there is wide evidence for involvement of both regions in processes of stopping, we concluded that our cued go/nogo task was not challenging enough to reveal impaired inhibition in these patients. This interpretation asks for a study in which lesion patients are faced with paradigms calling for inhibitory effort of different strength. I expect that simple forms of inhibition still can be performed by patients, whereas more demanding stopping would be impaired. Extending these findings, further studies might reveal if simple and complex stopping rely on the same neural network. One study, using more complicated stopping goals, suggests complex stopping to rely on the same network as simple forms (Wessel and Aron, 2014). This however, needs to be confirmed by further work.

All three studies showed consistently that prefrontal activity increased as a function of cognitive control, being highest when motor actions have to be changed or inhibited. This hypothesis might be further tested, including different levels of nogo-signal probability, as for instance in steps of 25% between 0% and 100%. Prefrontal activity for actual stopping is expected to be inversely related to the likelihood of nogo-signals, being highest for an inhibition in the 25%-condition. A similar finding has already been observed in the striatum, here activity increased as a function of the likelihood of having to stop motor responses (Vink et al., 2005). Also, in the following of target-signals, when stopping is anticipated but does not have to be realized, prefrontal regions should be activated the more the lower the nogo-signal probability. Importantly, such results would speak for a role of PFC regions in proactive stopping, as the processing of nogo-signal probability is a preparatory mechanism.

In the third study, we highlighted the importance of the ipsilateral motor cortex in inhibiting and changing motor actions. Here alpha oscillations seemed to act as a gate, selectively preparing for upcoming actions. A future study might take advantage of transcranial alternating current stimulation (tACS) to test this assumption. tACS offers the possibility to modulate brain oscillations at distinct frequencies (Herrmann et al., 2013). Specifically, when subjects prepared to possibly change a standard motor action, mu decreased over the ipsilateral sensorimotor cortex. When stimulating this region in the alpha band in such a condition, preparatory processes should be disturbed and increased reaction times and possibly decreased accuracy are expected. tACS might be combined with EEG to study neural effects of the oscillatory intervention. However, the problem that tACS clearly alters the EEG signal is not yet solved (Noury et al., 2016). Thus, brain stimulation and EEG recordings might be separated in time. Moreover, from the observed patterns in Study III we drew the conclusion that ipsilateral motor cortex was involved in inhibiting the contralateral side when cancelling actions. This hypothesis can be tested with the help of TMS. In such a study, ipsilateral motor cortex could be stimulated with inhibitory TMS protocols as repetitive TMS or theta burst (Di Lazzaro et al., 2005; Hallett, 2007). This, in contrast to sham stimulation, should result in increased MEPs of the contralateral side, when actually inhibiting a response. Generally, despite decades of research, the field of motor inhibition is still advancing and using new techniques and designs still novel insights into stopping behavior can be expected. Importantly, these advances might help to inform treatment for neuropsychiatric patients suffering from impaired inhibitory functions.

6 References

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