Diplomarbeit

The Influence of Cross-sex Hormone Therapy on Brain Activation During the Stop Signal Task Measured with Ultrahigh-field 7T Functional Magnetic Resonance Imaging

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Abstract

AIM:
The stop signal task (SST) is a widely used functional magnetic resonance imaging (fMRI) paradigm implemented for the specific activation of brain regions associated with motor inhibition and performance monitoring. A possible influence of sex hormones is suggested by sex differences in inhibition related regional brain activation measured with the SST. As the influence of cross-sex hormones on cognitive processes measured by the SST has yet to be explored, we aimed to investigate the effect of cross-sex hormone therapy in transsexuals on motor inhibition and performance monitoring related regional brain activation using the SST and ultrahigh-field 7T fMRI.

METHODS:
17 transsexual subjects, 9 female-to-male (FtM) and 8 male-to-female (MtF) included in this study underwent two 7T fMRI scans (fMRI scan session one and fMRI scan session two) during which they performed a SST with an event-related design. The first and second scan sessions were performed at baseline and after approximately four weeks of cross-sex hormone therapy, respectively. Functional data was acquired using a Siemens Magnetom 7T scanner while standard preprocessing and statistical analysis, which consisted of one-sample T-tests and repeated measures analysis of variance (RM ANOVA), were carried out using SPM8.

RESULTS:
Over all subjects, motor inhibition and performance monitoring related neural activity could be located to regions typically associated with these processes. In addition, time, group and interaction effects were found within task relevant regions. An interaction effect was found within the left supplementary motor area (SMA) for the contrast SS vs BL. Interestingly, in *post-hoc* one-sample T-tests, MtF subjects showed significant activation in this anatomical region before cross-sex hormone therapy, while significant activation in this region was shown by FtM after four weeks of cross-sex hormone therapy.

CONCLUSIONS:
Activation across all subjects within regions associated with motor inhibition and performance monitoring allows us to validate our implementation of the SST, a prerequisite for further analysis of hormone therapy effects. While the group and time effects do not necessarily allow for a conclusion on the role cross-sex hormone therapy may play, interaction effects point towards a possible hormonal influence on motor inhibition related activity.

Zusammenfassung

ZIEL:
Die Stop Signal Aufgabe (SSA) ist ein (fMRT) Paradigma, das Gehirnareale, die mit motorischer Inhibition und Beobachtung des eigenen Verhaltens assoziert sind, aktiviert. Geschlechtsunterschiede in SSA-assoziierten zerebralen Aktivierungsmustern lassen auf eine mögliche Rolle von Geschlechtshormonen in der Entstehung dieser Unterschiede schließen. Der Einfluss gegengeschlechtlicher Hormone auf Aktivierungsmuster der SSA ist jedoch bisher weitgehend unbeforscht und die dieser Sudie zugrunde liegende Fragestellung. Die Hormontherapie bei transsexuellen Personen bietet eine innovative Möglichkeit, den Einfluß gegengeschlechtlicher Hormone auf die SSA-assozierten Aktivierungsmuster zu untersuchen.

METHODIK:
17 transsexuelle Probanden, 9 Frau-zu-Mann (FzM) und 8 Mann-zu-Frau (MzF), nahmen an dieser Studie teil. Jeder Proband nahm an jeweils zwei 7T Ultra-hochfeld-fMRT Messungen teil, während dessen die SSA durchgeführt wurde. Die erste Messung fand jeweils vor, die zweite vier Wochen nach Beginn der gegengeschlechlichen Hormontherapie statt. Die Datenerfassung erfolgte mit Hilfe eines Siemens Magnetom 7T Scanners. Für die Datenauswertung wurde eine Varianzanalyse mit Messwiederholung (RM ANOVA) und one-Sample T-Tests gerechnet. Vorverarbeitung und Datenanalyse erfolgte mit dem Programm SPM8.

RESULTATE:
Unabhängig von Gruppenzugehörigkeit und Messzeitpunkt konnten aufgabenspezifische Aktivierungen gezeigt werden, ein Befund, der auf die erfolgreiche Implementierung der SSA-Aufgabe in Rahmen eines fMRT-Paradigmas hinweist. Ferner konnten mittels RM ANOVA Zeit-, Gruppen- und Interaktionseffekte innerhalb dieser aufgabenrelevanten Areale gefunden werden. Ein Interaktionseffekt zeigte sich im linken supplementär motorischen Areal, welcher in *post-hoc* one-Sample-T-Tests von einer signifikanten Aktivierung in MtF in der ersten fMRT-Messung und einer signifikanten Aktivierung in der zweiten fMRT-Messung in FtM begleitet wird.

DISKUSSION:
SSA Aktivierungsmuster decken sich mit den in der Literatur für diesen Task, wie auch für die motorische Inhibition und Beobachtung des eigenen Verhaltens, beschriebenen. Diese Datenübereinstimmung validiert die Implementierung der SSA im Rahmen dieser Studie und ermöglicht somit die weitere Interpretation von Zeit-, Gruppen-, und Interaktionseffekten. Obwohl Zeit- und Gruppeneffekte primär nicht auf einen direkten Einfluss der gegengeschlechtlichen Hormontherapie schließen lassen, wird dies teilweise durch Interaktionseffekte ermöglicht. Interaktionseffekte in Task-relevanten Arealen, in Zusammenschau mit in der Literatur gezeigten Geschlechtsunterschieden innerhalb dieser Areale, deuten auf eine Hormonabhängigkeit von regionalen Aktivierungsveränderungen hin.

Introduction

This study intends to investigate the role of cross-sex hormone therapy on brain activation patterns associated with motor inhibition and performance monitoring. Transsexual subjects seeking cross-sex hormone therapy performed a SST during a 7T ultra-high field fMRI measurement before and four weeks after begin of hormone treatment. As inhibition and performance monitoring are cognitive processes attributed to executive control, this project will include conceptual information on executive control in general followed by more specific background information on inhibition and performance monitoring. Conceptual models presented in this section are relevant to this project as they lay the groundwork for research applying modern neuroscientific methods in an attempt to define and localize these processes to particular brain regions. After a thorough summary of localization evidence in order to allow for later comparison of our results, background information will also be given on the SST, transsexualism, and fMRI as they are integral to this project's design. After an overview of our methodology, results and discussion will be structured based on our two objectives; to validate our implementation of the SST in order to allow for further investigation of the effects of time, transsexual group, and hormone therapy on brain activation during task performance.

1.0 Background Information

1.1 Executive Control and Working Memory: Interrelated Processes for Dynamic Control

1.1.1 Terminology

The terms "cognitive control," "executive control" and their corresponding "executive functions" are often used in an unspecific and overlapping manner as they have yet to be concretely and coherently defined. These concepts are necessary for the dynamic coordination of processes required to accomplish goals in a flexible manner appropriate for a given situation [2, 3]. Many attempts to define them resort to a list of functions, a characterization that only insufficiently emphasizes their complex overlapping and integrated nature [4]. For example, in their review of neuroimaging data, Smith and Jonides differentiate between attention and inhibition, task

management, planning, monitoring, and coding, the first two of which are deemed to be the most essential and interrelated [5]. Set shifting, the switching of attention from one stimulus and response pair to another is also often included in such lists [6]. Funahashi et al. describe that executive functions result from processes that screen surroundings in order to focus attention selectively on essential information, input necessary information and retrieve appropriate information from long term memory. Further, they manipulate and integrate gathered information and relay information to connected brain regions, all while suppressing irrelevant processes in order to inhibit inappropriate actions [2]. They are described by Lezak et al. on an abstract level as the processes that determine "'how' or 'whether' a subject goes about doing something" rather than the "'what' or 'how much'" aspects of a subject's actions [7]. Regardless of approach, themes emphasizing the controlling role of executive functions and their dynamic interaction with non-executive processes in the implementation of complex activities persist. As a result, executive control impairment is made visible through the disorganization of nonexecutive functions [8]. The complexity of these concepts has motivated researchers to develop models on the basis of conceptual, lesion, animal, electrophysiological and imaging data.

1.1.2 Theoretical Models

A variety of models for executive control and its related executive functions have been developed on the basis of concepts from the realm of artificial intelligence. Though they are highly mathematical, they are relevant to this project because they reflect some of the first attempts to organize executive control into coherent models. They provide a framework to which data acquired through other neuroscience methods, such as neuroimaging, can be applied.

The Central Executive System and Hierarchical Control

Norman and Shallice present a hierarchical model in which actions are controlled at different levels and by different systems according to their familiarity and complexity. In this model, the Central Executive System (CES) controls actions, both motor and thought, by directing attention to and diverting attention from relevant and irrelevant information, respectively, and by managing the contents of memory storage. As the fundamental building blocks of this model, schemata are defined as highly specialized routine responses to a certain set of triggers, which are

often environmental. Once a schema is triggered, it inhibits competing schemata until a goal is attained, or another, higher priority, schema is activated. Though schemata are routine operations, which operation is used, and in which order, is not routine in nature and is ultimately controlled by the CES. The CES consists of two components, the lower level Contention Scheduling System (CS), for the regulation of automatic or familiar responses and the more advanced supervisory attention system (SAS), for the execution of intricate or novel actions. It is noted that, rather than replacing the CS, the SAS regulates the CS to allow for flexible adjustment of schema implementation to a dynamic environment. In the absence of the SAS, the slow and rigid CS may not adjust quickly to fluctuating environmental stimuli and therefore cannot inhibit resulting inappropriate schema [9, 10].

Shallice and Burgess further differentiate this model by defining the stages and subordinate processes through which the SAS and the CS function in novel situations. An unfamiliar situation requires an appropriate operating strategy. In the context of this model, a strategy is a temporary schema, either new or existing, which is activated by output from the SAS rather than by environmental stimuli, replaces the schemata that have been automatically triggered by surrounding stimuli and subsequently controls lower level schemata. In strategy development, a temporary schema is generated in a first stage either spontaneously, as a result of dissatisfaction with the current approach, explicitly, through problem solving, or by retrieving an appropriate schema from memory. Problem solving requires a goal and consists of sub-phases that include problem formation, the creation of a solution attempt and checking phases. Once the temporary schema is implemented with the help of working memory specific to the task at hand a monitoring stage may adjust or reject the temporary schema depending on its effectiveness [11, 12].

The Domino Model and the Decision Making Process

The Domino Model, which was developed by Fox and Das, takes the ability to analyze and utilize beliefs, and thus to justify actions, into consideration. In this model, beliefs about a situation cause the system to develop goals. Possible solutions to attain these goals are generated and then evaluated through a decision making process in which argument schemas are implemented and knowledge, both situation specific and general, is taken into account. Depending on the decision that is made, the system can either alter its beliefs about a situation

and the decision making process described above may repeat or plans to implement a solution can be made and ultimately action may be taken [12].

The Central Executive as Supervisory Organ

Baddeley attempts to structure executive control by introducing the concept of a central executive (CE), a supervisory organ that is analogous to Norman and Shallice's SAS [reviewed in 13]. In Baddeley's model the CE functions as sole controller of two subordinate systems. In addition to controlling the encoding, storage and retrieval of information, it allocates data to the two subsystems, which store and process information. Goldman-Rakic criticizes the hierarchical nature of Baddeley's model, suggesting that the CE may instead consist of a variety of specialized domains that serve "sensory, mnemonic, and motor control functions" [13, 14]. The CE concept itself, however, has been questioned by Parkin, who claims that the lack of consistent localization evidence undermines the validity of the model [15]. In defense, Baddeley emphasizes the conceptual nature of their model, which is therefore not disqualified by the diversity of localizations to which it has been attributed [16].

Working Memory and Executive Control

Baddeley's model is proposed in the context of working memory, which is essential to and an integral part of executive control [reviewed in 13]. Working memory stores and maintains fleeting sensory information so that it can be accessed and manipulated by processes that guide behavior [14, 17]. In another interpretation, working memory can be seen as the major system that houses both storage, or "maintenance," and executive, or "manipulation" functions [13, 18]. As a result of these discrepancies the terms working memory and executive control are often used in the literature in an interchangeable manner. Due to these conceptual overlaps we will address both in detail. The existence of working memory and said overlap with executive control is addressed in primate studies. It has been shown that when a delay is inserted between a presented stimulus and a required response, which, when repeated, is also known as a delayed response task, neurons in the Prefrontal Cortex (PFC) show sustained stimulus related activity [17]. Reverberations of neuronal activity in stimulus-associated networks are thus thought to represent the conservation of information in an active state so that it can be used to serve executive

functions [19]. While these studies primarily support the existence of working memory and localize it to the PFC, others attempt to show the subsequent manipulation of stored information by executive processes. During a delayed response task changes in the firing frequency of neurons from the primate PFC and medial thalamus have been shown. While most neurons showed increased firing during presentation of the stimulus and during the transition to and beginning of the delay, some neurons showed higher activity during the delay than during inter-trial periods. The activity presented by the second set of neurons is thought to correspond with the regulation of attention paid to a selection of stored information, which is in turn an executive control function [20].

1.1.3 Localization Evidence

The Prefrontal Cortex and Prerequisites for Executive Control

It is widely accepted that the PFC plays an integral role in the mediation of executive control. Royall et al. suggest that this assumption may be supported by studies that show that the PFC displays characteristics that can be seen as prerequisites for executive control. We have applied this concept and Royall et al.'s review to establish an overview of prefrontal function [8]. The prefrontal cortex shows connectivity to a vast array of cortical and subcortical areas through a variety of circuits between frontal, basal ganglia and thalamic regions. This connectivity is bidirectional, allowing the PFC to exert influence on the areas from which it receives input [8].

Secondly, the PFC is multimodal, a necessary feature if it is to house executive functions that require the integration of information from different systems. In an electrophysiological study, primates performed a task which required them to save both form and color, or "what," and location or "where," related information about an object to working memory. Over half of a selection of prefrontal neurons showed activity during the delay after presentation of both "what" and "where" stimuli. This activity is interpreted to be related to multimodal integration of information [21]. This information can then be used to form links between arbitrary sets of information through associative learning [17]. Findings from animal studies on multimodal integration and subsequent association of stimuli can been translated to humans through use of an fMRI task in which subjects are required to associate abstract visual stimuli with arbitrary manual

responses. Resulting regional activation was seen in distinct components of the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC), and anterior PFC as well as the lateral premotor cortex, the SMA and the striatum and implies that these regions may participate in the integration of information from differing modalities [17, 22].

Integration and association of multimodal information allows regularities between data to be noticed and for the subsequent selection of information significant to following rules. These steps are in turn essential if a subject is to achieve the results necessary to receive a task related reward. Again, a variety of primate studies demonstrate the essential role of the PFC in these information processes. During a task in which the location of the presentation of a cue effects whether a reward is doled out, most neurons from a preselected group in the lateral PFC only showed changes in activity when a cue was presented in a reward-relevant location. These neurons are therefore suggested to be associated with the selection and maintenance of information that is relevant to successful task performance [23]. Primate PFC neuron activity is also modulated by which rules must be followed, for example response in reaction to spatial versus response to non-spatial cues [24, 25]. Finally, when a primate expects a reward to appear in the delay after a reward-associated cue is presented, neurons in their PFC fire [3, 26]. FMRI studies strengthen this relationship by showing that the PFC is responsible for the selection of task specific stimuli [27] and that various areas within the PFC show differential activation during varying reward-associated phases of decision making processes [28].

Lesion, Animal and Neuroimaging Studies

Studies which illustrate that the PFC displays characteristics essential to executive control are supported by those that strive to create a direct and more tangible link.

Lesion studies infer that the loss of a function as a result of damage to a particular region implies that this region is relevant to this particular function. Patients with lesions of the PFC display shortcomings in strategy planning and application [29], response initiation and inhibition [30], focusing of attention [31] and decision-making [32]. These deficits can result in socially inappropriate behavior [33] and have been, though controversial, summarized as an undifferentiated "dysexecutive syndrome" [34]. Lesion studies have, however, only led to limited understanding of the PFC, as results are often contradictory [35]. Dysexecutive symptoms have

been attributed to a wide variety of subcortical structures, such as the thalamus and basal ganglia [36]. Lesions of the PFC are therefore a sufficient but not necessary cause for deficits in cognitive control. This can be explained by the fact that lesions in regions functionally connected to the PFC, and the areas that connect them, also result in loss of executive functions this particular circuit is responsible for. The diversity of the functional impairments made visible by prefrontal lesions may be partially explained by the control that executive functions exert on other process. Therefore, non-executive functions can also be affected [8].

In analogy to the complexity of results acquired from lesion studies, primate electrophysiological as well as neuroimaging studies, both fMRI and positron emission tomography (PET), also support a dynamic understanding of the relationship between executive control, the functions it fulfills and its anatomical localization. In addition, the ambiguity often shown between working memory and executive control, as two systems that are neither formally, in models, nor functionally differentiable from one another is retained in research that strives to locate the two entities. It is difficult to maintain a strict delineation between the two as, if working memory is to be controlled by executive functions, activation in areas dedicated to working memory may imply activity of executive control. This ambiguity is made even more obvious in models that consider working memory to be the umbrella term and divide it into two types of processes, short-term storage, or maintenance of "online" information and executive functions, such as manipulation [5, 37]. This may further be underlined by studies that suggest that working memory associated brain activation may depend not only on the type of information stored but also on the intensity and way in which it is being influenced by executive control.

A multitude of neuroimaging studies show activation of the PFC during storage and manipulation of working memory and attempt to subdivide and correlate aspects of these functions to corresponding localizations. Built upon similar findings from primate studies [38], some neuroimaging investigations claim to localize spatial working memory to the VLPFC and non-spatial working memory to the DLPFC [39, 40]. Others criticize this model by illustrating that similar areas within the DLPFC are activated regardless of modality. It is instead suggested that working memory may show a lateralized pattern in which spatial memory leads to activation of the right hemisphere while non-spatial memory is associated with activation of the left hemisphere [41]. Modifications of a lateralized approach emphasize that while non-spatial, such as verbal, working memory does indeed result in higher activation of the left VLPFC, spatial

working memory is associated with bilateral DLPFC activation [42, 43]. However, studies emphasizing a lack of evidence for both distribution patterns have also been performed [44]. In line with the dichotomy between spatial and non-spatial working memory, a differential distribution of verbal and visual working memory to the left and right hemisphere, respectively, has also been presented [45].

In addition to being dependent on the modality of the information stored in a particular task, localization of executive control and working memory in the PFC has also been shown to depend on the type and intensity of executive control exerted, hereby adding another dimension of variability to the relationship between function and localization. Owen et al. present a two-stage model of spatial working memory in which prefrontal areas are differentially activated depending on the type of executive control that is required. The mid-VLPFC is shown to be responsible for the organization and execution of a sequence of spatial moves retained in working memory while the mid-DLPFC shows activation when active monitoring and manipulation of spatial working memory is required [46]. Though this study is based on PET data, fMRI studies reinforce the role of the DLPFC in tasks that require the active maintenance of working memory [47] and both expand the range of and specify which roles are assigned to this region. While data from a working memory task presented by Van Hecke et al. suggests a dorsal-ventral manipulation-maintenance gradient [48], Wagner et al. further differentiate between the roles played by these two regions by showing that the VLPFC is activated during maintenance of information while the DLPFC is activated during maintenance and during monitoring. In this task, monitoring corresponds with the selection and reordering of information so that it can be adjusted in a goal relevant manner. Further, the temporal affiliation, in which DLPFC is activated after VLPFC, displayed by these two regions suggests a hierarchical functional relationship [49]. In contrast, while Wager et al. confirm that tasks that require utilization of executive functions generally activate more dorsal prefrontal areas than storage-only tasks, they specify that this pattern is not present for all executive functions. In their review of both PET and fMRI studies the authors summarize that areas within the DLPFC are more likely to be activated during continuous updating and temporal organization of information [50-52]. The VLPFC, in contrast, shows more frequent activation during demand for manipulation of information. In addition, when attention is paid to information stored in working memory, an area within the medial prefrontal cortex that corresponds to the dorsal anterior cingulate cortex is activated [50]. Lastly, the DLPFC has been

shown to be activated during tasks that promote the formation of associations between information it is holding "online" [51, 52].

Lateralization patterns similar to the modality-dependent ones described above can also be found when intensity of executive control rather than storage modality is investigated. Verbal memory only lateralizes to the left frontal cortex in the context of low executive demand while executive demand increases lateralization of spatial working memory to the right hemisphere [50]. Studies on the effects of executive demand intensity on regional activation show that the DLPFC and working memory load display a linear relationship while DLPFC activity is not affected when difficulty of the task itself is manipulated [47]. Stuss et al. redefine executive control by differentiating between three independent but interrelated executive processes that also show a lateralized distribution. "Energization," or initiating and maintaining a response is said to be localized to the bilateral superior medial frontal cortex, task setting, or the ability to establish a relationship between a cue and a response to the left lateral frontal cortex, and monitoring, or the process of checking task performance and adjusting behavior to the right lateral frontal cortex [34].

Localization evidence for executive control of working memory is, however, not restricted to the PFC. The medial temporal cortex, though most often implicated in storage of long term memory, may be associated with storage of both spatial and non-spatial working memory. Interestingly, this function may also show a modality-specific lateralized distribution, as lesions to the right and left medial temporal cortex show deficits in spatial and verbal working memory, respectively [53]. In addition to the expected involvement of the DLPFC, parietal cortical areas have also been shown to be associated with active maintenance and their activity has been demonstrated to be correlated with working memory load [37]. During an fMRI task designed to test dynamic spatial working memory, parietal cortical areas, in addition to the DLPFC, showed activation that was dependent on the number of spatial locations and the dimensionality of the display. The authors suggest that these findings display that collaboration between the DLPFC and the parietal cortex is an essential feature of spatial working memory and its executive control [54]. When subjects are prompted to either "maintain" or "reorder" two object lists in their working memory, activation of the DLPFC, the parietal cortex and the basal ganglia result. Basal ganglia may be particularly relevant in the selection of processes necessary for reordering of stored information [48].

Adding another level of complexity to the regulation of executive control, the regions described above interact with each other in a dynamic manner. Executive control is frequently associated with a general bilateral fronto-striatal circuit in which the PFC is connected to the cerebellum and the basal ganglia by way of the thalamus. This fronto-striatal circuit is said to be responsible for the creation and maintenance of stimulus response representations while the frontal and cerebellar areas interact to optimize planned actions [6]. On the other hand a PFC-posterior parietal cortex circuit has also been described [55]. Diwadkar et al. argue that the co-modulation of the activity of both the PFC and parietal cortical areas by demand illustrates their collaborative nature and portray this interaction as essential to spatial working memory [54]. The PFC, the hippocampus, and the amygdala have been shown to be both anatomically and functionally related. In this circuit, the hippocampus is monosynaptically and unidirectionally connected to the prefrontal cortex, the hippocampus is bidirectionally connected to the amygdala, as is the prefrontal cortex. It is implicated in the transfer of information in the service of working memory and its control [56]. The caudate and hippocampus have been shown to interact indirectly together with orbitofrontal and posterior cingulate cortex (PCC) regions as part of a circuit that mediates set shifting [57]. More local circuits have also been described. Proposed interplay between the lateral PFC and the ventromedial PFC (VMPFC) suggest that the VMPFC may regulate emotional input to the lateral PFC during demanding tasks [58]. The existence of neuronal networks involving the prefrontal cortex is defined above as a prerequisite for the involvement of this area in executive control. Utilization of these networks, as described here, supports this connection.

These often contradicting findings show that both the subdivision of areas associated with working memory and executive control and the application of strict neuroanatomical correlates to classic executive control models is questionable. While this can partially be ascribed to the difficulty of creating neuropsychological tests that differentiate between individual executive functions, it is, in the least, a sign of the complexity of this system [35]. Neither a singular executive entity that resides in its entirety within the PFC, nor a rigorously subdivided system of differentially located executive and working memory functions are compatible with the lesion, animal nor imaging studies described above. Research therefore suggests that abstract models of executive control must remain such and that research must focus on, and be interpreted in the

context of, a dynamic understanding of the relationship between working memory and executive control anatomy and function.

1.1.4. Clinical Relevance of Executive Control

The diversity of executive control deficits associated with a variety of neuropsychiatric diseases underline both the clinical relevance and the complexity of this system. Executive impairments can arise in depression independent of age, depression severity, or depression subtype and can persist after clinical recovery is attained [59]. Appropriately, depressed patients may express altered activity in regions implicated in executive control during an fMRI working memory task. Patients with depression show greater activation of the lateral PFC and anterior cingulate cortex than non-depressed subjects, which suggests that they may require greater activation in these areas to achieve similar performance levels [60, 61]. While obsessive-compulsive disorder is often associated with impaired inhibitory control, also an executive function, which can result in the inability to suppress thoughts, it may also be linked to more general deficits in executive control. Patients suffering from this disorder may show impairments of DLPFC, inferior parietal lobe and posterior cingulate cortex function [62]. Schizophrenic patients show defects in selecting and maintaining information that is relevant for performance in a certain situation in working memory through adjustment of attention. In an fMRI study attempting to explain these deficits, schizophrenic patients showed lower activation within a region in the DLPFC (Brodmann area 9) but greater activation in other regions of the right middle and superior frontal gyri [63]. In contrast, during two types of working memory tasks and in comparison to control subjects, the DLPFC in schizophrenic patients has been shown to exhibit higher activation during a task that demanded memory retention, while displaying lower activation during anticipation of a response. A compensatory effect in which a network is differentially activated depending on demand explains these task-specific activation differences [64]. Hyperfrontality has also been shown to be negatively related to performance in an fMRI working memory task [65]. These findings may be the result of inefficiency in which higher PFC activation is necessary though performance remains poor [66]. Impairment of executive control in patients with Parkinson may also be present in unmedicated patients in early stages of the disease, in which degeneration is restricted to basal ganglia. These deficits therefore underline the importance of the basal ganglia in executive functions [4]. Thus, findings that focus on the clinical relevance of executive control

can underline connections between regions, symptoms, and corresponding functions and confirm the importance of studying this issue.

1.2 Performance Monitoring: Inhibition, Error Detection and Behavioral Adjustment

1.2.1 Conceptual Information

Inhibition has been described as "a hallmark" of executive control [67] and as being among "the most elementary and the most interrelated" of executive functions [55]. It supports general executive control by contributing to the dynamic regulation of behavior in response to environmental factors and goals through suppression of actions that are no longer appropriate to a certain situation [67]. In analogy to executive control, our understanding of inhibition as a cognitive function is, at least vaguely, based on early electrical models, in this case, of motor control. Craik introduced the concept of a "human operator" which functions as an "intermittent correction servo" by providing periodic and ballistic inhibitory processes. Inhibitory processes are said to be triggered at certain time intervals, as a whole, and to have a predetermined time course. The behavioral result of active processes and their corresponding inhibitory processes is not dependent on the magnitude of the signals that trigger them, but of their temporal relationship. As a result of these characteristics, a physiological refractory period during which the second of two presented stimuli cannot be processed arises [68, 69]. This model assumes that two independent stimuli-action entities can only be processed in a serial manner, a theory that is contended by suggestions of parallel processing. In addition to the question of whether and how processes may interact, the influence attention capacity and the availability of other cognitive resources may have on processing outcome has also been integrated into, and become a defining characteristic of, further developments of this model [70]. When inhibition fails and errors are made these are monitored and detected and subsequent behavior is adjusted accordingly. These integrated processes are defined as performance monitoring [71-73].

1.2.2 Measuring Performance Monitoring: The Stop Signal Task

The SST, as originally introduced by Logan and Cowan in 1984, shows similarities to both general executive control concepts and to Craik's 1948 model. In this model of inhibition,

behavior is explained as the result of horse race. After an inhibitory stimulus, two independent ballistic processes commence and whichever process wins determines the behavioral result. Thus, the race outcome, and therefore the probability of incorrectly responding despite an inhibitory cue, depends on the time delay between presentation of the two opposing stimuli. Craik's influence on the horse race model can be seen in the independence and ballistic nature attributed to the two racing processes, while the suggestion of control through an executive system that forms intentions and issues commands to subordinate systems through modification of attention, carries traits of Baddeley's working memory model [reviewed in 13]. Though Logan and Cowan do not specifically describe in which way an executive system and its corresponding subordinates would interact with their race model, they do, however, claim that the two models are compatible. Though the SST is developed in the context of motor control, Logan, Cowan et al. suggest that their inhibition model may also be applicable to more abstract cognitive skills [74, 75].

The SST is widely used [1, 67, 75-82], is a simple reaction time task and can be evaluated to elucidate aspects of motor control such as a motor response, response conflict and motor inhibition as well as related aspects of performance monitoring such as error detection and behavioral adjustment, all of which are ultimately aspects of executive control [67]. The SST essentially consists of frequent go signals, in reaction to which a subject must make a motor response, which usually takes the form of a button press. The go signal may or may not be followed by a more infrequent stop signal, after which a subject must suppress the motor reaction originally prompted. Based on Logan and Cowan's race model, the time frame between presentation of go and stop signals, also known as the stop signal delay (SSD), can be adjusted in order to modify the difficulty of each trial, secure sufficient unsuccessful inhibitions for evaluation of the task and ultimately to evaluate a subject's inhibitory efficiency [75]. Activation measures were shown to be highly comparable when an SST with performance adjusted SSD is compared to an SST with a constant SSD. Adjustment of SSD is therefore appropriate in studies in which performance deficits must be controlled for and in which an adequate number of trials resulting in failed motor inhibition are desired [83]. The stop signal reaction time (SSRT), which can only be estimated as successful inhibition lacks a behavioral marker, is essential to this task and is described as the time between presentation of the stop signal and successful inhibition of the motor response. It is estimated through subtraction of the optimal SSD from the mean Go trial reaction time and can be interpreted as the time required for a stop signal to be processed. Therefore, the shorter the SSRT, the more efficient the inhibitory process is. The optimal SSD is

the delay at which 50% of inhibitory trials can be successfully inhibited [1, 76, 77]. Through comparison of various trial outcomes such as go success (GS), go error (GE), stop success (SS) and stop error (SE) the behavioral entities described above can be represented [1, 76, 77, 79, 81, 84]. Additional tasks that also investigate similar inhibitory aspects of behavior are the Go/No-Go task and the Stroop task. Though slightly different in design, the Go/ No-Go task is conceptually closely related to the SST and investigates similar behavioral patterns in that it requires Go trial responses and No-Go trial inhibitions and therefore also induces response conflict and performance monitoring including error detection and behavioral adjustment [85-89]. In contrast, the Stroop task is specifically designed to induce response competition by differentiating between congruent and incongruent trials and is therefore relevant in the investigation of areas associated with competition monitoring. The task provides the Stroop effect, which describes the association of longer reaction times with incongruent trials, as a measurement of conflict monitoring activity [5, 90, 91].

1.2.3 Localization Evidence

As with other executive functions and executive control as a whole, a wide variety of studies attempt to localize performance monitoring to particular cerebral regions and networks in order to develop functional models and, ultimately, to support a modular understanding of executive control functions. Results are, however, often both scattered and contradictory.

Event-Related Potential Studies

Orienting data on neural processes associated with errors, conflict monitoring and behavioral adjustment has been gathered in the context of EEG studies. As an event-related potential (ERP), error related negativity (ERN) arises 100 to 150ms after an incorrect response and is generally thought to be generated in the medial prefrontal cortex (mPFC), more specifically in the anterior cingulate cortex (ACC). It has been interpreted as the result of a mismatch in the comparison of the actual response as it was executed and an internal representation of how the response was intended [92]. Interestingly, ERN's have also been shown to occur after correct responses. As correct responses also include a comparison process, albeit one that does not result in contradictory results, the ERN has been connected to the comparative process and not to its result

[93]. Ullsperger and von Cramon associate the ERN with error processing, further specify its location by pinpointing it to the cingulate motor area in the anterior cingulate sulcus and differentiate it from response competition, which they locate to the pre-supplementary motor area (pre-SMA) and other medial frontal regions [94]. It has also been specified that the ERN is associated with error detection, and not with inhibition or error correction [95, 96]. Both error processing and response competition are, however, said to subsequently activate performance monitoring which is associated with a positive deflection occurring approximately 370ms after an error occurs. ERP studies lay a framework of error-associated measures that can in turn be applied as a basis for the interpretation of fMRI studies [94].

fMRI Studies: Inhibition

Adaptation of the SST to an fMRI setting allows for the elucidation of brain regions activated during performance during this task. A comparison of SS and SE trials with the intention of isolating regions associated with successful inhibition of motor responses resulted in activation within the right and left middle frontal gyri, right inferior frontal gyrus (IFG), and right cingulate gyrus and the right inferior occipital gyrus [76]. Similar patterns of cerebral activation have been shown in Go/No-go tasks, allowing us to interpret them analogously. Successful inhibition during No-go trials have been related to activation in frontal regions such as the middle frontal gyrus/DLPFC [86, 87, 97-100], inferior frontal regions such as the inferior frontal cortex/VLPFC [86, 97, 99-101], medial frontal regions such as the middle frontal gyrus [79] and the supplementary motor area or preSMA [97-100] and, lastly, the ACC [79, 86, 87]. In addition, parietal regions [99] including the inferior parietal lobule [86, 87, 97] and the temporoparietal junction [79, 100], the intraparietal sulcus [100] and the angular gyrus [97], as well as the lingual gyrus [86], the fusiform gyrus [79, 97] and the insular region [97, 99, 100] have been described in association with inhibition. Interestingly, successful inhibition is also associated with areas related to motor execution, such as the basal ganglia [102, 103] and the cerebellum [79, 97, 98, 102] both of which are also shown to be activated during go trials [98, 103], as well as the SMA/pre-SMA, as mentioned above. Discrepancies remain, however, in regard to the laterality of activated regions. While some authors maintain that activation of the DLPFC is bilateral [82, 86, 91] others claim that activation in this area is primarily restricted to the right hemisphere [80, 82, 87, 97, 101, 104]. Garavan et al. suggest that lateralization of inhibition associated activation

to the right hemisphere may be even more widespread and might include multiple frontal and parietal regions [87, 97]. Moreover, a contested review [82] by Aron et al. goes so far as to localize inhibitory activity to the right IFG alone [104]. Hampshire et al. directly challenge Aron et al.'s assertion by showing left IFG, pre-SMA, and bilateral IPC activation related to inhibition in a modified SST task [82].

Rubia et al. attempt to explain the diversity of regions described by suggesting that activity in the context of inhibition may partially depict a broad spectrum of associated cognitive functions including selective attention, target detection, response competition, and decision-making. A task similar to the SST specifically evaluated to isolate inhibition from other "non inhibitory cognitive functions" by subtraction of unsuccessful inhibitions minus baseline from a previously subtracted value of successful inhibitions minus baseline, resulted in sole activation of the right inferior prefrontal cortex, hereby supporting Aron et al.'s claim [80]. Li et al. also accept that regions isolated through comparison of SS to SE in the SST may be confounded by changes in attention during "signal monitoring and post response processing" as well as emotional factors such as frustration and monitoring processes that respond to error. In order to more specifically isolate response inhibition, Li et al. assume that SSRT is a representation of response inhibition function and that shorter SSRT would result from stronger activation of regions involved in this process; these regions are thus interpreted as the neural correlates of successful inhibition. In this context, comparison of short to long SSRT resulted in activation of the left SFG and the left precentral gyrus, as well as the left ACC. In addition, SSRT and blood oxygen level dependent (BOLD) activity displayed a negative correlation in a superior frontal ROI, further underlining the region's specific role in inhibition [76]. In contrast, in the intention of controlling for SST related attention processes, Sharp et al. compare simple SST inhibitory trials to a control or "continue" trial, which includes task irrelevant stimuli that capture attention, but do not facilitate a change in response, and therefore activate regions associated with attention. This comparison, which aims to elucidate inhibition specific regions, reveals activation in the pre-SMA, and a region reaching from the paracingulate cortex to the right middle frontal gyrus [81].

In addition to studies seeking to isolate inhibitory activity, others explore possible alternative or more specific explanations for activation patterns. To expose efficiency in response inhibition in particular, Hirose et al. implemented an efficiency index defined as the difference in percentage of successful No-Go trials between subjects and healthy controls for the same Go trial reaction

time. Application of this index resulted in left temporo-parietal junction and the left inferior frontal gyrus activation, hereby associating these regions with efficient inhibition [100]. In addition, Grahn et al. suggest that the ACC may be involved in sustained attention, as it is required during inhibitory tasks, rather than inhibition per se [105]. Further, Hampshire et al. discuss whether activation of the IFG in the context of the SST reflects involvement in inhibition, or whether, in fact, it is activated as a result of its role in the identification of task relevant cues. By application of a modified SST that keeps stimulus conditions constant while varying response conditions the authors showed that right IFG activation is not specific to inhibition, but rather that the region is activated during cue detection, regardless of whether the stimulus is followed by a response, an inhibition or neither [82].

Dependence of stop related activity on factors such as task difficulty, subject absentmindedness and working memory involvement has been investigated to further specify regional inhibitory role distribution. For example, Garavan et al. suggest dissociation of response inhibition into two systems based on trial difficulty. Data displaying greater right DLPFC and bilateral ACC activation for easy and difficult inhibition trials, respectively, was gleaned from a Go/No-Go task allowing for adjustment of trial difficulty and is presented to support this proposition. In support of system dissociation, comparison of successful inhibitions to inhibition failures, revealed greater activation of the middle frontal gyrus and the inferior parietal lobule in less absentminded subjects, while more absentminded subjects showed greater ACC activation during difficult trials [87]. Mostofsky et al. suggest that patterns of activation associated with inhibitory activity are dependent on working memory load and therefore the level of cognitive control required. While No-Go trials during a simple SST were associated with pre-SMA activity, No-Go activation in and SST modified to implicate greater working memory load resulted in activation of the right middle frontal gyrus [98].

fMRI Studies: Error Detection

In the context of inhibition failure and resulting error related processes, some of these regions, such as the SFG, the middle frontal gyrus (MFG) and the medial frontal gyrus as well as basal ganglia and inferior parietal regions are shown to exhibit bilateral, concurrent negative signal changes [102]. These results are controversial, however, as contrasting SST and Go/No-Go studies have also shown positive activity changes in the middle frontal gyrus [71, 87], inferior

frontal cortex [87, 103], medial frontal regions/SMA [76, 86, 87] and posterior and inferior parietal regions [80, 87]. The SST has also been shown to activate a wide spectrum of medial regions such as the ACC [71, 79, 80, 86, 87] the posterior cingulate cortex [86], the mesial frontopolar cortex [80], the precuneus [66] and lingual regions [76]. In addition, the insular cortex [76, 86], the frontal operculum [86], superior temporal regions and the thalamus [76] have also been shown to be activated during error related processes. As is the also the case in both Go and successful No-go trials, unsuccessful inhibitory trials are also associated with changes in activation in regions related to motor execution [76, 103].

Some authors emphasize that regions activated during errors overlap with those activated during inhibition and behavioral adjustment, subsequently attempt to isolate those specific to error detection, and finally suggest functional relationships between regions activated during these processes. Garavan et al. show that regions activated during successful and failed inhibition are redundant and in turn, based on temporal evaluation of a related ERP study, suggest that successful inhibition is dependent on the timely activation of these regions [87]. In contrast Menon et al. demonstrate only partial overlap between regional activity patterns during inhibition and error detection, the authors therefore isolate the rACC, the posterior cingulate, the precuneus, and the right anterior insular cortex as a collection of regions specific to error detection [86]. As is the case with successful inhibition, error detection is also thought to be accompanied by confounding processes, such as those related to attention, which, when controlled for, confirm the specificity of the ACC's role to error trials [81]. In contrast Liddle et al. demonstrate that activation of the ACC is common to both Go and No-Go trials while the DLPFC and the VLPFC show greater activity during No-Go trials. The authors therefore propose that the ACC may fulfill a role common to both trials, such as decision making and monitoring, while the DLPFC and VLPFC remain specific to inhibition [89].

fMRI Studies: Conflict Detection

Similarly, as ACC activity in inhibitory trials is present regardless of whether trial outcome is successful or not, the ACC has been implicated in conflict monitoring, rather than of error detection per se [106]. This function may allow the region to assess the need for cognitive control processes and therefore to mediate bottom up control [96, 107]. Mediation of conflict monitoring by the ACC is underscored by an increase in the region's activity in the face of rising error rates,

and therefore of greater response competition [106] and by the demonstration of its sole activation during incongruent, but not during congruent trial conditions in an appropriately modified task [108]. In addition, Stroop tasks demonstrate an association between incongruent trials, longer reaction times signalizing higher response competition [91], and ACC activation [90]. After conflict is detected, it may be effectively reduced through activation of the DLPFC, which ultimately exerts control [109], in line with its general role in executive function [47].

The possibility that the ACC may fulfill both error detection and conflict monitoring has also been addressed [85]. The broad spectrum of regional activity reported in relation to these two processes, from the caudal-dorsal cognitive ACC (ACcd) [79, 96] to the rostral-ventral affective ACC (ACad) [71, 78, 86] may support a dual role for the region. Data presented by Kiehl et al. attempts to bridge the gap between regionally different findings by localizing competition monitoring to the ACcd and error detection to the ACad [79]. However, even the basic assumption of the ACC as a mediator of response conflict is controversial, as other regions, such as the SMA and regions in the DLPFC may instead fulfill this role, leaving the ACC to specifically detect error and suggesting it may not be responsible for conflict monitoring at all. The author's do, however, consider the possibility of regional overlap between processes [94]. Lack of conflict dependent modulation of ACC activity in contrast with conflict sensitive activation of the pre-SMA is also shown in a Go/No-Go task and strengthens arguments against ACC and for SMA involvement in conflict monitoring. These authors, however, interpret their data to support a dissociation of neural processes associated with conflict monitoring and error detection [88], in contrast to Ullsperger et al. In addition, anticipatory activity attributed to the ACC [110-112] may not be compatible with conflict monitoring activity, as it instead supports a more "top-down" role for the ACC in cognitive control [96]. Supporting data showing greater activation of the ACC during Stroop task trials lacking response conflict leads Roelofs et al. to support the assumption that the ACC may be more directly involved in regulation itself, rather than monitoring processes, such as conflict monitoring [113].

fMRI Studies: Behavioral Adjustment

Lastly, depending on information gleaned from behavioral monitoring, behavior may be adjusted to improve task performance. In the context of the SST, behavioral adjustment may take the form

of post-error slowing (PES), a lengthening of the reaction time of a post error Go trial, when compared to the preceding Go trial. In order to investigate which cerebral regions are responsible for PES, comparison of post stop error Go trials with a reaction time increase to those without were performed. Resulting activation was located to the right VLPFC. Although post-inhibitory success slowing (PSS) has also been described, comparison of trials with and without reaction time lengthening does not yield any activation. Li et al. therefore postulate that PES and PSS are modulated by separate neuronal networks and thus compare regional activity associated to PES to that of PSS, which results in activation of the bilateral VLPFC, the right middle frontal gyrus, the fronto-polar region. However, VLPFC activation did not correlate with the extent of PES, undermining a direct relationship, though this is interpreted to support the VLPFC's role as controller, rather than effector in PES. In addition, neither inhibition nor error related activity in the medial prefrontal cortex have been shown to correlate with PES [114], though subjects with shorter SSRT have been shown to exhibit greater PES [76]. Ide et al. more directly address the relationship between error and PES related activity through use of Granger causality mapping. The authors show that the SMA, the cerebellum as well as pontine and medial thalamus regions cause VLPFC activation and that error related activity within these regions is correlated to PES related VLPFC activity [84].

Lesion Studies

Lesion studies that describe a deficit associated with non-functioning of a certain region suggest that this region is essential for, and not merely involved in, a particular function. Lesion studies of areas associated with inhibitory control therefore support neuroimaging data. For example, lesions of the ACC have been associated with inattention, apathy, dysregulation of autonomic functions, akinetic mutism and emotional instability. Neurocognitive measures of language, visual, motor and memory skills, however, have been shown to remain intact [96, 115]. The variety of deficits described suggests a broad role for the ACC in executive control. More specific to our study, a right focal ACC lesion has been associated with impairment in a stroop-like task that differentiated between manual and verbal responses. The deficit was restricted to manual responses, which underlines the role of the ACC in motor control [116]. In contrast, patients with more widespread frontal lesions, even though they include the ACC, exhibit normal performance in a stroop-like test investigated with EEG. This contradiction emphasizes the

intricate distribution of functions in this region. Interestingly, in an SST task performed by the same subjects, the SSRT did not differ between patients and controls. Patients did, though not to a statistically significant extent, fail to adjust their behavior in response to errors, as measured by the presence of PES, when compared to the control group [117]. SSRT changes have, however, been shown in the context of lesions to the right IFG. Aron et al. showed a correlation between SSRT, and therefore the time a subject need to inhibit a response, and damage to this region [118]. In contrast, a study investigating anatomically more extensive, both unilateral and bilateral frontal lesions, failed to show differences in SSRT between patients and healthy controls. There was also no effect of lesion laterality in any SST measures [119]. Animal studies allow for the induction of more specific lesions to regions implemented in motor inhibitory control. While lesions induced in the subthalamic nucleus (STN) and the infralimbic cortex did not show effects on SSRT, as opposed to lesions to the orbitofrontal cortex which do, rats with STN lesions showed faster go trial reaction times and decreased inhibition accuracy. This suggests that the inhibitory impairment shown as a result of STN lesions is independent of the SSRT [120, 121]. In contrast, lesions to the medial striatum resulted in SSRT slowing [120]. When interpreting lesion studies investigating areas associated with functions related to inhibition one must consider the limited availability of subjects with carefully delineated lesions, and ensuing lack of result specificity, into account.

1.2.4 Alternative Functions, Interactions and Networks

Alternative functions attributed to regions associated with response inhibition, error monitoring, and behavioral adjustment link inhibition as an individual executive function to executive control as a whole, introduce possible interactions, and redefine the specific role regions play within inhibition as a whole. The ACC is often associated with processing of emotions [122, 123] and both positive and negative feedback [124, 125]. In order to consolidate the ACC's emotional roles with those associated with executive control, of which inhibition [86], error detection [79] conflict monitoring [106] are relevant for our study, Bush et al. describe, in their review, a dichotomy between the rostral-ventral affective ACC (ACad), and the caudal-dorsal cognitive ACC (ACcd), which can be separated on the basis of cytoarchitecture and projection patterns [96]. Support for the distribution of functions among these two regions is backed through the juxtaposition of ACcd activation during a simple counting stroop task, in which subjects were

asked to respond with the number of words written, regardless of the word's meaning, [126] and ACad activation during performance of an emotional counting stroop, in which some of the words presented had emotional connotations [127], both of which were investigated in the same group of patients. Interestingly the two regions behave according to a "reciprocal suppression model" and are therefore deactivated during tasks that activate the other. However, the cognitive and affective functions for which the ACC is assumed responsible may not necessarily be mutually exclusive, as Kanske et al. suggest that emotion increases functional connectivity between the vACC (Acad) and the dACC (Accd) [128].

In addition to models attempting to define the relationship between emotion and cognitive control, a group of partially contradictory network models has been developed to provide a thorough description of inhibition, error, and behavioral adjustment related neuronal activity as measured through the SST and Go/No-Go tasks. A targeted investigation attempting to structure the wide variety of areas activated in the context of inhibitory motor control shows that in addition to the right IFG [103], portrayed as indispensible to response inhibition [104], the right subthalamic nucleus (STN), the right pre-SMA, the right globus pallidus (GP), and other regions including the right parietal cortex and the right insula are activated during contrast of successful and failed inhibitions. This information, together with the observation that inhibition related activity in the IFC and the STN are correlated with each other as well as negatively correlated with SSRT, lead the authors to support the model of a right lateralized "response inhibition network" [103]. A further development of the model uses diffusion weighted imaging (DWI) to demonstrate a white matter tract connecting the IFC and the STN as well as connections between both regions and the pre-SMA, therefore offering structural evidence to support the concept of cooperation between these regions [129]. However, a similar investigation failed to show connectivity between the IFC and the STN and therefore presents an inhibitory control network in which the IFC detects stop signals and reacts by relaying information to the pre-SMA, which ultimately exerts inhibitory control through the basal ganglia (BG) [130]. Ide et al. use Granger causality mapping to show a "cerebello-thalamo-cortical pathway" including similar regions and supporting a "flow of information" from the cerebellum to the thalamus and SMA [84]. In contrast, an alternative network that has been suggested and is described above incorporates the ACC as a conflict monitor and prefrontal regions as effectors of inhibitory control [131] and is supported by evidence of functional connectivity between these regions [132]. Stevens et al. use multivariate analysis to define as circuit specific to errors and encompassing the caudal cingulate

zone, superior, medial, and inferior frontal regions and superior and transverse temporal regions, as well as motor, insular, cerebellar, and thalamus regions. Interestingly, this circuit is similar to one that is activated during correct button presses, but lacks positive activity changes in the rIFG, DLPFC and the striatum, which may corresponds with the role these regions play in inhibitory motor control [102].

1.2.5 Clinical Relevance of Inhibitory Control

SST and Go/No-Go task performance and related cerebral activity patterns have shown changes in task relevant regions in a variety of psychiatric disorders from obsessive compulsive, attention deficit hyperactivity disorder and affective disorders, to schizophrenia and addiction or substance abuse. This information confirms the broad applicability of these tasks for measuring variations in inhibitory control and performance monitoring and creates a link between measurements attained from these tasks and clinical manifestations. For example, patients with obsessive compulsive disorder performing a Go/No-Go task show enhanced activity in posterior cingulate, ventromedial frontal cortex, insular, lingual, temporal, parietal, cerebellar and a group of premotor regions such as the premotor cortex, left cerebellar hemisphere and left caudate, many of which are implicated in inhibitory control and associated processes [133, 134] Similarly, hypoactivity is observed in regions such as the ACC [134]. Correlation, both positive and negative, of task relevant regions with measurements of disease severity [133] as well as demonstration of longer SSRT [135] and therefore delayed response inhibition [136] underline the importance of inhibition control deficits in OCD as well as the suitability of SST and Go/No-Go tasks to measure them. Though association with SSRT changes remains controversial [137, 138], changes in task related activity have also been explored in patients with ADHD. While inhibition has been linked to under-activation of a fronto-striatal network [139], patients show hypoactivity in the ACC, the left VLPFC, the preSMA, the left precentral lobe and bilateral inferior parietal lobe during errors [140, 141]. Activity changes in the ACC are also implicated in affective disorders such as depression and bipolar disorder, during inhibitory and error detection related activity [142-144]. In keeping with this trend, patients with schizophrenia may also present slower SSRT as well as lower activation in the right IFG [145], ACC, and DLPFC, and higher activity in thalamic regions [146]. In addition, impulsivity scores correlate with VLPFC activation in this disease [147]. Lastly subjects with a wide variety of addiction and substance use

related disorders, from opiate dependence to chronic cocaine and cannabis consumption, show changes in SST and Go/ No-Go tasks when compared to healthy controls [92, 148, 149] Though direction of activity change may vary, similar regions are often implicated suggesting at least partial consistency in patterns of activation associated with SST and Go No Go in varying subject groups.

1.2.6 Sex Differences in Inhibitory Control

Our understanding of inhibitory control and performance monitoring, as measured through the SST and Go/No-Go task, is expanded through demonstration of the strong influence a subject's level of absentmindedness [87, 92], awareness [150], practice [126], preparation [151], and their age or developmental stage [152, 153] may have on both behavioral performance and cerebral activity patterns. In addition, sex differences have been demonstrated in the presentation of clinical conditions shown above to be associated with deficits in cognitive control [154-158]. Therefore, the investigation of sex differences, and their neurobiological correlates, in inhibition and performance monitoring is motivated by demonstration of the dynamic modification of these processes by other, both physiologic and pathologic, factors of influence, as well as the existence of sex differences in clinical manifestations of cognitive control loss. Though they are few, this research includes studies using the stop signal and Go/No-go tasks.

Interestingly, despite evidence that men and women do not differ in general SST behavioral performance, including go and stop success rate, mean reaction time, SSRT, and post error slowing, regional cerebral activation differences have been shown for a variety of contrasts [1, 77]. For example, when SS and SE are contrasted to isolate inhibition, men show greater activation than women in a variety of regions including the anterior cingulate cortex, the orbital frontal gyrus, two regions within the SFG, a region within the pre-SMA, and the cerebellum [1]. An alternative comparison, which utilized short compared to long SSRT as a representation of response inhibition has led to contradicting results. While Li et al. initially demonstrate that men show greater activation of the lentiform nucleus, the parahippocampal gyrus, the posterior cingulate cortex, the ACC, and the MFG as well the thalamus for this comparison, a later publication by the author fails to show a sex difference in this context [1, 77]. Regardless, greater inhibition related cerebral activation in men than in women in the context of comparable behavior is interpreted to portray that men require greater neural resources to achieve the same behavioral

results [77]. Women, however, show greater activation within the ACC and the thalamus when SE and SS are compared in order to isolate neural correlates of error processing. In addition, while men show greater activation of the inferior parietal cortex, two regions within the superior frontal cortex, and inferior temporal gyrus when post stop error and post Go trials are compared to elucidate post error processes, women show greater activation of these regions when the contrast is reversed. Lastly, while men and women do not differ in the neural correlates of PES, women, but not men, activate the PCC during PSS [1]. In contrast to the SST, investigation of sex differences using the Go/ No-Go task, does result in sex differences in behavioral results, as well as within the ACC [159]. In order to investigate the role of hormones as potential mediators of these differences, Colzato et al. analyze healthy women throughout their menstrual cycles to reveal longer SSRT in the follicular phases than in the luteal or menstruation phase that correlated positively with estrogen levels [160].

1.3. Transsexualism

1.3.1 Definitions: Diversity Rather Than Pathology

Research focusing on transsexualism is a subject that must be approached with utmost caution, especially because of the stigma, and therefore prejudice and discrimination transsexuals often face. Nevertheless, the subject must be addressed in this study considering the integral role transsexual subjects play in its realization. It must, however, be emphasized that our study focuses on changes induced by cross-sex hormone therapy, rather than transsexualism per se, and that we adopt the outlook that "being transgendered, transsexual, or gender non-conforming is a matter of diversity, not pathology" as set forth by the 7th Version of the Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, World Professional Association for Transgender Health [161]. In order to discuss the issue in a differentiated manner, a selection of definitions must be discussed. Gender is defined as the "sense one has of being male or female" [162], whereas sex is most often assigned at birth based on external or internal genitalia. Gender non-conformity refers to "the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex." Gender dysphoria, or "discomfort or distress that is caused by a discrepancy between a subject's gender identity and that person's sex assigned at birth" [161], may result, though not necessarily. In

addition, not all subjects with gender dysphoria, exhibit a gender identity disorder. Gender identity disorder is defined by the Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM IV-TR, American Psychiatric Association, 2000) when the following criteria are met:

DSM IV-TR (302.85) Gender Identity Disorder in Adolescents or Adults

(Permits diagnosis if all 4 criteria are met)

- A strong and persistent cross-gender identification
- Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex
- The disturbance is not concurrent with a physical intersex condition
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

The International Statistical Classification of Diseases and Related Health Problems (ICD-10, World Health Organization, 2010) defines transsexualism as a Gender Identity Disorder. This diagnosis (F64.0) may be given if the subject expresses:

ICD-10 (F64.0) Transsexualism

(Permits diagnosis if all 3 criteria are met)

- The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatment
- The transsexual identity has been present persistently for at least two years
- The disorder is not a symptom of another mental disorder or a chromosomal abnormality

While labeling these phenomena as disorders is, of course, controversial, the World Professional Association for Transgender Health, formerly the Harry Benjamin International Gender Dysphoria Association, emphasize in a previous version (Sixth Version) of their Standards of Care that the definition may be justified due to the mental suffering these subjects are prone to face [163]. Other terminology has been coined in an attempt to create definitions without a pathological connotation. For example, the expression transgender is used as an "umbrella term to refer to a diverse group of individuals who cross or transcend culturally-defined categories of

gender [164]" while Transqueer is used to describe persons who do not restrict their gender identity to a "binary understanding of gender" [161]. As made evident through DSM IV-TR and ICD-10 definitions presented above, transsexualism is not only defined by what it is, but also by what it is not. Transsexualism is neither transvestism, which is characterized by "wearing clothing or adopting a gender role presentation that, in a given culture, is more typical of the other sex, nor is it a disorder of sex development, and therefore not a somatic condition" [161, 165-168]. The lack of a consistent somatic component is, for example, depicted by the fact that 97.55% of transsexuals have been shown to display a 46 XX karyotype [169], though exceptions have been presented [170].

1.3.2 Epidemiology

Data on the prevalence of transexualism is strewn across a broad spectrum, for example 1: 2900 for FtM transsexuals and 1:8900 for MtF transsexuals in Singapore [171] or 1:12,900 for MtF and 1:33,800 FtM in Belgium [172]. The most commonly cited study to address transsexual prevalence presents rates of 1:11,900 males and 1:30,400 females [173]. Ratios of FtM and MtF transsexuals also vary, such as 2.3 MtF transsexuals for every FtM transsexual in Germany [174], or a ratio of 1.2:1, with only a discrete predominance of MtF transsexuals, in a study involving multiple European countries. MtF transsexualism is, however, typically accepted as more common [171-173, 175]. Male and Female transsexuals presented for reassignment between 20 to 25 and 25 to 30 years of age, respectively [173]. This distribution suggests a lower age of onset for FtM transsexuals, as is confirmed by Nieder et al. [176]. In addition, 34.5% of FtM and 32.4 % of MtF are in a relationship, 9.5% of FtM and 35.0% of FtM either gave birth to or fathered a child [176], and in general, transsexuals more commonly live in an urbanized environment [173]. The Harry Benjamin International Gender Dysphoria Association stresses that a variety of issues may lead to distortion of actual epidemiologic data, including alack of recognition of gender problems when psychiatric comorbidities are diagnosed [163].

1.3.3 Etiology

Research into the etiology of transsexualism carries a strong endocrinologic emphasis, made visible through a focus on the role of exposure to prenatal androgens. Available studies largely

utilize the context of congenital adrenal hyperplasia (CAH), which provides an androgen exposed environment for fetuses, as a higher percentage of FtM transsexualism has been reported among this patient group [177]. These studies show that 46XX CAH patients display masculinization of later gender related behavior [178] and male typical play behavior, the second of which correlates with dissatisfaction with female gender in adulthood [179]. Interestingly, increasing severity of CAH disease may also be associated with higher propensity for male behavior [178]. However, Meyer-Bahlburg et al. differentiate that while prenatal androgenization may masculinize gender related behavior, it does not necessarily lead to masculinized gender identity [180]. In addition, boys exposed to increased levels of prenatal androgens, however, do not exhibit altered play behavior [179], suggesting that processes relevant for the development of FtM transsexualism are likely to override this mechanism [181]. Gooren et al. summarize that, while prenatal androgen exposure does predispose for development of a male gender identity, this relationship is not definite [181]. Of additional interest is the strong association that has been shown between FtM transsexuals, polycystic ovarian syndrome, and resulting hyperandrogenemia [182], which underlines the role of endocrinologic mechanisms in the development of transsexualism.

Through the selection of genes investigated, genetic studies also follow an endocrinologic focus. Transsexuals have been shown to differ from controls in the mean length of a repeat polymorphism within a gene encoding for the estrogen receptor beta gene [183]. Also, frequencies of a particular allele of the CYP 17 gene, which is associated with elevated plasma levels of estrogen (E2), progesterone, and testosterone [184] show significant differences between FTM transsexuals and female controls [185], underlining the role of these hormones in transsexual development. However, investigation into the role of polymorphisms within the androgen receptor and aromatase genes, offer less clear results [183, 186].

Gene polymorphism studies are supplemented by twin studies that show transsexual concordance between monozygotic twin pairs, sibling pairs, and father-son pairs [187]. This pattern is however, contradicted by descriptions of discordant monozygotic twin pairs [188]. The role of life experiences has therefore also been investigated through discussion of family patterns [189] and of an association with childhood trauma [190, 191]. Therefore, though patterns emerge, solid evidence of consistent etiologic processes is lacking.

1.3.4. Comorbidity

Transsexuals have been described as more vulnerable to comorbidities, possibly as a result of stressors associated with stigma, prejudice and discrimination [161]. In fact, 71% of a group of subjects with GID displayed criteria for a current and/or lifetime Axis-I disorder, respectively [192]. Contrasting studies, however, may be interpreted to suggest that gender dysphoria and transsexuality are often isolated phenomena. For example, though 25% of subjects with gender dysphoria reported prior problems with substance abuse, less than 10% showed problems associated with mental illness, genital mutilation, or suicide attempts [193]. In addition, while transsexual subjects generally score higher than healthy controls on symptoms checklists, they rate lower than patients with personality disorders [194].

1.3.5 Clinical Management

Though the diagnostic process is based on criteria defined by DSM-IV and ICD-10, it is extensive in order to compensate for a lack of objective tests [189]. Real life experience of living as the desired sex, while often falsely interpreted as a solid diagnostic criteria, is essential for the transition process as it allows for the exploration of gender identity. Therapy typically consists of a triad of interventions including hormone therapy, real life experience, and surgical treatment, though psychotherapeutic support is also of great importance. The Harry Benjamin International Gender Dysphoria Association's Standards of Care for Gender Identity Disorders recommend assessment by at least two senior specialists and differentiate between eligibility and readiness as to when therapeutic intervention should commence. In summary, subjects may be eligible for hormone therapy at the age of 18, when they can demonstrate considerable knowledge of associated benefits and risks and after a documented real life experience of three months or a considerable period of psychotherapy, usually at least 3 months. Readiness criteria, in contrast, focuses on progress related to consolidation of gender identity and real life, stable or stabilizing mental health status, and suspected future compliance [163]. Suggested therapy for adults primarily includes testosterone for FtM patients, possibly in combination with progestins for cessation of uterine bleeding and estrogen and anti-androgens, both each alone and in combination, for FtM patients [162]. Intended effects of testosterone include male hair growth, lowering of voice pitch, and body masculinization, while estrogens are applied in order to

facilitate feminization of body fat distribution, breast growth, and libido and erection reduction as well as possible mood lightening. Application of anti-androgens in addition to estrogens may specifically discourage further male hair growth [162, 195]. Possible risks, for example, for metabolic symptoms as a result of FtM therapy and venous thromboembolisms, though primarily of relevance in the context of orally applied ethinylestradiol, and depression as may be provoked by MtF therapy, must be considered in therapy management. Skeletal and hepatic effects as well as an increased risk for hormone sensitive cancers must be also considered [195-197]. A more detailed account of the hormone therapy applied in our study is included in the Methods section. To further support patients, surgical procedures such as genital gender reassignment surgery, mastectomy/breast enlargement, voice surgery and facial feminization surgery may be performed [198, 199], though genital surgery is typically not commenced until completion of at least 12 months of continuous hormone therapy. In addition, psychotherapy focused on education and establishment of realistic goals may be of benefit [163].

1.3.6 Quality of Life

Quality of life studies have demonstrated beneficial effects of therapeutic intervention. Hormone therapy applied to transsexuals has been shown to be associated with increased quality of life [200], while postoperative patients give low self ratings of insecurity level related to their bodies [201]. These findings affirm the importance of an interdisciplinary approach to therapy.

1.4 Neurobiological Basis of Sex Differences: Cross-sex Hormone Therapy as Investigatory Approach

In general, in order to investigate the neurobiological basis of sex differences, information is gleaned from studies that track the menstrual cycle as well as reproductive and menopausal changes in women, apply exogenous hormones and analyze endogenous hormone levels, all in relationship to the psychological function or psychiatric symptom of interest. Few studies, however, have used fMRI to investigate the effects of long-term cross-sex hormone application on the brain in transsexual persons.

While structural differences in transsexuals have also been investigated [202, 203], fMRI studies on cross-sex hormone treatment, as stated above, are few and far between. Using fMRI in both

MtF and FtM transsexuals, Sommer et al. showed that, in both groups, cross-sex hormone treatment increased brain activation in response to a language task and that total language related activity correlated with estradiol levels after cross-sex hormone treatment [204]. In the same study, hormone treatment did not result in an increase of mental rotation associated activation. Total activation during the mental rotation task was, however, correlated with testosterone-levels after hormone therapy. In contrast, Schöning et al. suggest that transsexual persons may exhibit *a priori* neurobiological differences by comparing brain activation during a mental rotation task in two groups of MtF transsexuals, one prior to and one receiving cross-sex hormone therapy, to that of a group of subjects without Gender Identity Disorder (GID). Men without GID displayed greater activation of the left parietal cortex while both transsexual groups, regardless of hormone therapy status, showed stronger activation of temporal-occipital region [205]. Carillo et al. also demonstrate mental rotation task associated activation patterns that differ between MtF transsexuals undergoing opposite-sex hormone treatment and male as well as female controls, but do not differ from FtM transsexuals undergoing treatment [206]. However, the effect of long term cross-sex hormone therapy on behavioral results and cerebral activation during the SST has yet to be investigated.

1.5 MRI

1.5.1 MRI Principles

Magnetic Resonance Imaging, as first propagated in 1973 by both Lauterbur et al. and Mansfield et al., has developed into a spectrum of differentiated methods, a selection of which find particular relevance in neurobiological research [207, 208]. As a non-invasive imaging modality free of ionizing radiation, MRI produces excellent soft tissue contrast for effective differentiation of grey and white tissue and, when applied to obtain functional data, allows for the registration of dynamic cognitive processes with ample spatial and adequate temporal resolution [209, 210].

Hydrogen is essential to proton-based MRI due to its ubiquitous presence in the human body and the composition of its nucleus of a solitary proton. Nearly 100% of naturally abundant hydrogen is in the isotope form ^{1}H. This characteristic allows the particle to exhibit spin around a Z-axis, which, together with its positive charge and mass, results in a magnetic field. Supercharging magnet coils integrated into MRI systems produce a homogenous magnetic field, or B_0, to

synchronize naturally randomly oriented spins into a parallel organization. This component is crucial for image quality, as B_0 strength correlates linearly with the Signal to Noise Ratio (SNR) and magnetic field homogeneity is essential for production of a homogenous signal. Therefore, field strengths upwards of 9 Tesla (T) are used in experimental settings [210-212].

In a process known as excitation, an alternating magnetic field, or B_1 is applied by a transmitter radiofrequency system, known as such because waves applied exhibit a frequency in the Mega Hertz (MHz) range. Image quality depends on the consistency of the strength of the radiofrequency waves applied. Energy is absorbed by ^{1}H atoms, which, as a result, pivot or align with, and precess around, the axis of the magnetic field. However, in order for spins to effectively absorb energy, it must be applied within their larmor frequency (ω). The larmor frequency is linearly dependent on the strength of the magnetic field and the gyromagnetic proportion (γ), a characteristic that is specific to individual particles. For example, the larmor frequency attributed to ^{1}H atoms increases from 64 MHz at 1.5 T to 128MHz at 3 T. This relationship is expressed by the larmor equation.

$$\omega = \gamma * B_0 \tag{1.1}$$

Cessation of radio frequency waves causes the spins to dephase, or realign with B_0, regain their lower energy state, and hereby produce a radiofrequency signal that is detected by receive only coils. In order to allow for spatial localization of MR signals, gradient coils produce time-varying, orthogonal gradient fields (G_x, G_y, G_z). Rapid acquisition of large examination volumes relies on the capability of this system to swiftly switch the highest possible gradient amplitudes (mT/m), within the shortest possible time frame. A combination of these characteristics is also known as the gradient slew rate (mT/m/ms). In addition, linearity of gradients applied upholds image quality by preventing image distortion [211, 212].

Sequence choice, a variety of MR parameters, and tissue characteristics are relevant for MRI modality, contrast and resolution. Sequences are predetermined combinations of radiofrequency pulses and gradient switching patterns, which, in combination with a certain set of data acquisition parameters, are defined as a protocol. The most important MR parameters are TE, or echo time, and TR, or repetition time, which indicate the time between radio frequency excitation and signal acquisition, and the time between two radiofrequency excitations, respectively. TR and

TE combination and length determine the relative weighting of tissues to one another. For example, protocols with short TR and TE yield T1weighted images (T1w), while application long TR and TE results in a T2 weighted image (T2w and T2*w). Analogously, image weighting can also be explained as the interaction of tissue properties with a selection of time constants describing signal build up and decay after excitation. The longitudinal or spin-lattice relaxation time (T_1) indicates the rate at which magnetization builds up after excitation; tissues with longer T_1 appear hypointense on T1w images. In contrast, the transverse or spin-spin relaxation times (T_2 and T_2*) refer to signal decay; tissues with longer T_2 appear hyperintense on T2w images. T2w and T2*w images differ primarily in selection of excitation and gradient pulses applied. T2w images are the result of spin echo sequences, or application of a 180° radiofrequency pulse after a 90° pulse to expedite maximum signal strength during signal acquisition, while T2*w images are created through the use of gradient echoes. Though they also facilitate more effective signal acquisition, gradient echoes utilize application of counteractive gradients in order to relocate MRI signal to the middle of signal acquisition. fMRI most often applies T2*w signal acquisition, as this can be acquired quickly [209-213].

Echo Planar Imaging (EPI) allows for rapid signal acquisition and is therefore also of particular importance for fMRI. As a single shot technique, all data from a certain slice is acquired after a single radio frequency excitation [209].

Data acquired during MRI is in k-space, or Fourier space, which may be seen as "a mathematical model for spin-gradient interaction," and is then transformed into a 2-dimensional image using Fourier Transformation [211].

1.5.2 fMRI

This study utilizes BOLD contrast based fMRI. In addition to its implementation in experimental settings, fMRI has also been developed for clinical applications, especially in the realm of preoperative planning [214-217].

Blood Oxygen Level Dependent Contrast

BOLD contrast is based on the finding that, in T2*w images, as are standard in BOLD fMRI, deoxygenated hemoglobin (Hb) is paramagnetic while oxygenated hemoglobin is diamagnetic [211, 218]. As a result, deoxygenated Hb dephases more rapidly and signals are retained longer in regions that contain more oxygenated, and less deoxygenated, Hb [210]. Deoxygenated Hb was first defined as a natural intravascular contrast agent in 1990 in mice using gradient echo sequences at high field strengths [218, 219]. Application of this concept to humans using simple paradigms to detect function dependent variations in contrast has allowed for the establishment of a contrast: activity relationship [220-222]. This relationship, however, is complex, as it must link neural activity, oxygen supply and metabolism, and blood flow.

BOLD signal has been shown to be dependent on regional oxygen metabolism, regional cerebral blood volume, and regional cerebral blood flow. While increased oxygen consumption and larger regional blood volumes increase deoxyhemoglobin, larger regional cerebral blood flow decreases deoxyhemoglobin amount. However, an increase in neural activity leads to an increase in all three of these factors. As these are dynamic parameters, BOLD signals that are detected as a result of these changes follow a time course. First, a stimulus is followed by the fast response or early dip, which is likely to be caused by an increase in oxygen metabolism, and therefore increase in deoxyhemoglobin, that precedes an increase in blood volume and flow. This early dip, which peaks at approximately 2 seconds post-stimulus [223], is of particular interest for BOLD based fMRI as it may represent an uncoupling of oxygen consumption and cerebral blood flow. In addition, its localization may actually more specifically reflect that of the neural activity of interest than the main BOLD effect, which peaks about 5 seconds after stimulus occurrence [224], does [225-227]. Lastly, the main BOLD response, or signal of interest in BOLD fMRI studies, is followed by a post-stimulus undershoot which is linked to sustained oxygen consumption even after blood flow and volume have returned to their pre-activation state [228]. However, which aspect of neural activity is represented by these changes remains unclear. While it has been shown that the hemodynamic response correlates with local field potential, LFP [229], it has also been suggested that BOLD signal may reflect neural input and processing rather than neural output [230].

fMRI Task Design

Application of an appropriate task design facilitates efficient localization of cognitive processes in BOLD based fMRI experiments. In blocked design experiments, the additive nature of the hemodynamic response is harnessed and tasks are performed for an extended and blocked amount of time in order to facilitate the development of a consistent BOLD signal in regions associated with the mental process of interest. Event-related designs monitor BOLD signal related to individual trials, therefore allowing for isolation of neural activity attributed to individual mental subprocesses. While rapid stimulus presentation and randomization of trials made possible through event-related designs may reduce anticipation and habituation, these benefits also carry the risk of BOLD signal overlap [231].

fMRI Data Preprocessing and Analysis

Prior to analysis using a General Linear Model [232], data must be preprocessed. In order to allow for the assumption that all fMRI data related to a single trial was acquired simultaneously, time shifts that result from slice based data procuration, must be corrected in a processes known as slice timing correction. Motion correction allows for the restriction of movement artifacts by aligning a single image with the image mean using translation and rotation. During coregistraton, functional and structural data is aligned while normalization adapts each subject's data to that of a template brain, such as the Montreal Neurological Institute (MNI) template or Tailarach. Lastly, spatial smoothing convolutes images with a Gaussian kernel, which commonly consists of 4-12 mm at FWHM [233] .

2.0 Objectives

First, we aim to validate our application of the SST for the measurement of SST motor activity, motor inhibition and the performance monitoring related process of error detection. This will be achieved by showing consistencies between activation patterns attained through comparison of all participating subjects with those described in the literature to be associated with motor inhibition and performance monitoring in general as well as to those specifically described in the context of the SST.

Second, sex differences in inhibition and performance monitoring, made evident through imaging and behavioral data, as well as through differences in clinical manifestations of inhibition and performance monitoring deficits raise the question of whether the above mentioned sex differences are associated with sex steroid hormones. In addition, activity associated with other executive cognitive processes has been shown to be dependent on cross-sex hormone therapy. We thus aim to investigate the influence of cross-sex hormone therapy on aspects of executive cognitive control including motor inhibition and the performance monitoring related function of error detection, in FtM and MtF transsexuals, using 7 Tesla ultrahigh-field fMRI. Implementing the SST as a model, we aim to analyze changes in patterns of cerebral activation in response to hormone therapy administration. Results will allow us to define motor, inhibitory and performance monitoring related regions that may show hormone dependence, and therefore to analyze the role that sex steroid hormones are postulated to play in sex differences that have been observed in these processes.

3.0 Hypothesis

1. Regional brain activation patterns measured over all subjects during the SST will be concordant with findings described in the literature. Activation findings will be consistent with regions associated with motor activity, motor inhibition and performance monitoring, specifically error detection, both in general and on a task specific level.

2. Task specific brain activation will change significantly as a result of cross-sex hormone therapy in FtM and MtF transsexual persons. Regions of particular interest include those generally associated with motor activity, response inhibition and error detection, in addition to those in which sex differences in the SST have been shown.

4.0 Materials and Methods

4.1 Study Design

This project is part of a larger study entitled "Effects of steroid hormones on human brain function, structure and connectivity: A longitudinal study using 7 Tesla Ultrahigh-field Magnetic Resonance Imaging" that is financed by a grant awarded to Assoc. Prof. Rupert Lanzenberger,

M.D., P.D. by the FWF Austrian Science Fund (P 23021, 2010– 2013). Recruitment for this study, which is of single-blind, mono-center design, began in January 2011 and is ongoing. 20 FtM, 20 MtF, 20 female controls and 20 male controls will be included in this study and will participate in 5 study visits: a screening visit, three 7T ultrahigh-field fMRI visits (the first at baseline, the second four weeks after start of cross-sex hormone therapy, and the third four months after start of cross-sex hormone therapy, as well as a final visit).

Data included in this diploma thesis, which is part of the ongoing project described above, includes 17 subjects comprising 9 FtM and 8 MtF. FMRI SST data from the first two 7T ultrahigh-field fMRI visits was analyzed.

4.2 Subjects

9 FtM transsexual persons 19 to 35 years of age (mean age ± SD = 26.0 ± 6.0 years) and 8 MtF transsexual persons 20 to 39 years of age (mean age ± SD= 29.5 ± 7.0 years) seeking long term cross-sex hormone therapy at the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder (Dr. Ulrike Kaufmann, MD) at the Medical University of Vienna, were recruited to partake in this study.

4.2.1 Inclusion/Exclusion Criteria

The following criteria were used to determine suitability of potential subjects for this project:

Inclusion criteria for transsexual subjects:
• DSM-IV diagnosis of Gender Identity Disorder (DSM-IV: 302.85; ICD-10: F64.0) by a structured clinical interview (SCID)
• General physical health based on history, physical examination, ECG, laboratory screening
• Willingness and competence to sign informed consent forms
• 18 -50 years of age

Exclusion criteria for transsexual subjects:
• Severe neurological or internal disease
• Abnormal results in routine laboratory screening or general physical examination
• Chronic or continuous medication intake
• Steroid hormone treatment within 2 months of inclusion (including hormonal contraception and phytohormones)
• Treatment with psychopharmacological medication
• Current drug abuse (determined using a urine drug screening test at the screening visit)
• Pregnancy (determined using a urine pregnancy test at the screening visit and at the first MRI scan)
• Failure to comply with the study protocol or to follow the instructions of the investigating team
• Lack of MRI suitability, intracorporeal metal (including all metal implants and stainless steel grafts excluding dental amalgam implants), severe claustrophobia

4.3 Visits

Subjects participating in this project partook in a screening visit to establish suitability, in addition to two fMRI visits, which took place at baseline and at one month after commencement of cross-sex hormone therapy. The screening visit included a medical check-up consisting of a physical examination, an electrocardiogram (ECG) and a blood draw for sampling of routine parameters. A urine drug screening was completed at the screening visit and urine pregnancy tests were performed in FtM subjects at the screening and first fMRI visits. The first study visit also included a Structured Clinical Interview for DSM-IV diagnosis (SCID) performed by an experienced psychiatrist to investigate possible psychiatric symptoms. Findings warranting a psychiatric diagnosis were, however, not necessarily considered exclusion criteria because of the frequency of psychiatric comorbidities in transsexual persons.

The time period between start of cross-sex hormone therapy and fMRI scan session two was approximately 4 weeks (range = 23-51 days).

4.4 Hormone Therapy

Transsexual participants received cross-sex hormone treatment in line with protocols routinely implemented at the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder (Dr. Ulrike Kaufmann, MD) at the Medical University of Vienna. FtM subjects obtained either 1000 mg/12 weeks testosterone undecanoate (Nebido® 250mg/ml, 4ml vial, intramuscular) or 50 mg/day testosterone (Testogel® 50mg/5g bag, transdermal). If menstruation persisted, FtM participants received 10-15 mg/day lynestrenol (Orgametril® 5mg, oral) or 75 μg/day desogestrel (Cerazette® 75μg, oral).

MtF participants recieved 50 mg/day cyproterone acetate (Androcur® 50 mg tablet, oral). Additionally, MtF subjects, especially those over 40 years of age, received 100 μg estradiol/day (Estradot®/Estramon® 100μg/24hrs, transdermal therapeutic system (TTS) applied twice a week) while those under 40 years of age received 4 mg/day estradiol hemihydrate (Estrofem® 2 mg, oral). Alternatively, subjects received estradiol hemihydrate 0,75-1,5 mg/day (Estro-Gel® 0.75mg/1,25 g/day, transdermal). In the case of extensive hair loss, patients had the option of taking 2,5 mg/day of the 5-alpha-reductase-inhibitor Finasteride (Actavis®/Arcana®/Aurobindo® 5 mg, oral).

In some cases, MtF and FtM received a GnRH-analogue with options including 105 μg/day triptorelin acetate (Decapeptyl® 100μg in 1 ml prefilled syringe, s.c.), triptorelin acetate 4.12 mg/month (Decapeptyl® 4.12mg / 172mg powder for suspension for injection s.c. or i.m.), or 11.25 mg/3 months leuprorelin acetate (Trenantone® 11,25 g/130mg powder for suspension for injection s.c.) may have been used if appropriate.

4.5 MRI

4.5.1 fMRI

fMRI measurements were performed using an ultrahigh-field 7T whole-body MR scanner (Siemens Medical, Germany) installed at the MR center of excellence, Medical University of Vienna. Ventral brain regions, which were of interest for this project, are susceptible to signal loss as a result of intra-voxel dephasing effects. These effects are due to their close anatomical

proximity to tissue borders and air cavities, which go hand in hand with susceptibility changes, resulting in field inhomogeneity. In order to compensate for this effect and to incorporate the benefits of increased sensitivity and specificity associated with ultrahigh-field scanning, a protocol optimized for imaging these brain regions at 7T was developed. This protocol was based on a similar protocol previously implemented at 3 T to measure brain regions susceptible to similar effects [234] and utilized parallel imaging, optimized excitation pulses and readout bandwidths.

Functional data was acquired with a single-shot gradient-recalled EPI with TE=23ms, a matrix size of 128 by 128 by voxels and a field-of-view of 210 by 210 mm. In order to allow for the high spatial and adequate temporal resolution we acquired 32 slices within a repetition time of 1400ms. Before normalization, voxel size, which changed slightly due to a software update, was either 1.5mm x 1.5mm x 3mm or 1.48mm x 1.48mm x 3mm. Standard preprocessing was performed using SPM8 and an in house template and included slice timing correction, normalization into standard MNI- space and smoothing with a Gaussian kernel of 8mm FWHM.

4.6 Stop Signal Task

A SST similar to that used by Li et al. was implemented in this study in order to elucidate brain areas activated during motor activity, motor inhibition, and error detection [1]. This paradigm is a reaction time task consisting of 60 trials, of which 42 (70%) are "Go" and 18 (30%) are "Stop" trials. Subjects completed 2 consecutive runs, each of which lasted 7 minutes, with a rest period of at least 30 sec after each run. The first 10 trials of each run were Go trials while the following 50 trials were randomized between trial outcomes though the ratio described above was retained. The inter-trial interval was jittered between 1 and 3 seconds.

Each run began with a fore-period randomized between 1 and 3 seconds in which subjects were asked to focus on a fixation cross presented on a projection screen. This cross was followed by a white dot, which was followed by a stimulus cue (go signal, white circle) in response to which subjects were prompted to respond quickly with a button press. 30% of go signals were followed by a second stimulus (stop signal, white "X"). Subjects were instructed to refrain from making a response when this second stimulus appeared. The difficulty of the stop trials was dependent on the time between the go and stop signals, or stop signal delay (SSD), and was modified through

adjustment of the SSD. The SSD began at 200ms and, if a go trial was successful, was elongated by 64ms. However, if a subject failed to inhibit their response and a stop error (SE) resulted the SSD was shortened by 64ms. This SSD staircase approach was used to ensure that stop trials ended in approximately 50% stop success (SS) and 50% SE. Other behavioral parameters defined by this paradigm, though not directly evaluated in this project, that are essential for understanding task design include the Go trial reaction time (RT) defined as the time period between go signal and button press, and the stop signal reaction time (SSRT), which can only be computed as the lack of a button press can not be measured by this paradigm design. Li et al. do so by taking the RT and the optimal SSD, or the SSD in which subjects successfully inhibit 50% of trials, into account [1, 77].

As this project is part of a larger study, the SST was included in a list of six other paradigms that were not analyzed for this project, a structural measurement for co-registration, and a resting state activity measurement. The subjects were presented the paradigms in a randomized order and subjects performed a trial run outside of the scanner, prior to fMRI measurement, to familiarize them with the tasks.
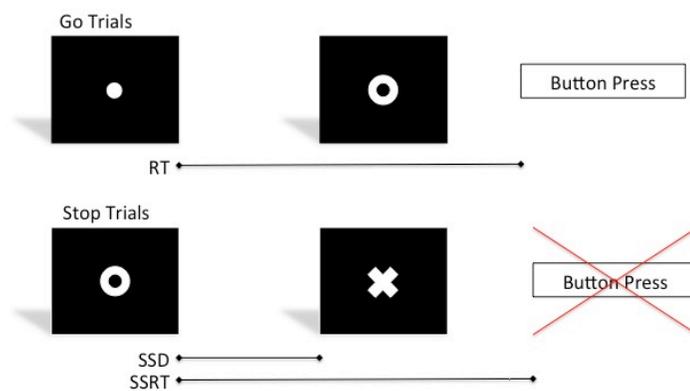

Figure 4.1: Schematic illustration of the SST, based on Li et al. [1], as is implemented in this study. RT: Go trial reaction time, SSD: Stop Signal Delay SSRT: Stop signal reaction time

4.6 Statistical Analysis

First and second level analysis was performed using SPM8. In order to analyze regions associated with motor activity in the context of performance monitoring, motor inhibition and error detection, a General Linear Model based on the task implemented by Li et al. [1] was used. The model applied defined "go success" (GS), "stop success" (SS) and "stop error" (SE) as regressors. As Go trial outcomes depend on the RT, and stop trial outcomes depend on the SSD, these parameters were also incorporated into the design matrix as first level regressors.

First level analysis included the contrasts GS vs baseline (BL), SS vs BL and SE vs BL in order to reveal regions associated with motor action in the context of performance monitoring, successful motor inhibition and error detection, respectively. To allow for isolation of both SS and SE from the motor processes that accompany them the contrasts GS vs SS and GS vs SE were implemented. In addition, for delineation of processes that differentiate SS and SE, the contrast SS vs SE was applied.

In second level analysis, for investigation of general task related activity over all subjects, at both fMRI scan sessions, one-sample T-tests were performed for each contrast.

In order to elucidate changes over time, group differences and their interaction, for each of the contrasts listed above, RM ANOVA was implemented using group (FtM, MtF) as the between subjects factor and time, or fMRI scan session (fMRI scan session one, fMRI scan session two), as the within subject factor. To further investigate effects specific to a certain group for a certain scan, RM ANOVA was followed by *post hoc* one-sample T-tests.

For each of the statistical tests, results are primarily given as p<0.05 FWE-corrected values. If results were not significant at this threshold values are reported at p<0.001 uncorrected.

4.7 Ethical Section

This study has been approved by the Medical Unversity of Vienna ethics committee (EK 644/2010) and was performed in accordance with the Declaration of Helsinki (1964), including current revisions, the Austrian Arzneimittelgesetz, the EC-GCP guidelines, and the guidelines for Good Scientific Practice required at the Medical University of Vienna. All subjects were asked for written informed consent prior to their inclusion in the study and were insured through the Department of Psychiatry in accordance with §32 of the Austrian Medicines Act. Subjects were

informed that they may withdraw from the study at any time and that the investigator may remove any subject from the trial if exclusion criteria were met.

5.0 Results

5.1 Task Related Activation over all Subjects

One-Sample T-Tests performed across all subjects for the contrasts GS vs BL, SS vs BL, SE vs BL, GS vs SS, GS vs SE and SS vs SE revealed activity within regions typically associated with motor activity, motor inhibition, and error detection.

The contrast GS vs BL, implemented for localization of regions representing motor activity in the context of performance monitoring, showed significant activation within motor regions including the left supplementary motor area (BA=6, T=8.88) as well as left (BA=6, T=7.67) and right precentral gryus (BA=4, T=9.58). In addition, left (BA=48, T=10.07) and right (BA=48, T=8.17) insular regions were activated together with left (BA=48, T=8.15) and right (BA=6, T=7.16) inferior frontal, right middle frontal (BA=46, T=6.95) and left midcingulate cortex (BA=32, T=7.87). A variety of occipital (T=8.93-6.91), temporal (T=8.57-6.88) and parietal (T=9.77-6.03) regions, together with a left lingual (BA=19, T=9.78) area, also showed activation as a result of this contrast. All T values are significant at p<0.05 FWE-corrected at the voxel and cluster level. Regions exhibiting activation during this contrast are summarized in Table 5.1.

Table 5.1: One Sample T-Test, all subjects, contrast Go Success vs Baseline

Anatomical Region (AAL)	(BA)	Cluster size (*k*)	MNI (mm) x,y,z	Peak T Value
Insula, L	48	1597	-36,18,4	10.07[†‡]
Inferior frontal cortex, pars opercularis, L	48		-50,12,4	8.15[†‡]
Insula, R	48	385	38,14,2	8.17[†‡]
Inferior frontal cortex, pars opercularis, R	6	35	58,10,16	7.16[†‡]
Middle frontal cortex, R	46	81	34,52,30	6.95[†‡]
Postcentral G, R	3	1593	48,-32,62	9.77[†‡]
Precentral G, R	4		42,-18,66	9.58[†‡]
Precentral G, L	6	213	-48,-2,52	7.67[†‡]
Supplementary motor area, L	6	880	-6,-6,70	8.88[†‡]

	BA		MNI	
Midcingulate cortex, L	32		-10,16,40	7.87[†‡]
Lingual G, L	19		-36,-86,-14	9.78[†‡]
Middle occipital cortex, L	37	1802	-46,-66,0	8.93[†‡]
Middle temporal cortex, L	37		-54,-60,0	8.57[†‡]
Inferior occipital cortex, R	19	527	44,-78,-8	6.91[†‡]
Inferior parietal cortex, L	40	304	-54,-44,40	7.18[†‡]
Superior temporal cortex, L	42		-58,-44,24	6.88[†‡]
Supramarginal G, R	40	13	58,-44,38	6.03[†‡]

AAL: automated anatomical labeling, BA: Brodmann area
P<0.05, FWE-corrected at [†]voxel and [‡]cluster level

Figure 5.1: Regions showing significant activation (p<0.05 FWE-corrected) for the contrast GS vs BL in a one-sample T-test over all subjects. Crosshair at MNI coordinates (A) 48,11,2 (B) -3,-9,58. The color table indicates T values. Anatomical regions are summarized in Table 5.1.

The contrast SS vs BL, which allows us to elucidate regions activated during successful motor inhibition, also resulted in significant activation of motor regions such as the left precentral gyrus (BA=44, T=12.14), which stretched into activation of the bilateral SMA (p<0.001 uncorrected), though not at FWE-corrected levels. Also, in analogy to the activation patterns observed for the contrast GS vs BL, prefrontal regions such as the left inferior (T=11.44) and middle (BA=46, T=6.36) as well as right middle (BA=45, T=6.29) and superior frontal cortices (BA=6, T=6.11) were also significantly activated when SS and BL were contrasted. This contrast also demonstrated significant activation of the left precuneus (BA=7, T=5.90) and right insula (BA=48, T=8.73) as well as temporal (T=11.81-10.73) and occipital cortical (BA=19, T=10.68) areas. The ACC (T=3.94, p<0.001 uncorrected) also exhibited activation for the contrast.

Activation within these regions, however, did not survive FWE-correction. All T values are significant at p<0.05 FWE-corrected at the voxel and cluster level, unless otherwise specified. Regions displaying activation for SS vs BL are summarized in Table 5.2.

Table 5.2: One Sample T-Test, all subjects, contrast Stop Success vs Baseline

Anatomical Region		Cluster size (k)	MNI (mm)	Peak T Value
(AAL)	(BA)		x,y,z	
Precentral G, L	44	5410	-48,8,32	12.14[†‡]
Inferior frontal cortex, pars orbitalis, L	-		-34,20,-12	11.44[†‡]
Middle frontal cortex, L	46	44	-30,54,30	6.36[†‡]
Middle frontal cortex, R	45	18	44,46,18	6.29[†‡]
Superior frontal cortex, R	6	11	26,-6,74	6.11[†‡s]
Inferior temporal cortex, L	37	5274	-54.-60,-4	11.81[†‡]
Middle temporal cortex, R	21	3761	58,-50,14	10.73[†‡]
Inferior occipital cortex, R	19		44,-80,-6	10.68[†‡]
Insula, R	48	769	34,18,4	8.73[†‡]
Precuneus, L	7	7	-6,-76,56	5.90[†‡]
Anterior cingulate cortex, R	-	20	4,40,20	3.94[+*]

AAL: automated anatomical labeling, BA: Brodmann area
P <0.05, FWE-corrected at [†]voxel and [‡]cluster level
P <0.001, uncorrected at [+]voxel and [*]cluster level
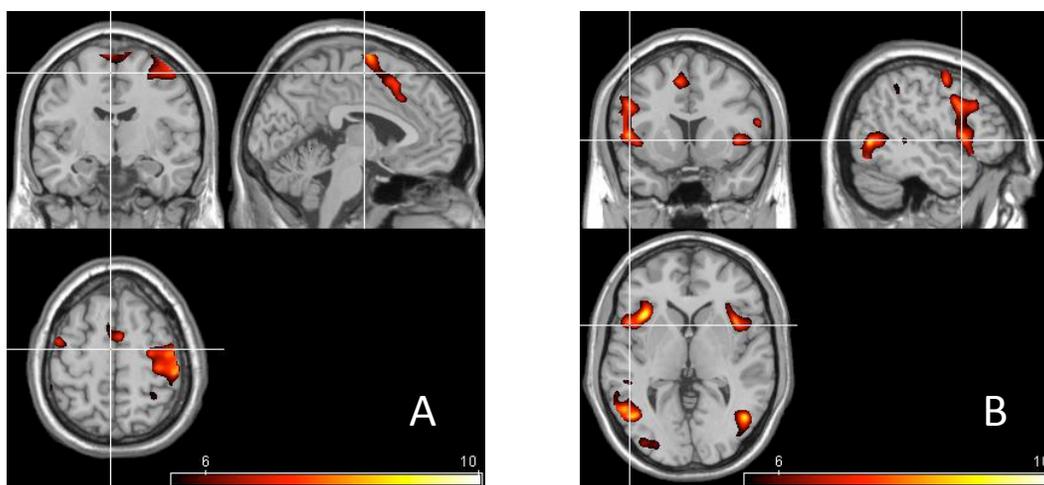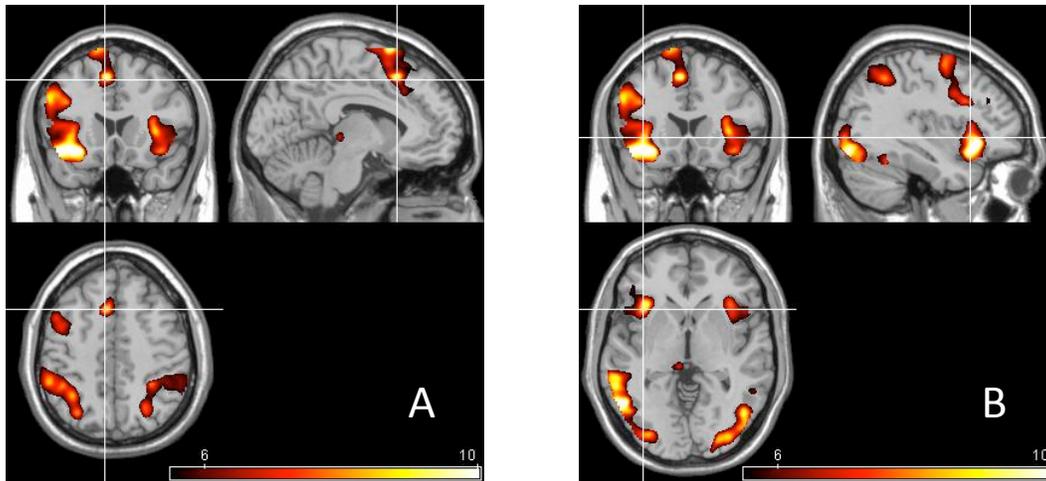

Figure 5.2: Regions significantly activated (p<0.05 FWE-corrected) for the contrast SS vs BL in a one-sample T-test over all subjects. Crosshair at MNI coordinates (A) -7,19,47 (B) -36,19,-1. The color table indicates T values. Anatomical regions summarized in Table 5.2.

SE vs BL was utilized for investigation of regions associated with error detection and resulted in activation of motor regions such as the left SMA (BA=32, T=10.87), left (BA=6, T=8.61) and right (BA=4, T=9.79) precentral cortices and cerebellum (T=8.16). In addition to right inferior (BA=44, T=8.80) and left superior (BA=6, T=9.71) frontal, temporal (T= 9.66-8.59), parietal (BA=7, T=6.07), and occipital regions (BA=18, T=5.76), the bilateral insular (left: BA=47, T=12.33, right: BA=48, T=13.87), bilateral midcingulate (left: T=6.70, right: T=5.72) bilateral thalamic (left: T=6.48, right: T=7.42), and left hippocampal (BA=37, T=5.74) activation was observed. As was the case with the contrast SS vs BL, the ACC was also activated during error detection. Activation within this region was part of a cluster that extended from the left SMA (p<0.001 uncorrected, See Figure 5.3), it did not, however, survive FWE-correction. All T values are significant at p<0.05 FWE-corrected at the voxel and cluster level, unless otherwise specified. Corresponding activation patterns are summarized in Table 5.3.

Table 5.3: One Sample T-Test, all subjects, contrast Stop Error vs Baseline

| Anatomical Region		Cluster size (k)	MNI (mm)	Peak T Value
(AAL)	(BA)		x,y,z	
Insula, R	48	1462	38,14,2	$13.87^{\dagger\ddagger}$
Inferior frontal cortex, pars opercularis, R	44		58,14,18	$8.80^{\dagger\ddagger}$
Insula, L	47	2349	-36,18,-4	$12.33^{\dagger\ddagger}$
Precentral G, L	6		-44,-6,60	$8.61^{\dagger\ddagger}$
Supramarginal G, R	48	3805	54,-42,32	$11.39^{\dagger\ddagger}$
Precentral G, R	4		42,-16,62	$9.79^{\dagger\ddagger}$
Supplementary motor area, L	32	2178	-6,14,46	$10.87^{\dagger\ddagger}$
Superior frontal cortex, L	6		-14,-4,72	$9.71^{\dagger\ddagger}$
Superior temporal cortex, L	42		-60,-44,22	$9.66^{\dagger\ddagger}$
Middle temporal cortex, L	37	3190	-52,-58,-2	$9.36^{\dagger\ddagger}$
Inferior temporal cortex, L	37		-48,-66,-4	$8.59^{\dagger\ddagger}$
Thalamus, R	-	61	14,-18,4	$7.42^{\dagger\ddagger}$
Thalamus, L	-	39	-4,-20,4	$6.48^{\dagger\ddagger}$
Hippocampus, L	37	59	-22,-32,-4	$5.74^{\dagger\ddagger}$
Midcingulate cortex, L	-	28	-8,-28,46	$6.70^{\dagger\ddagger}$
Midcingulate cortex, R	-	6	12,-26,44	$5.72^{\dagger\ddagger}$
Superior parietal cortex, R	7	35	22,-60,52	$6.07^{\dagger\ddagger}$
Inferior occipital cortex, R	18	11	30,-90,0	$5.76^{\dagger\ddagger}$
Cerebellum, vermis, R	-	516	0,-40,-4	$8.16^{\dagger\ddagger}$
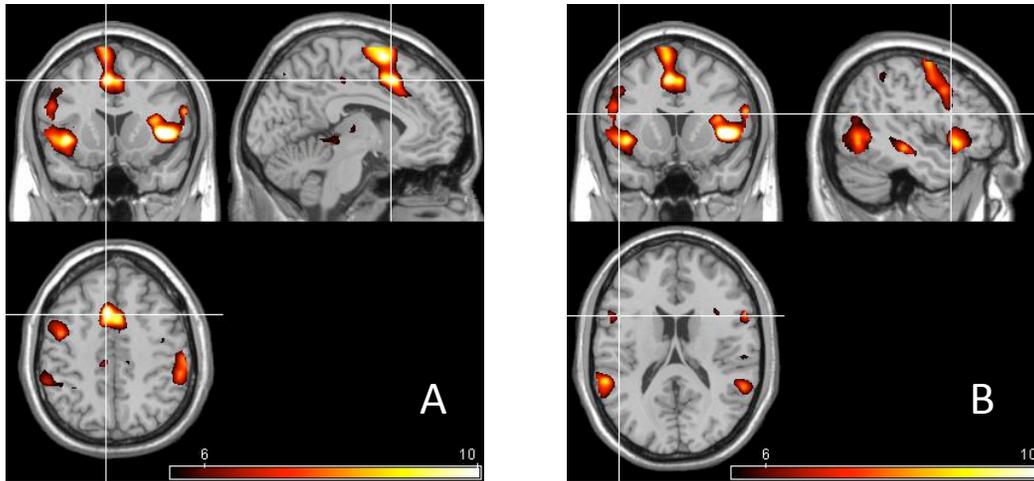
Figure 5.3: Regions showing significant activation (p<0.05 FWE-corrected) for the contrast SE vs BL in a one-sample T-test over all subjects. The pointer is localized to the periphery of activation within the left SMA that extends into the ACC. Crosshair at MNI coordinates (A) -6,14,46 (B) -46,13,18. The color table indicates T values. Anatomical regions are summarized in Table 5.3.

As activation within motor regions was not only present for the contrast Go vs BL, but also for SS vs BL and SE vs BL, the contrasts GS vs SS and GS vs SE were performed in order to isolate activation associated with successful motor inhibition and error detection from that attributed to accompanying motor processes.

While GS resulted in greater activation of the bilateral SMA (left: BA=6 T=6.86, right: T=9.97), right postcentral gyrus (BA=3, T=8.80) and left cerebellum (BA=19, T=5.88) when compared to SS, SS activated a broad spectrum of regions when the contrast was reversed. This activation, in reality a deactivation for the contrast GS vs SS, incorporated a variety of frontal regions such as the bilateral medial superior (left: 32, T=-6.93, right: BA=9, T=-6.46) and bilateral superior (left: T=-6.96, right: BA=8, T=-5.93), bilateral middle (left: BA=9,T=-6.93, right: BA=8, T=-6.99) and bilateral inferior (left: BA=47, T=-5.79, right: BA=45, T=-6.30) frontal cortices. In addition, GS vs BL resulted in deactivation of the left ACC (BA=11, T=-7.31) and bilateral precuneus (left: BA=7, T=-5.71, right: T=-6.50). All T values are significant at p<0.05 FWE-corrected at the voxel and cluster level.

The contrast GS vs SE revealed activation, and therefore greater activity during GS, in the left putamen (T=4.41, p<0.001 uncorrected). Greater activation for SE was observed, amongst other regions, within the right precentral (BA=6, T=-5.85) and postcentral (BA=4, T=-5.95) cortices, the cerebellum (T=-7.56) and the bilateral SMA (left: BA=6, T=-8.29, right: BA=8, T=-6.50). Additionally, the right insula (BA=48, T=-10.98) showed activation. All T values are significant at p<0.05 FWE-corrected at the voxel and cluster level, unless otherwise specified.

Logan and Cowan suggest that cognitive processes involved in SS and SE trial outcomes are partially overlapping [75]. In order to isolate processes specific to either SS or SE from their redundancies, the contrast SS vs SE was performed. This contrast revealed greater activation during successful inhibition in right angular gyrus (BA=39, T=4.76). SE resulted in greater activation of the right precentral (BA=6, T=-8.33) and post central gyri (BA=3, T=-9.69) bilateral putamen (left: BA=11, T=-4.92, right: BA=11, T=-3.64) and bilateral insula (left: BA=47, T=-7.01 right: BA=48 T=-9.39). In addition, SE resulted in greater activation of the left inferior frontal cortex (T=-5.23) and right midcingulate cortex (BA=32, T=-9.83) reaching into the bilateral SMA (p<0.001 uncorrected, see Figure 5.4C). All T values are significant at p<0.001 uncorrected at the cluster and voxel level. Activation patterns revealed by GS vs SS, GS vs SE and SS vs SE contrast are summarized in Table 5.4.

Table 5.4: One Sample T-Test, all subjects, contrast Go Success vs Stop Success, Go Success vs Stop Error and Stop Success vs Stop Error

Anatomical Region (AAL)	(BA)	Cluster size (k)	MNI (mm) x,y,z	Peak T Value
Contrast GS vs SS				
Supplementary motor area, R	-	303	6,2,50	9.97[†‡]
Supplementary motor area, L	6		-4,-6,62	6.86[†‡]
Postcentral G, R	3	776	48,-20,56	8.80[†‡]
Cerebellum, L	19	30	-22,-64,-24	5.88[†‡]
Superior temporal cortex, R	22		60,-56,22	-8.44[†‡]
Angular G, R	39	908	42,-56,36	-7.48[†‡]
Middle Occipital Cortex, R	39		42,-74,30	-6.96[†‡]
Anterior cingulate cortex, L	11	360	-6,38,6	-7.31[†‡]
Medial superior frontal cortex, L	32		2,50,22	-6.93[†‡]
Medial superior frontal cortex, R	9	21	12,54,42	-6.46[†‡]

Region				
Middle frontal cortex, R	8	94	36,8,58	-6.99[†‡]
Superior frontal cortex, L	-	27	-16,14,70	-6.96[†‡]
Middle frontal cortex, L	9	94	-34,10,50	-6.63[†‡]
Superior frontal cortex, R	8	22	16,20,60	-5.93[†‡]
Inferior frontal cortex, pars orbitalis, R	45	24	50,36,-2	-6.30[†‡]
Inferior frontal cortex, pars orbitalis, L	47	12	-46,32,-12	-5.79[†‡]
Middle occipital cortex, L	-	50	-38,-80,40	-6.84[†‡]
Superior temporal pole, L	38	56	-40,24,-18	-6.61[†‡]
Middle temporal cortex, R	21	44	62,-22,-8	-6.60[†‡]
Precuneus, R	-	63	8,-50,40	-6.50[†‡]
Precuneus L	7	7	-4,-70,58	-5.71[†‡]
Superior parietal cortex, R	7	50	28,-74,50	-6.09[†‡]
Contrast GS vs SE				
Putamen, L	-	67	-28,-4,6	4.41[+*]
Insula, R	48	1034	34,22,12	-10.98[†‡]
Supramarginal G, R	48		54,-42,32	-8.38[†‡]
Superior temporal cortex, R	42	619	56,-48,24	-7.55[†‡]
Middle temporal cortex, R	37		56,-54,4	-7.23[†‡]
Middle temporal cortex, L	20	129	-48,-26,-10	-8.03[†‡]
Superior temporal cortex, L	42	237	-60,-42,18	-7.50[†‡]
Inferior occipital cortex, L	37	221	-50,-70,-2	-6.19[†‡]
Supplementary Motor Area, L	6	808	-8,8,64	-8.29[†‡]
Supplementary Motor Area, R	8		6,22,56	-6.50[†‡]
Vermis	-	380	4,-36,-4	-7.56[†‡]
Midcingulate cortex, R	23	32	4,-22,44	-6.03[†‡]
Postcentral G, R	4	14	50,-18,52	-5.95[†‡]
Precentral G, R	6	13	46,-12,60	-5.85[†‡]
Contrast SS vs SE				
Angular G, R	39	159	48,-66,48	4.76[+*]
Midcingulate cortex, R	32		2,8,46	-9.83[+*]
Postcentral G, R	3	22143	44,-22,52	-9.69[+*]
Precentral G, R	6		36,-24,68	-8.33[+*]
Insula, R	48	2182	34,22,12	-9.39[+*]
Insula, L	47		-32,18,-4	-7.01[+*]
Inferior frontal cortex, pars orbitalis, L	-	1479	-36,18,-16	-5.23[+*]
Putamen, L	11		-20,18,-2	-4.92[+*]
Putamen, R	11	11	20,14,-2	-3.64[+*]
Middle temporal cortex, L	20	280	-48,-26,-10	-6.18[+*]

Precuneus, R	-	132	12,-44,54	-4.33[+*]
Superior occipital cortex, L	19	271	-18,-84,38	-4.33[+*]
Fusiform G, L	37	17	-42,-50,-16	-4.05[+*]
Inferior parietal cortex, L	40	28	-30,-48,48	-3.92[+*]

AAL: automated anatomical labeling, BA: Brodmann area
P <0.05, FWE-corrected at [†]voxel and [‡]cluster level
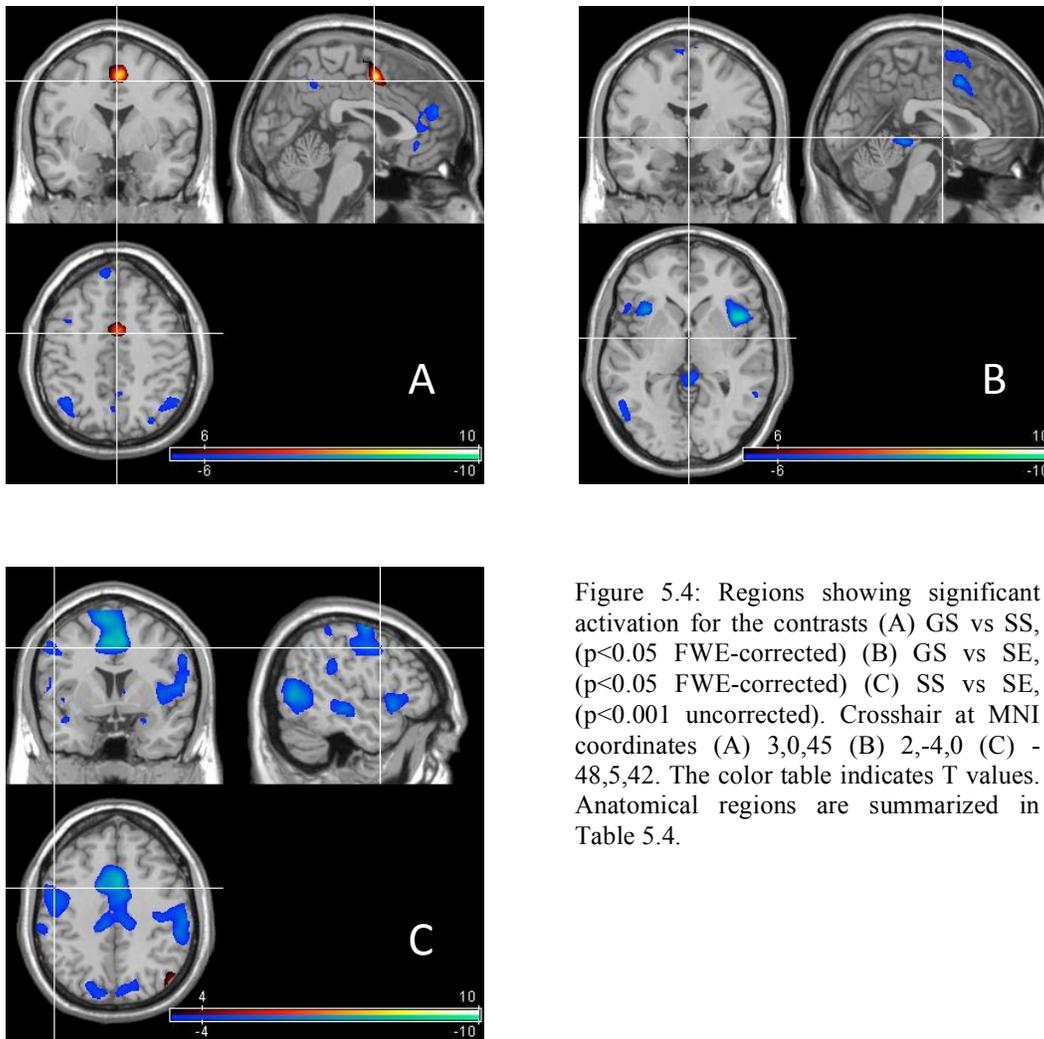P <0.001, uncorrected at [+]voxel and [*]cluster level

Figure 5.4: Regions showing significant activation for the contrasts (A) GS vs SS, (p<0.05 FWE-corrected) (B) GS vs SE, (p<0.05 FWE-corrected) (C) SS vs SE, (p<0.001 uncorrected). Crosshair at MNI coordinates (A) 3,0,45 (B) 2,-4,0 (C) -48,5,42. The color table indicates T values. Anatomical regions are summarized in Table 5.4.

5.2 Repeated Measures Analysis of Variance

RM ANOVA analysis, performed using group (FtM, MtF) as between subjects factor and fMRI scan session (fMRI scan session one, fMRI scan session two) as the within subjects factor, revealed significant effects within regions deemed task relevant both in our one-sample T-test

analysis and in the literature. Main and interaction results presented for these contrasts are restricted to regions relevant to the SST.

5.2.1 Time Effects

Significant differences between fMRI scan session one and fMRI scan session two in regions characteristic of the SST demonstrate the effect of time. Significant time effects within task relevant regions were found for the contrast GS vs BL. For example, the left SMA (BA=32, T=8.90) as well as left middle (BA=46, T=5.58) and left inferior (pars triangularis: BA=48 T=4.50, pars opercularis: BA=44, T=4.74) frontal cortices showed greater activation during the first scan session in comparison to the second.

The same temporal pattern was shown by the right putamen (BA=48, T=5.94) and caudate (BA=25, T=5.70), bilateral precuneus (left: BA=7, T=4.65, right: T=4.41), bilateral hippocampus (left T=5.01, right BA=27, T=4.63) and left thalamus (T=5.72).

Regions that exhibited greater activation during fMRI scan session two than scan session one included bilateral medial superior frontal cortex (left: BA=10, T=-4.28, right: BA=32, T=-4.27) and right middle fronto-orbital cortex (BA=10, T=-4.45) as well as the right superior (BA=8, T=-5.25) and left inferior (pars triangularis: BA=45, T=-4.58, pars orbitalis: BA=47 T=-4.04) frontal cortices. In addition, the left parahippocampus (BA=30, T=-5.17), right SMA (BA=8, T=-3.87), left precuneus (BA=30, T=-4.22) and right precentral gyrus (BA=6, T=-4.32) showed greater activation for fMRI scan session two. All T values are significant at p<0.001 uncorrected at the cluster and voxel level. Corresponding activation patterns are summarized in Table 5.5.

Table 5.5: RM ANOVA Main Effect Scan (fMRI scan session one vs fMRI scan session two), contrast Go Success vs Baseline

Anatomical Region		Cluster size	MNI (mm)	Peak T Value
(AAL)	(BA)	(k)	x,y,z	
Contrast GS vs BL				
Supplementary motor area, L	32	48	-8,22,46	8.90[+*]
Middle frontal cortex, L	46		-38,50,18	5.58[+*]
Inferior frontal cortex, pars triangularis, L	48	251	-36,34,20	4.50[+*]

Inferior frontal cortex, pars opercularis, L	44	83	-50,10,14	4.74[+*]
Putamen, R	48	387	24,12,10	5.94[+*]
Caudate, R	25		10,18,6	5.70[+*]
Thalamus, L	-	45	-14,-18,20	5.72[+*]
Postcentral G, R	43	9	62,-10,34	5.04[+*]
Hippocampus, L	-	47	-14,-36,10	5.01[+*]
Hippocampus, R	27	25	20,-34,2	4.63[+*]
Precuneus, L	7	30	-14,-66,58	4.65[+*]
Precuneus, R	-	22	12,-46,54	4.41[+*]
Superior frontal cortex, R	8	67	24,18,60	-5.25[+*]
Inferior frontal cortex, pars triangularis, L	45	27	-50,38,6	-4.58
Inferior frontal cortex, pars orbitalis, L	47	10	-44,30,-8	-4.04[+*]
Middle fronto-orbital cortex, R	10	15	2,46,-2	-4.45[+*]
Medial superior frontal cortex, L	10	14	-4,64,14	-4.28[+*]
Medial superior frontal cortex, R	32	5	6,40,38	-4.27[+*]
Parahippicampus, L	30	40	-26,-22,-22	-5.17[+*]
Precentral, R	6	22	32,-10,58	-4.32[+*]
Precuneus, L	30	11	-2,-56,14	-4.22[+*]
Supplementary motor area, R	8	11	8,26,66	-3.87[+*]

AAL: automated anatomical labeling, BA: Brodmann area
P <0.001, uncorrected at [+]voxel and [*]cluster level
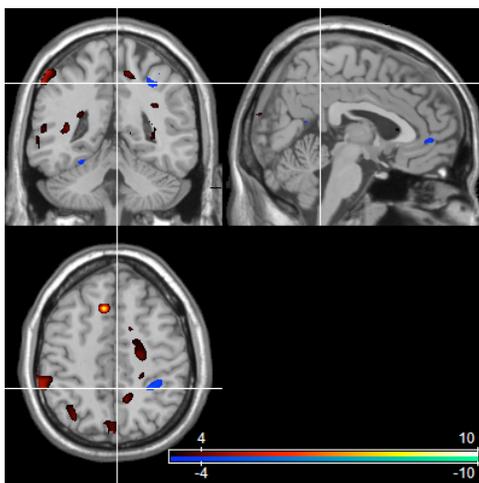

Figure 5.5: Regions showing a significant main effect of time (p<0.001 uncorrected) for the contrast GS vs BL. Regions showing positive activation for this contrast express significantly higher activation for fMRI scan session one while regions exhibiting negative activation show significantly greater activity during fMRI scan session two. Crosshair at MNI coordinates 4,-44,47. The color table indicates T values. Anatomical regions are summarized in Table 5.5.

Interestingly, a positive effect of time for the contrast GS vs BL within the left middle frontal cluster (p<0.001 uncorrected, voxel, for peak see Table 5.5) was accompanied by significant activation during fMRI scan session one but not scan session two for both MtF and FtM in *post-hoc* one-sample T-tests (p<0.001 uncorrected, voxel, see Figure 5.6). Other than GS vs BL, no

other contrasts showed significant results at p<0.001 uncorrected in *post-hoc* one-sample T-tests within anatomical regions also showing significant time effects.
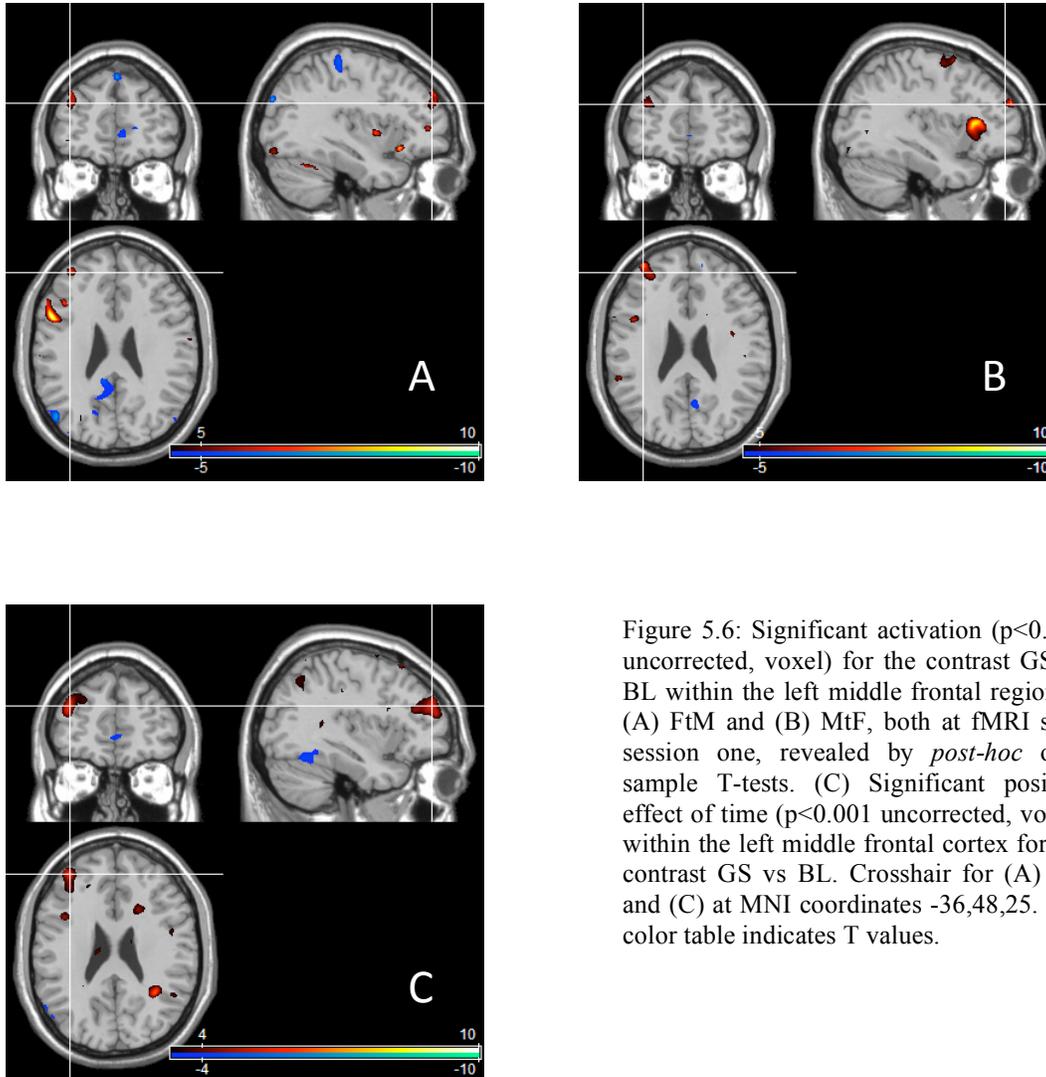

Figure 5.6: Significant activation (p<0.001 uncorrected, voxel) for the contrast GS vs BL within the left middle frontal region in (A) FtM and (B) MtF, both at fMRI scan session one, revealed by *post-hoc* one-sample T-tests. (C) Significant positive effect of time (p<0.001 uncorrected, voxel) within the left middle frontal cortex for the contrast GS vs BL. Crosshair for (A) (B) and (C) at MNI coordinates -36,48,25. The color table indicates T values.

5.2.2 Group Effects

Between group effects were also found in task relevant regions for the contrast GS vs BL and SS vs BL. For the contrast GS vs BL, significantly greater activation was found within FtM in the left medial superior frontal cortex (BA=32, T=6.02). MtF showed greater activation than FtM in the left inferior (pars orbitalis BA=38 T=-5.29, pars triangularis: BA=44 T=-4.38) and right middle (BA=46, T=-4.36) and superior (BA=10, T=-3.97) frontal cortices as well as the right

precentral gyrus (BA=4, T=-8.70) and cuneus (BA=18, T=-4.81) and left midcingulate cortex (T=-4.53).

 FtM showed greater activation than MtF in the left precentral gyrus (BA=6, T=5.92) when SS was contrasted with BL. Greater activation in MtF than in FtM for the contrast SS vs BL was found in motor regions such as the right precentral (BA=6, T=-4.45), bilateral postcentral gyrus (left: BA=3, T=-6.49, right BA= 2, T=-4.41) and right cerebellum (B=18, T=-4.44) as well as in the bilateral insula (left: BA=48, T=-4.99, right: BA=48 T=-4.41). In addition, the right ACC (BA=32 T=-4.84) and a cluster including peaks in the left midcingulate cortex (T=-4.46) and the right precuneus (T=-4.07) showed greater activation in MtF for this contrast, together with the right amygdala (BA=34, T=-4.56) and right superior (BA=11, T=-4.65) and inferior (BA=47, T=-4.24) frontal cortices. All T values are significant at p<0.001 uncorrected at the cluster and voxel level. Corresponding activation patterns are summarized in Table 5.6.

Table 5.6: RM ANOVA Main Effect Group (FtM vs MtF), contrasts Go Success vs Baseline and Stop Success vs Baseline

Anatomical Region		Cluster size	MNI (mm)	Peak T Value
(AAL)	(BA)	(k)	x,y,z	
Contrast GS vs BL				
Medial superior frontal cortex, L	32	9	0,42,32	6.02[+*]
Precentral G, R	4	63	46,-12,44	-8.70[+*]
Inferior frontal cortex, pars orbitalis, L	38	133	-48,24,-8	-5.29[+*]
Inferior frontal cortex, pars triangularis, L	44	16	-44,16,32	-4.38[+*]
Middle frontal cortex, R	46	18	24,44,28	-4.36[+*]
Superior frontal cortex, R	10	6	32,60,12	-3.97[+*]
Cuneus, R	18	147	18,-76,24	-4.81[+*]
Midcingulate cortex, L	-	16	-10,-20,48	-4.53[+*]
Contrast SS vs BL				
Precentral G, L	6	67	-54,4,30	5.92[+*]
Postcentral G, L	3	208	-36,-30,46	-6.49[+*]
Postcentral G, R	2	107	28,-44,60	-4.41[+*]
Precentral G, R	6	6	46,-10,46	-4.45[+*]
Cerebellum, R	18	15	18,-62,-14	-4.44[+*]
Insula, L	48	18	-32,-22,14	-4.99[+*]
Insula, R	48	8	40,-4,-4	-4.41[+*]

Anterior cingulate cortex, R	32	25	14,44,10	-4.84[+*]
Midcingulate cortex, L	-	95	-6,-40,54	-4.46[+*]
Precuneus, R	-		12,-42,56	-4.07[+*]
Superior frontal cortex, R	11	24	20,62,12	-4.65[+*]
Inferior frontal cortex, pars orbitalis, L	47	5	-48,26,-6	-4.24[+*]
Amygdala, R	34	7	24,6,-18	-4.56[+*]

AAL: automated anatomical labeling, BA: Brodmann area
$P < 0.001$, uncorrected at [+]voxel and [*]cluster level

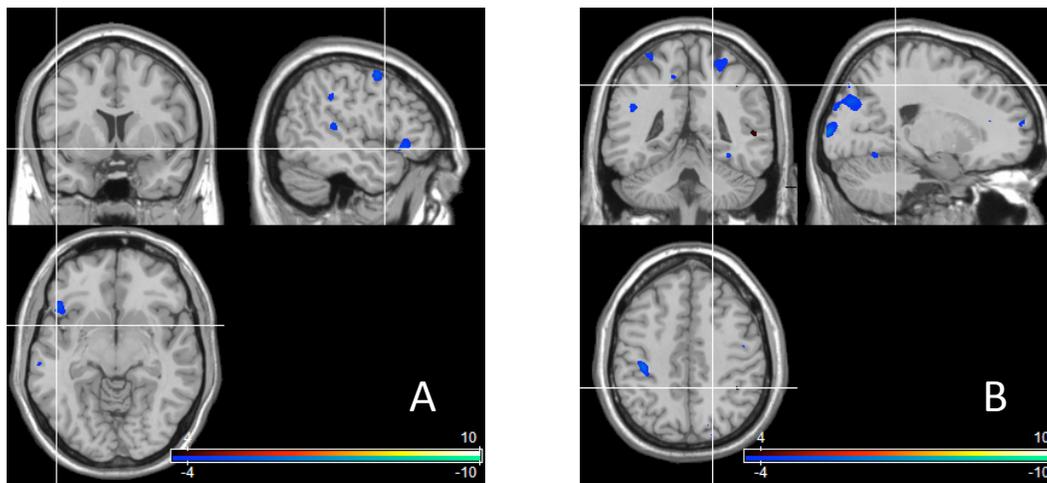

Figure 5.7: Regions showing a significant (p<0.001 uncorrected) main effect of group for the contrast (A) GS vs BL and (B) SS vs BL. Regions showing positive activation are more highly activated in FtM while regions displaying negative activation show higher activation in MtF. Crosshair at MNI coordinates (A) -47,7,-8 (B) 22,-45,45. The color table indicates T values. Anatomical regions are summarized in Table 5.6.

Interestingly, a negative group effect for the contrast GS vs BL was also found within the left precentral gyrus (p<0.001 uncorrected, voxel). This cluster is not listed in Table 5.6 as the peak is outside of the MNI template. In addition, *post-hoc* one-sample T-test showed significant activation within this region for MtF, but not FtM at both scan sessions (p<0.001 uncorrected, voxel, see Figure 5.8).
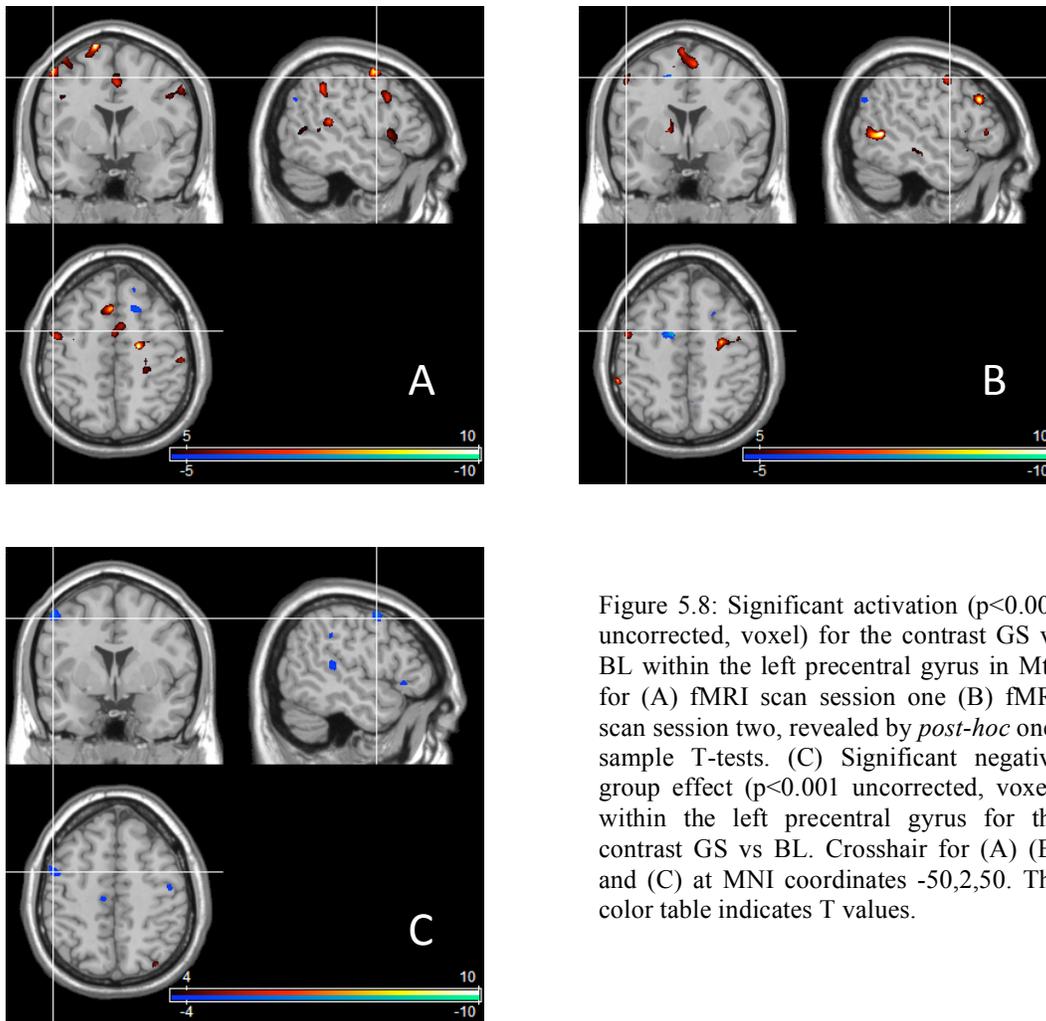
Figure 5.8: Significant activation (p<0.001 uncorrected, voxel) for the contrast GS vs BL within the left precentral gyrus in MtF for (A) fMRI scan session one (B) fMRI scan session two, revealed by *post-hoc* one-sample T-tests. (C) Significant negative group effect (p<0.001 uncorrected, voxel) within the left precentral gyrus for the contrast GS vs BL. Crosshair for (A) (B) and (C) at MNI coordinates -50,2,50. The color table indicates T values.

In addition, the positive group effect for the contrast SS vs BL within the left precentral gyrus cluster described above (p<0.001 uncorrected, voxel, for peak see Table 5.6) was accompanied by significant activation within this region for FtM, but not MtF at both scan sessions (p<0.001 uncorrected, voxel, see Figure 5.9) in *post-hoc* one-sample T-tests. Other than GS vs BL and SS vs BL, no other contrasts showed significant results at p<0.001 uncorrected in *post-hoc* one-sample T-tests within anatomical regions also showing significant group effects.
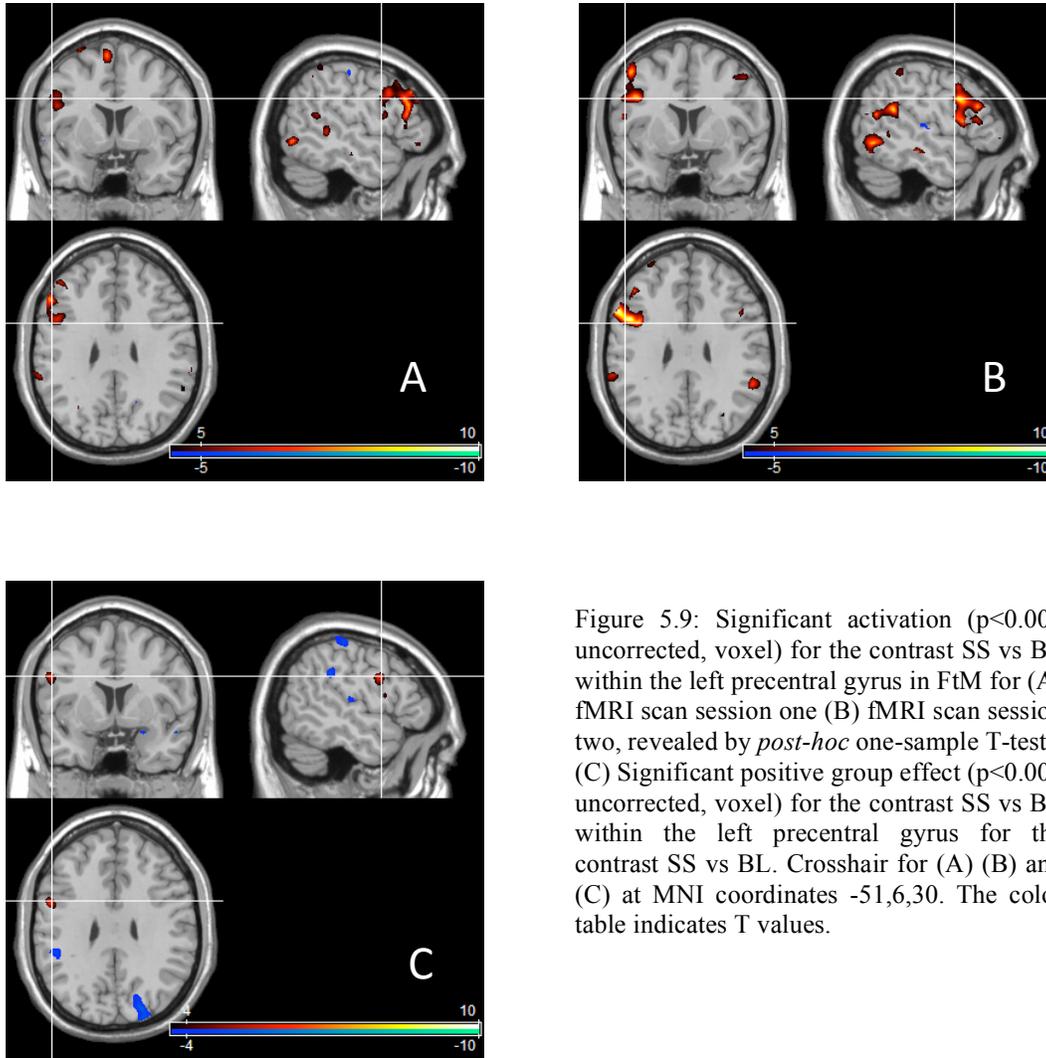
Figure 5.9: Significant activation (p<0.001 uncorrected, voxel) for the contrast SS vs BL within the left precentral gyrus in FtM for (A) fMRI scan session one (B) fMRI scan session two, revealed by *post-hoc* one-sample T-tests. (C) Significant positive group effect (p<0.001 uncorrected, voxel) for the contrast SS vs BL within the left precentral gyrus for the contrast SS vs BL. Crosshair for (A) (B) and (C) at MNI coordinates -51,6,30. The color table indicates T values.

5.2.3 Interaction Effects

RM ANOVA revealed negative group and time interaction effects within the right precentral gyrus (BA=6, T=-5.68) and inferior frontal cortex (BA=44, T=-4.44) together with the left medial superior (BA=32, T=-4.48) and middle frontal cortices (BA=8, T=-4.94). All T values are significant at p<0.001 uncorrected at the cluster and voxel level. Corresponding activation patterns are summarized in Table 5.7. The interaction effect within the left medial superior frontal cortex extends into the left SMA (see Figure 5.10). Interestingly, in *post-hoc* one-sample T-tests, MtF showed significant activation within this region for fMRI scan session one while the SMA was significantly activated in FtM

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during fMRI scan session two (p<0.001 uncorrected, voxel). *Post-hoc* one-sample T-tests reveal that, in the left medial superior frontal cortex, right precentral cortex, and middle frontal cortex activation levels rose within FtM while they sank within MtF, a pattern that, though not significant, mirrors that exhibited by the ACC. In contrast, within the right inferior frontal cortex, FtM showed higher activation than MtF in *post-hoc* one-sample T-tests, though also not at significant levels.

Other than SS vs BL, no other contrasts showed significant results at p<0.001 uncorrected in *post-hoc* one-sample T-tests within anatomical regions also showing significant interaction effects.

Table 5.7: RM ANOVA Interaction, contrast Stop Success vs Baseline

Anatomical Region (AAL)	(BA)	Cluster size (*k*)	MNI (mm) x,y,z	Peak T Value
Contrast SS vs BL				
Precentral G, R	6	139	50,2,24	-5.68^{+*}
Middle frontal cortex, L	8	11	-30,24,62	-4.94^{+*}
Medial superior frontal cortex, L	32	12	-8,22,44	-4.48^{+*}
Inferior frontal cortex, pars opercularis, R	44	30	42,16,32	-4.44^{+*}

AAL: automated anatomical labeling, BA: Brodmann area
P <0.001, uncorrected at $^{+}$voxel and *cluster level
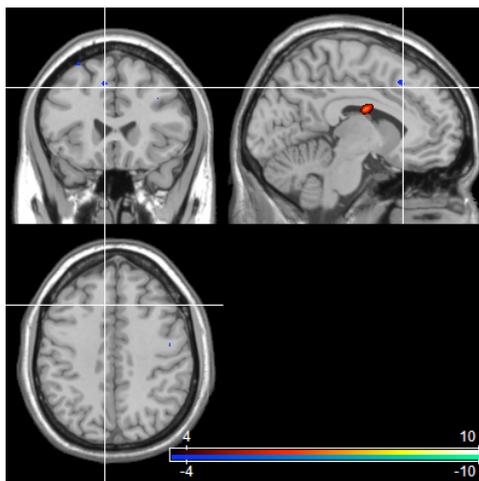

Figure 5.10: Regions showing a significant interaction effect (p<0.001 uncorrected, voxel) for the contrast SS vs BL. The pointer is localized to the periphery of activation found within the left SMA, which extends from a cluster in left the medial superior frontal cortex. Crosshair at MNI coordinates -7,24,42. The color table indicates T values. Anatomical regions are summarized in Table 5.7.

6.0 Discussion

6.1 Task Validation

This study was performed in order to analyze the effects of cross-sex hormone therapy in transsexuals on SST brain activation patterns. This objective was addressed through application of 7T fMRI measurements before and four weeks after start of hormone therapy and subsequent analysis with RM ANOVA. However, objective analysis of activation changes requires task validation in order to confirm that observed changes are specific to the task and to the cognitive processes it measures. For this purpose, trial-outcome comparisons were applied, three of which included a comparison to baseline activity. These contrasts were chosen in order to allow for observation of trial specific activation patterns for the purpose of task validation rather than to specifically isolate activation of particular regions or elucidate particular cognitive sub-processes. We were able to validate our implementation of the SST because the activation patterns elucidated through one-sample T-tests performed across all subjects reflect those described in the literature. These consistencies are present both on a general level, activation was found within regions typically associated with the processes reflected by the contrasts we performed, and on a task specific level, as activation patterns showed consistencies with those described for the SST in particular.

6.1.1 Go Success versus Baseline

We applied the contrast GS vs BL in order to locate regions associated with motor activity. Though this contrast does not provide direct information on inhibitory control, we used the presence of solid motor activation as a parameter to confirm successful task implementation. In addition, it has been emphasized that certain processes induced and measured through the SST overlap partially or process in parallel manner [71, 75]. Therefore, activity measured by GS vs BL, which is induced in a setting together with other processes, such as inhibition and error detection, may be more accurately described as motor activity in the context of performance monitoring.

Accordingly, resulting activation was observed in regions associated with motor activity, including the left SMA and primary somatosensory regions. These regions have been associated

with Go trials, and therefore motor activity, during both stop signal and Go/ No-go tasks. However, other regions typically associated with voluntary action and activated during Go/No-go task Go trials in particular, such as basal ganglia and cerebellar regions were not shown to be activated at FWE-corrected levels [98, 103, 235]. This contrast did, however, show activation of a spectrum of frontal regions including left inferior and right inferior and middle frontal regions. While frontal activation was present within premotor regions which are involved in a variety of motor circuits [235], and activation of the middle frontal cortices has been concretely described in Go/ No-Go task Go trials [102], frontal activity observed during successful Go trials may also reflect their involvement in general response initiation, though this phenomenon is especially described in the context of verbal responses [30]. However, as discussed above, one must assume that trial specific activity within the SST, especially when contrasted with BL activity, is affected by processes induced by other trial types, such as response monitoring and inhibition. Therefore, activation of inferior and middle frontal cortices we observed during Go trials may also be the result of countermanding but coinciding inhibitory processes. This role is well established for inferior and middle frontal regions [86, 87, 97-100]. In addition, though the insula is shown to be typically activated during general motor action [236], the activity we elucidated in this region through application of a GS vs BL contrast may also reflect the error related [76, 86] or inhibitory roles that have been consistently attributed to this area [97, 99, 100].

Anterior cingulate regions, specifically the cingulate motor areas located within the cingulate sulcus have also been associated with motor action [237, 238]. The activation we observed, though situated in a part of the anterior cingulate cortex, specifically the midcingulate cortex, does not correspond with these regions. Therefore, activation of the ACC during Go trials may more likely be a result of the region's role in inhibition, error detection, and conflict monitoring, which will be discussed below.

6.1.2 Stop Success versus Baseline

Similar functional overlaps within regions are also made evident when other contrasts are applied. For example, despite the trial defining factor of successful inhibition, the left precentral gyrus, together with the supplementary motor area, though at a lower statistical threshold (p>0.001 uncorrected), show activation when SS and BL are contrasted. Activation of motor

regions, including the SMA [79], basal ganglia [103], and cerebellar [102] regions is commonly described in both stop signal and Go/No-go trials. Though we can not exclude that subjects may have inhibited their response "at the last minute" and had already initiated a motor response, though without subsequent button press, activation of motor regions in the context of successful inhibition may reflect the aspects of a cue response that occur prior to commencement of their inhibitory counterparts [75]. In addition, the basal ganglia activation described in the literature may reflect their role in the execution of inhibitory control. Aron et al. propose that the subthalamic nucleus plays an essential role in the execution of inhibitory control itself [103]. Though well described in the literature, we did not find activation within the basal ganglia or cerebellum for the contrast SS vs BL at FWE-corrected levels.

However, we did find significant activation within right middle and superior and left middle and inferior frontal regions. Activation within inferior and middle frontal regions is shown to be highly relevant for inhibitory control [104]. These regions are routinely activated in both stop signal and Go/No go tasks analyzed for the specific isolation of inhibitory activation [86, 99]. Congruent with our data, the superior frontal cortex has also been associated with successful response inhibition. For example, Li et al. elucidate activation of the superior frontal gyrus through comparison of subjects with short and long SSRT. SSRT is implicated as a marker for, and its corresponding activation patterns are essential mediators of, successful inhibition [76].

We were also able to show activation within medial frontal regions including the ACC reaching into the SMA for the contrast SS vs BL, though not at FWE-corrected levels. Not only is activation of the ACC during inhibitory control well described in the literature in the context of successful response inhibition [79, 87], the ACC is seen as a central detector for the necessity of control application [131]. The SMA, is also relevant in the neural pathway of inhibitory control in that it may serve as a connector between inferior frontal areas and basal ganglia regions and therefore function as part of a fronto-striatal inhibitory network [129]. Additionally, successful inhibition resulted in activation of the precuneus. The precuneus is considered an association cortex and is appropriately interconnected with a variety of cortical and subcortical regions. Though it is implicated in a spectrum of functions from visuospatial processing and episodic memory retrieval to evaluation of consciousness and self-regulation [239], it is also suggested to be involved in motor control, though this role may focus on the processing and internal representation of visospatial information necessary for coordination of motor action. Though

precuneus activation may therefore be particularly relevant in the coordination of complex motor action requiring bimanual responses but is also suggested to be significant for visualization of motor responses in simple button press tasks [239-241]. We therefore propose that the precuneus activation we observe reflects its associative role in motor control.

6.1.3 Stop Error versus Baseline

The SST in this study was adapted using an SSD staircase method that ensured that 50% of stop trials resulted in errors, based on Li et al. [76]. We assume that error related neural activity during unsuccessful stop trials reflects error detection [71]. Activation of motor regions such as that observed within precentral, supplementary motor and cerebellar regions is to be expected for this contrast as subjects executed a button press. Regions similar to those activated during response inhibition also showed activation for error detection, including frontal and insular regions. The association of these regions with error detection, is also represented in the literature [76, 86, 87, 103]. Activation shown within the frontal cortex may also be induced by subject's awareness for their errors [150].

The contrast SE vs BL also revealed activity within the ACC, more specifically within the midcingulate cortex. As we could also show activation within the ACC for the contrast SS vs BL, the activation patterns we observed in this region are conform with Carter et al.'s suggestion that the this region may be associated with detection of response conflict, which is present during both successful and unsuccessful inhibitory trials, rather than inhibitory control or error detection themselves [106]. In addition, the anterior cingulate is an integral component of effective regulation, especially through its connections to, and role as part of, the executive control system [242]. Activation of the ACC as a result of contrasting SE vs BL may therefore also reflect affective aspects that may accompany failed inhibition. Interestingly, errors also resulted in bilateral thalamus activation. Though not shown in the investigation by Hester et al. mentioned above, the thalamus has been related to error awareness [243].

6.1.4 Isolation from Motor Activity: Go Success versus Stop Success and Go Success versus Stop Error

Both successful and unsuccessful inhibition were associated with activity within regions typical of motor action. The contrasts GS vs SS and GS vs SE were applied in order to differentiate activation resulting from those attributed to performance monitoring from those related to coinciding motor processes [75]. Positive activation within the contrast GS vs SS delineates regions that display greater activation during GS than during SS trials, such as the typical motor regions SMA, postcentral gyrus, and cerebellum. According to our approach, regions exhibiting greater activation during response inhibition than during successful Go trials, such as, frontal, anterior cingulate and precuneus regions, are specific for the inhibitory processes that counteract.

This approach is of particular relevance for the contrast GS vs SE, as both trial outcomes, by definition, include motor action. Interestingly, successful Go trials and unsuccessful inhibition attempts differed in regards to which motor areas they activated. GS resulted in stronger activation of the putamen, though at uncorrected levels, while unsuccessful inhibition resulted in greater activation of the precentral gyrus, cerebellum and SMA. Interestingly, the cerebellum also exhibited activity during the contrast SE vs BL. However, this contrast does not define whether resulting cerebellar activity is a product of its involvement in the motor, or in the competing inhibitory processes, that take place in the context of stop errors. Significantly higher activation of the cerebellum during errors in comparison to successful Go trials, both of which involve a button press, leads us to propose that error related cerebellar activity may largely be the result of the region's direct involvement in error related processing. In fact, Ide et al. propose that the cerebellum, which shows connectivity with the SMA and the thalamus, mediates post error processing by influencing activation of the VLPFC [84].

BOLD signal primarily reflects the input to and processing within a particular region [230]. Therefore, one might assume that regions which show greater activation for this contrast, such as the motor regions mentioned above, the post central gyrus and the insula, receive more error associated neural input than they do input related to GS trials. In addition, this contrast underlines that these regions also exhibit activity that is specific to error related processes.

6.1.5 Stop Success versus Stop Error

Activation patterns associated with the contrast SS vs SE, though they are influenced by cognitive and affective factors that differ between these two trial outcomes, allow us to observe

activity that differentiates the two from each other [76]. While successful inhibition led to greater activation of the angular gyrus, a variety of regions showed significantly higher activation for error trials, including motor regions such as the precentral gyrus, putamen and SMA. This activation pattern also holds true for the postcentral gyrus, insula, inferior frontal, and midcingulate gyrus. We described common activation of the ACC during both SE and SS and proposed that it may be interpreted to support the concept that this region must be involved in a process common to both trial outcomes, such as conflict detection [106]. However, deactivation of the midcingulate region of ACC during SS vs SE may contradict this theory.

The contrast SS vs SE is often applied in the literature, allowing us compare our results on a contrast specific level. We were not able to show the superior, middle and inferior frontal, nor the cingulate activation presented in this context by Li et al. However, the activation we observed, which was greater for SE than for SS trials, within precentral and insular regions corresponds with, though not with the same hemispheric distribution, those presented by the paper mentioned above [76].

The contrasts investigated also displayed activation within a variety of temporal, occipital, and parietal regions. As subjects are confronted with sensory input during fMRI scanning, which must me processed for successful task performance, we theorize that activation within these regions is attributable to their roles as associative cortices.

These results suggest that, though we are able to show compatibility between activation patterns described in the literature to be related to motor activity in the context of performance monitoring, inhibition and error detection, even on a task-specific level, we were not able to reproduce activation patterns on a contrast-specific level. However, the consistencies we can confirm with the literature, even if primarily of a process-specific level, support our implementation of the SST and confirm that contrasts we applied do indeed measure the performance monitoring and inhibitory processes they intend to.

6.2 The Effect of Time, Group, and Hormone Therapy on Stop Signal Task Activation Patterns

6.2.1 The Effect of Time on Stop Signal Task Activation Patterns

Differences in regional brain activation were observed between the first and second fMRI scan sessions in various regions that are relevant to performance of the SST. The discussion of these results must be approached with caution, as they can only be definitely interpreted as a difference in activity between the fMRI measurements but may also be the consequence of a variety of variables that differ between the sessions. For example, these changes may be the result a hormone therapy induced effect that is unspecific to the regimen applied or of practice.

Practice has been shown to affect behavioral and electrophysiological data measured during the SST. Manuel et al. show that SSRT decreases significantly when data from the beginning and end of an hour-long practice session is compared. This behavioral change is accompanied by decrease in activation within the IFG, pre-SMA, precentral cortex and basal ganglia [244]. As SSRT is an index of inhibitory control [76] and we interpret the contrast GS vs BL to represent not only isolated motor activity but motor activity accompanied by performance monitoring and inhibitory processes, the decreased activation we observed within the SMA, IFG, putamen, and caudate for this contrast during the second fMRI scan session may be interpreted in this context. However, this study differs from our project on numerous levels, including differing cue modality, this study applied acoustic while we applied visual stimuli, trial evaluated, GS vs BL focuses on go trials while SSRT is elucidated from stop trials, and time frame. While we compare two stop signal scan sessions chronologically separated by at least four weeks, Manuel et al. compare data separated only by one hour from within one continuous SST session. Therefore practice may be taken into account, but not considered sole cause, of the time-induced activation changes we observed.

In addition to the inferior frontal, SMA, and basal ganglia areas described above, the middle frontal cortex also showed greater activation during the first fMRI scan session for the contrast GS vs BL. It is proposed that greater activity suggests a need for greater neural resources, such as in the case of gender differences in SST related activity [77]. We therefore propose that these activation changes represent a greater need for neural resources, within these regions, for processes elucidated through the contrast GS vs BL, during the first SSRT attempt. Interestingly, the majority of regions described are associated with inhibition in the literature [76, 79, 86, 101] or in our findings. This may suggest, together with the assumption that inhibitory processes are more demanding than simple motor ones, that the neural resources required during Go trials when practice-level is still low are primarily devoted to Go phase inhibitory processes.

As the SST is novel for the subjects prior to the first scan session, greater activation of the hippocampus during the first fMRI scan may reflect the region's role in motor memory consolidation [245] while activation of the post central gyrus [246], thalamus [247] and precueneus [239] may be the result of their involvement in somatosensory functions or different aspects of awareness, which may be more highly involved when executing a new task.

However, other areas of activation within similar regions including inferior frontal cortices, the precuneus and SMA show greater activation for the second fMRI scan session. Therefore, areas within the same anatomical regions were differently affected by time. These interregional variations in the effect of time on activity leads us to postulate that performance monitoring and inhibitory processes and corresponding stereotactic correlates may be much more intricately regulated than the literature suggests.

6.2.2 The Effect of Group on Stop Signal Task Activation Patterns

Similarly, group differences within task associated regions revealed by RM ANOVA for the contrasts GS vs BL and SS vs BL may be dependent on a variety of neurobiological differences between the two groups. Gender differences, specifically greater activation in men than in women, in inhibition related activation have been reported within the superior, middle and inferior frontal cortices, the ACC and insula [1, 77]. Our analysis resulted in greater activation in MtF, compared to FtM within these regions, except for the middle frontal gyrus, for the contrast SS vs BL. Similarly the contrast GS vs BL, which, as established above, is also colored by inhibitory and performance monitoring processes, revealed higher levels of activity in MtF within the superior, middle and inferior frontal cortices as well as the midcingulate cortex. However, as this comparison does not differentiate between first and second fMRI scan, we can not conclude whether these changes are the result of differences in biological sex that may persist even after hormone treatment, as would be supported by Li et al. [1, 77], rather than hormonal differences. These however, seem unlikely, as hormone profiles change significantly for both groups between both scan sessions. Although the amygdala is not directly implicated in inhibition, the region is made relevant by its role in emotion processing [248] together the role emotions such as frustration play in the interpretation of SST behavior and activation [77]. Greater activation of the right amygdala in MtF than in FtM for the contrast SS vs BL may therefore be interpreted in the

context of, and provide insight into, known gender differences in activation patterns associated with emotion processing [249].

6.2.3 Interaction Effects on Stop Signal Task Activation Patterns

Interaction effects more assertively point towards a possible sex-hormone influence as they take the effects of time and group into account. We found negative interaction effects within the right precentral, left middle frontal, left medial superior frontal, and right IFG for the contrast SS vs BL. Accordingly, as mentioned above, sex differences in inhibition activity have been shown within middle and inferior frontal cortices [1, 77]. We also found a negative interaction within the left SMA extending from activation within the left medial superior frontal cortex. This region was significantly activated during the first fMRI scan session in MtF, when subjects were naïve to cross-sex hormone therapy, and during the second fMRI scan session in FtM, after four weeks of cross-sex hormone therapy. This activation pattern, together with the probable endocrinologic profiles of these subject groups and may suggest a possible role for testosterone in mediation of inhibition related activity with this region. Evidence of greater motor inhibition related activity within this region in men, than in women supports this concept [77].

6.3 Limitations

Although we are able to show time and group effects in regions consistently associated with inhibition and performance monitoring as well as postulate a hormonal influence revealed through an interaction effect, several limitations prevent us from elucidating direct evidence of a an effect of cross-sex hormone therapy. While our sample size, through small, is comparable to similar studies [204, 205] this specific project's lack of a control group not receiving cross-sex hormone therapy as well as of measurements of sex hormone levels for correlation with activation findings, prevent us from confidently describing hormone effects. While hormone levels and activation patterns within control subjects have not been evaluated in this specific project, they have been collected within the larger study of which this project is a part, and will be incorporated into future analysis.

7.0 Conclusion

The SST is a widely applied task for the measurement of motor inhibition and performance monitoring [75]. Disparities in SST regional brain activation [1, 77] and a direct influence of estrogen levels on the SSRT, an SST behavioral parameter, have been shown. The application of cross-sex hormone therapy in transsexual persons is a novel approach for the investigation of a possible link between these known gender differences in a clinically relevant task and a possible influence of sex hormones. We were able to both validate our implementation of the SST and observe a variety of time, gender and interaction effects within task relevant regions. Further investigation of activation patterns on a single group and scan session basis allows us to suggest a possible role of sex hormones in the regulation of motor inhibition.

8.0 Abbreviations

ACad: Rostral-ventral Affective ACC

ACC: Anterior Cingulate Cortex

ACcd: Caudal-dorsal Cognitive ACC

BL: Baseline

BOLD: Blood Oxygen Level Dependent

CAH: Congenital Adrenal Hyperplasia

CE: Central Executive

CES: Central Executive System

CS: Contention Scheduling

DLPFC: Dorsolateral Prefrontal Cortex

DWI: Diffusion Weighted Imaging

ERP: Event-Related Potentials

ERN: Event-Related Negativity

fMRT: funktionelle Magnetresonanztomographie

FtM: Female-to-Male

FzM: Frau-zu-Mann

GS: Go Success

IFG: Inferior Frontal Gyrus

MFG: Middle Frontal Gyrus

mPFC: Medial Prefrontal Cortex

MtF: Male-to-Female

MzF: Mann-zu-Frau

PES: Post-Error Slowing

PFC: Prefrontal Cortex

Pre-SMA: Pre-Supplementary Motor Area

PSS: Post-success Slowing

RM ANOVA: Repeated Measures Analysis of Variance

SAS: Supervisory Attentional System

SE: Stop Error

SFP: Superior Frontal Gyrus

SMA: Supplementary Motor Area

SSA: Stop Signal Aufgabe

SSD: Stop Signal Delay

SSRT: Stop Signal Reaction Time

SST: Stop Signal Task

SS: Stop Success

VLPFC: Ventrolateral Prefrontal Cortex

VMPFC: Ventromedial Prefrontal Cortex

9.0 Tables and Figures

Table 5.1: One Sample T-Test, all subjects, contrast Go Success vs Baseline

Table 5.2: One Sample T-Test, all subjects, contrast Stop Sucess vs Baseline

Table 5.3: One Sample T-Test, all subjects, contrast Stop Error vs Baseline

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