Response inhibition, white matter pathways and structural parcellation of the right inferior frontal gyrus

A diffusion tensor imaging study

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IV
Summary

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Author statement: The present thesis is an independent research project. The idea and design were developed in collaboration with supervisor René Huster and co-supervisor Liisa Raud. Data was collected by the author and Liisa Raud. Hypothesis development, data processing and analysis were done independently by the author.

Supervisor: Professor René Huster
Co-supervisor: Liisa Raud

Abstract: The right inferior frontal gyrus (rIFG) has been implicated in a range of cognitive functions, including response inhibition. However, a systematic investigation of its white matter pathways is still lacking. Here, diffusion weighted images (DWI) were acquired from 24 participants. Subsequently, 22 of the participants performed a delayed response task and a stop signal task (SST). An atlas-based deterministic tractography procedure was computed on the obtained DWIs. The rIFG was structurally parcellated into three sub-regions (i.e. pars opercularis, pars triangularis, pars orbitalis) and was subsequently inspected for white matter pathways to target regions involved in response inhibition. In addition, a segmentation of the pars opercularis into a dorsal and ventral region was conducted. Fractional anisotropy of the dorsal opercularis to pre-/supplementary motor area (preSMA/SMA) tract was positively associated with go reaction time obtained from the SST. Strikingly, the fractional anisotropy of the ventral opercularis-preSMA/SMA tract was negatively associated with go reaction time. Finally, the fractional anisotropy of the tract from the vOp to the insula were negatively associated with stop signal reaction time (SSRT), while mean diffusivity of the tract between orbitalis and subthalamic nucleus was positively associated with SSRT.
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I would also like to thank all of the participants who took part in the study. You made this thesis possible. Thank you!

Most importantly, I would like to thank my family who have always supported and encouraged me throughout my life. I am forever grateful. This is for you.

It has been an amazing journey and I have cherished every second of it.
## List of abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>dOp</td>
<td>Dorsal part of the pars opercularis</td>
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<tr>
<td>DRT</td>
<td>Delayed response task</td>
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<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
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<tr>
<td>goRT</td>
<td>Reaction time in go-trials</td>
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<td>M1</td>
<td>Primary motor cortex</td>
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<tr>
<td>MD</td>
<td>Mean diffusivity</td>
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<tr>
<td>preSMA/SMA</td>
<td>Pre-/supplementary motor area</td>
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<td>rIFG</td>
<td>Right inferior frontal gyrus</td>
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<tr>
<td>SSD</td>
<td>Stop signal delay</td>
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<tr>
<td>SSRT</td>
<td>Stop signal reaction time</td>
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1 Introduction

The right inferior frontal gyrus (rIFG) is a functionally complex brain region that has been associated with a wide range of cognitive functions, including response inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004; Cai et al., 2014; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007) action observation (Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2004), phonological processing (Hartwigsen et al., 2010), social cognition (Liu, Saito, & Oi, 2015), motor imagery (Guillot et al., 2008) and working memory control (Marklund & Persson, 2012). Of the abovementioned functions, it has been particularly associated with response inhibition. Yet, the rIFG remains a poorly understood region in terms of its structure-function association. Even in the field of response inhibition, the functional role of rIFG has been highly debated over the years (e.g., Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Erika-Florence, Leech, & Hampshire, 2014; Aron, Cai, Badre, & Robbins, 2015; Hampshire & Sharp, 2015b). A reason for this might be that the rIFG often is treated as a homogeneous region. However, recent evidence suggests that subparts of the rIFG are involved in different networks of cognitive functions (Hartwigsen et al., 2018).

Despite ample research on the functional heterogeneity of the rIFG, there is a clear lack of research on its underlying structural nature. The structure-function associations rely on the assumption that structure is associated with efficient neuronal communication and that this efficient communication is manifested in behavior. Previous research has found that functionally connected regions are also structurally connected (Van Den Huevel, Mandl, Kahn, & Hulshoff Pol, 2009) and processing timing is associated with white matter integrity (Stufflebeam et al., 2008). Thus, investigating fiber structure of the rIFG would be of vital importance. It could also aid our current understanding of neuropsychiatric disorders as structural and functional abnormality in the rIFG has been found in individuals diagnosed with ADHD (Depue, Burgess, Willcutt, Ruzic & Banich, 2010), and has been associated with auditory hallucinations (Sommer et al., 2008). Hitherto, no previous studies have systematically explored and mapped the structural connections of the rIFG. The present thesis aims to fill this gap by mapping the structural connections of three sub-regions of the rIFG. In addition, it will investigate the white matter pathways involved in the putative response
inhibition network, as well as their structure-function associations with inhibitory performance.

1.1 White matter pathways of the rIFG

Previous research has used a variety of techniques to investigate the structural connections of the rIFG. To investigate fiber tracts, researchers could utilize aldehyde-fixed (Haber, 1988) and unfixed tissue (McConnell, Ghosh, & Shatz, 1989) or Klingler’s method of brain dissection to investigate long range connectivity (Klingler & Gloor, 1960) during post-mortem examinations. In addition, the advancement of neuroimaging techniques allows us to investigate fiber tracts in vivo. It should be noted that there is an impressive amount of studies that have used macaque monkeys to investigate fiber connections as well (Stephan et al., 2001). However, in terms of the IFG, it has been difficult to identify the homolog region in non-human primates (Petrides & Pandaya, 1999; Rizzolatti & Craighero, 2004).

The rIFG is located in the right ventrolateral frontal cortex and consists of three sub-regions corresponding to specific Brodmann areas (BA). This includes the pars opercularis (BA 44), pars triangularis (BA 45) and pars orbitalis (BA 47; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012). Although few studies have systematically investigated the white matter pathways of rIFG sub-regions, previous research has provided some preliminary insight into the cytoarchitecture of the rIFG. The rIFG has been observed to have structural connections to the pre-supplementary motor area (preSMA; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Johanesen-Berg et al., 2004; King et al., 2012; Swann et al., 2012), middle temporal gyrus, superior temporal gyrus (Glasser & Rilling, 2008; Loui, Li, & Schlaug, 2011), inferior parietal cortex (Ramayya, Glasser, & Rilling, 2009), subthalamic nucleus (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Isaacs, Forstmann, Temel, & Keuken, 2018), insula (Cloutman, Binney, Drakesmith, Parker, & Lambon Ralph, 2012) striatum and pallidum (Xu et al., 2016). In addition, the right opercularis and triangularis have structural connections to the dorsolateral and posterior sub-region of superior frontal gyrus (Li et al., 2013), while the pars triangularis has shown reliable structural connections to left and right putamen (Vik et al., 2015). Interestingly, dissection studies have identified bilateral tracts terminating at the rIFG. For instance, a fiber tract has been observed between the IFG and the lateral superior frontal gyrus (Kinoshita et al., 2012). The frontal aslant tract (FAT) is a recently described bilateral fiber tract connecting SMA, preSMA and pars opercularis (Catani et al., 2012;
Vergani et al., 2014), where the right FAT has been suggested to be involved in visually guided hand movements (Budisavljevic et al., 2017). Furthermore, the inferior fronto-occipital fasciculus (IFOF) is identified as a bilateral tract connecting the occipital cortex and the IFG (Forkel et al., 2014) and the disruption of the right IFOF has been found to induce impairments in non-verbal semantic cognition (Herbet, Moritz-Gasser, & Duffau, 2016).

1.2 Response inhibition

Ample evidence has suggested a critical role of the rIFG in response inhibition (see Aron, Robbins, & Poldrack, 2014 for a review). Response inhibition is the ability to suppress unwanted or inappropriate behavior (Verbruggen & Logan, 2009; Hampshire & Shark, 2015a), for instance, stopping an initiated movement towards a hot stove. As a sub-function of the cognitive control, it is an essential part of everyday life and it is crucial for goal directed behavior (Miyake et al., 2000). Further, response inhibition has been found to be heritable and has been suggested to be a potential endophenotype for neuropsychiatric disorders with core deficits in inhibitory control (Schachar, Forget-Dubois, Dionne, Boivin, & Robaey, 2011). Specifically, response inhibition is considered a neurocognitive deficit in attention deficit hyperactivity disorder (ADHD; Wodka et al., 2007), obsessive-compulsive disorder (Menzies et al., 2007), schizophrenia (Hughes, Fulham, Johnston, & Michie, 2012), anorexia nervosa (Collantoni et al., 2016) pathological gambling (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006) and drug addiction (Ersche et al., 2012). In addition, patients with Parkinson’s disease exhibit impaired inhibitory control compared to healthy controls (Obeso et al., 2011; Ye et al., 2015). Performance on response inhibition tasks also predicts daily alcohol consumption in heavy drinkers (Jones, Tiplady, Houben, Nederkoorn, & Field, 2018), total amount of intoxication and hangover days in young adults (Paz, Keim, & Rosselli, 2016), cigarette smoking dependence (Billieux et al., 2010), as well as weight loss and therapy success in obese children (Nederkoorn, Jansen, Mulkens, & Janse, 2007).

1.2.1 Measuring response inhibition. The stop signal task (SST) has been extensively used to study response inhibition. In the SST, the participants respond rapidly to a go-stimulus. However, on a minority of trials, a stop signal appears shortly after the go-stimulus and the participants are instructed to withhold their initiated go-response. The delay between the go-stimulus and the stop-signal (the so-called stop signal delay, SSD) varies across trials and is often tracked, based on the performance on stop trials. That is, the SSD increases after
successful stop trials and decreases after unsuccessful stop trials. The average SSD will then result in responding to a stop signal in approximately 50% of the trials. This procedure is based on the conceptualization of two independent race processes, the go and stop process (Logan & Cowan, 1984). This is known as the horse race model, suggesting that whenever the stop-process finishes first, response inhibition is successful. However, if the go-process finishes first and a response is made despite the stop signal, the inhibition process is considered unsuccessful (Verbruggen & Logan, 2008). The task allows for the calculation of the stop signal reaction time (SSRT) that represents the latency of the stop process. The SSRT is often estimated with two common methods. The integration method utilizes the go reaction time (goRT) distribution and uses the nth RT, where the n is given by the number of RTs in the RT distribution multiplied with the probability of responding given a stop signal. The SSRT is then calculated after subtracting the average SSD from the nth RT. The mean method simply estimates the SSRT by subtracting the mean SSD from the mean RT. It should be noted that the latter method has been a less reliable estimate of SSRT (Band, van der Molen, & Logan, 2003).

1.2.2 Reactive and proactive inhibition. Cognitive control has been postulated to operate through two distinct control modes, known as “proactive control” and “reactive control” (Braver, 2012). On the one hand, the proactive control mode maintains the goal relevant information through a top-down process. On the other hand, the reactive control mode operates as a bottom-up correction mechanism. As a subcomponent of cognitive control, reactive inhibition has been referred to as the ability to stop an initiated response, while proactive inhibition is related to the restraining of motor response, as a consequence of increased probability of a stop signal (Zandbelt et al., 2013). Although related, the cognitive control mode is not the same as response inhibition, but it could indeed modulate the inhibitory system. For instance, when the probability of a stop signal increases, people tend to slow down their responses, resulting in prolonged goRT (Chikazoe et al., 2009; Jahfari et al., 2010; Van Belle, Vink, Durston, & Zandbelt, 2014; Zandbelt & Vink, 2010). Specifically, participants show increased reaction times when a stop signal might appear compared to a task without a stop signal (Vink, Kaldewaij, Zandbelt, Pas, & Du Plessis, 2015), and exhibit decreased motor evoked potential in the responding hand in trials where they might withhold their response (Cai, Oldenkamp, & Aron, 2011). In addition, reactive and proactive inhibition also seem to recruit different neural networks (Chikazoe et al., 2009), while they are also associated with increased activity in a variety of regions in the frontal lobe (van Belle et al.,
This has implications for inhibitory tasks that use the goRT obtained from tasks that includes a stop signal. For instance, if the SST itself recruits a general cognitive control mode, the goRT might not measure automatic motor processes after all.

1.3 Fronto-basal-ganglia network in response inhibition

Converging evidence has implicated an association between a right lateralized fronto-basal-ganglia network and response inhibition (see Chambers, Garavan, & Bellgrove, 2009 for a review). Specifically, increased activity in the rIFG, pre-supplementary motor area (preSMA), insula, putamen, caudate, thalamus and subthalamic nucleus (STN) has been observed during inhibitory control tasks (Li, Yan, Sinha, & Lee, 2008; Levy & Wagner, 2011, Cai, Ryali, Chen, Li, & Menon, 2014). In addition, repetitive TMS on the rIFG has been found to impair stop signal inhibition, while this was not the case for stimulation of the left IFG (Chambers et al. 2007). The rIFG shows increased activity during motor inhibition (see Levy & Wagner, 2011 for a meta-analysis). Interestingly, the preSMA and rIFG have shown increased activity during reactive and proactive inhibition (Chikazoe et al., 2009; Zandbelt & Vink, 2010), while it does not show a significant increase when stopping is not required (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010). It has also been postulated that it is the pars opercularis that is crucial for response inhibition (Aron, Robbins, & Poldrack, 2014). Moreover, Hartwigsen and colleagues (2018) suggest that the pars opercularis exhibit a dorsal to ventral axis of motoric inhibition, where the former is involved in motor execution and the latter is involved in inhibition.

The abovementioned studies suggest a crucial role of the rIFG for inhibition. Aron and colleagues (2016) suggest that during response inhibition tasks, the go process involves the premotor cortex, striatum, pallidum, thalamus and primary motor cortex. On the contrary, the stop process recruits rIFG, preSMA, STN, pallidum and striatum. It has also been suggested that the rIFG projects a stopping signal to the basal ganglia to interfere with an already initiated go-process (Aron et al., 2007). This is interesting as patients with lesions to the frontal lobe or basal ganglia have been found to have increased SSRTs compared to an orthopedic control group. Moreover, damage to other cortical areas outside the frontal lobe did not significantly increase SSRT (Rieger, Gauggel, & Burmeister, 2003).
1.3.1 Basal ganglia. The basal ganglia have been implicated in motor control. The basal ganglia consists of clusters of neurons (nuclei) and are highly interconnected. Those include the caudate and putamen (striatum), external part of globus pallidus (GPe), internal part of globus pallidus (GPi), subthalamic nucleus (STN) and the substantia nigra (SN; Smith, Beyan, Shink, & Bolam, 1998). The striatum and the STN have been suggested to be input structures of the basal ganglia circuitry (Mink, 1996), hence they are critical target regions for motor execution and suppression. Furthermore, the thalamus shows direct projections to the motor cortex which would allow for motor execution (Nambu, Yoshida, & Jinnai, 1988). However, several distinct pathways in the basal ganglia have been proposed to have opposing effects on the thalamus, resulting in either execution or suppression of movements (Albin, Young, & Penney, 1989; DeLong, 1990).

In the classical model of the basal ganglia, the direct pathway involves a release of the tonic inhibition from GPi on the thalamus, which further results in execution of a prepared movement (Turner & Desmurget, 2010). On the contrary, the indirect pathway involves excitation of the GPi and SN pars reticulata, resulting in increased inhibitory effect on the thalamus, further suppressing a movement (Calabresi, Picconi, Tozzi, Ghiglieri, & Filippo, 2014). Later, a hyperdirect pathway was postulated to stop already initiated movements, indicating a crucial pathway for response inhibition. This pathway has been suggested to consist of the rIFC, preSMA and STN (Jahanshani, Obeso, Rothwell, & Obeso, 2015). Interestingly, increased local field potential beta activity in the STN has been associated with motoric inhibition in patients with Parkinson’s Disease (Ray et al., 2012) and a rodent study found increased activity in the STN after a stop signal cue, while increased neuronal activity in the SN pars reticulata was present in successful stop trials (Schmidt, Leventhal, Mallet, Chen, & Berke, 2013). The results suggest a critical role of the STN in response inhibition.

1.3.2 All roads lead to inhibition. The underlying mechanisms of the inhibitory network are still largely unknown. For instance, in terms of outright stopping, it has been stated that “It is not yet clear whether the rIFC triggers the STN directly, or via the preSMA” (Aron et al., 2014, p.177). However, Wiecki and Frank (2013) formed a computational model of inhibitory control and could simulate SST based on the horse-race model after they included a direct projection from the rIFG to STN into their model. Moreover, a simulated rIFG lesion impaired the stopping responses and reduced the SSD because the lesion would make the inhibitory process slower. Thus, the SSD would need to be shorter in order to produce a
successful stopping response. Their rationale behind the successful simulation of SST was based on the idea that a hyperdirect pathway from the rIFG to the STN would hinder the striatal response gating mechanism, which would result in successful inhibition. Previous studies have also suggested that the rIFG and preSMA could influence the primary motor cortex (M1) directly, hence bypassing the basal ganglia circuit (Mars et al., 2009; Buch, Mars, Boorman, & Rushworth, 2010). Surprisingly little attention has been given to a possible role of the rIFG-M1 connection in inhibitory control. Possibly, because it has been postulated that the F5a region in macaques is the homologue region to the human rIFC (Petrides, 2005; Rizzolatti, Fabbri-destro, & Cattaneo, 2009), and there are no direct projects from the F5a to the M1 (Gerbella, Belmalih, Borra, Rozzi, & Luppino, 2011). It has also been postulated that the striatum is involved in proactive inhibition as it could modulate the activity of M1, via rIFG and the preSMA/SMA region (Zandbelt & Vink, 2010). It is notable that much of the previous research emphasizes the role of the preSMA and excludes the SMA. In light of the recent discovery of the frontal aslant tract, this might be unfortunate as the fiber tracts from IFG terminate in the border of preSMA and SMA (Vergani et al., 2014), and the SMA has been found to be involved in both proactive and reactive control in macaques (Chen, Scangos, & Stuphorn, 2010).

1.4 Diffusion tensor imaging

The abovementioned studies show that the rIFG exhibits multiple white matter pathways to the putative response inhibition network and activity within this network relates to performance on inhibitory control tasks. There is also compelling evidence that variability in white matter pathways in healthy individuals relates to behavior (see Johansen-Berg, 2010 for a review), suggesting that the white matter variability in the rIFG connections could be associated with response inhibition as well. To map the structural connectivity in the brain, researchers could use diffusion tensor imaging to investigate the motions of water molecules in vivo. The diffusion of water molecules is influenced by underlying biological properties such as myelin, cell membranes and microtubules (Beaulieu, 2002). Consequently, the water molecules will diffuse more easily in the primary direction of the fiber bundles compared to the perpendicular direction. Furthermore, different diffusion parameters could provide quantitative measures of white matter pathways. Although the different parameters are often correlated, they are also indicators of different biological characteristics. Fractional anisotropy (FA) is used as an indicator of the microstructural integrity, while mean diffusivity (MD) is an
inverse index of membrane density and radial diffusivity indicates the degree of myelination (Alexander et al., 2011; Song et al., 2002). The parameters are often used to describe the connectivity strength between two regions through tractography techniques. Moreover, the degree of efficient communication (i.e. signal transfer) between regions is modulated by its underlying white matter integrity (Fields, 2008). Thus, investigation of white matter pathways from the rIFG to the putative response inhibition network is of crucial importance to understand behavioral differences in inhibitory control.

1.5 Connectivity

1.5.1 Structural connectivity and inhibitory control. In the literature, it is common to use a hyphen (-) between the two regions that show structural connections to each other. That is, IFG-STN refers to the tract between IFG and STN. This convention will also be used to describe connections between two regions in the remaining part of the thesis.

Several DTI studies have found associations between white matter integrity and behavioral measures of inhibition. For instance, increased FA in the anterior part of the IFOF, comprising the IFG, has shown to be related to better inhibitory performance (Forstmann et al., 2008), while RD in frontostrial network has been found to predict reaction times in inhibitory tasks (Liston et al., 2005). Specifically, King and colleagues (2012) found that the FA in right preSMA/SMA-STN, preSMA/SMA-striatum and RD in opercularis-STN tract were the best predictors of SSRT. To complement the latter predictor, lower MD in pars opercularis/triangularis-STN tract has also been associated with shorter SSRT (Rae et al., 2015), while FA in IFG-STN tract predicts hit rate in an inhibitory task (Hinton et al., 2018). The FA in the putative response inhibition network has also been found to predict inhibition across age. Increased FA within pars opercularis and preSMA is associated with lower SSRTs in children (Madsen et al., 2010), and FA in the bilateral IFG, preSMA and STN predicted SSRT in young and older adults (Coxon et al., 2012) However, another study found no significant association in structural connection in right IFC- STN, but that increased white matter strength between anterior cingulate cortex and rSTN predicted SSRTs (Forstmann et al., 2012).

1.5.2 Functional connectivity. Under the premise that anatomical structure is associated with functionality, it would be of interest to complement structural connectivity with functional
connectivity. Previous studies have shown that successful stopping is related to effective connectivity between the IFC and preSMA (Duann, Ide, Luo, & Li, 2009) and that right preSMA activity seems to precede that of rIFG in inhibition tasks (Swann et al., 2012). Fast inhibitors have also been found to have increased connectivity between rIFG and right caudate, while slow inhibitors exhibit the same connectivity pattern between preSMA and right caudate (Jahafari et al., 2011). On the other side of striatum, increased functional connectivity between right IFC and putamen has been found in Levodopa-induced dyskinesia (i.e. involuntarily movements) in patients with Parkinson’s disease (Cerasa et al., 2014).

1.6 Summary and research aim

1.6.1 Summary. The rIFG seems to be important for inhibitory control because 1) it shows increased activity during response inhibition tasks, 2) lesions or TMS-disruptions of this region impairs stopping responses, 3) it is structurally and functionally connected to the basal ganglia, 4) microstructural characteristics of its connectivity are associated with behavioral measures of inhibition. However, previous research has generally used the FA as the diffusional parameter and there is a clear lack of research on other parameters such as MD. This is important since the diffusional parameters are influenced by different biological underpinnings. Furthermore, it is still unclear which of the sub-regions of the rIFG that are involved in response inhibition. However, recently it has been suggested that the most posterior part of the rIFG, the pars opercularis, is involved in response inhibition (Aron, Robbins, & Poldrack, 2014). Moreover, Hartwigsen and colleagues (2018) found that the pars opercularis could be functionally segmented into a dorsal and ventral part, where the former is involved in action execution and the latter is involved in motor inhibition. This segmentation has also been supported by previous structural (Neubert et al., 2014) and receptor-architectonic (Amunts et al., 2010) studies.

1.6.2 Hypotheses

The research aim of this thesis is to elucidate the structural connectivity of the rIFG. Thus, it will parcellate the rIFG into three sub-regions (pars opercularis, pars triangularis and pars orbitalis) and investigate its white matter pathways. Furthermore, it will investigate the association between tracts involved in motoric system and behavioral measures of response inhibition. Specifically, the tracts seeding from the ventral and dorsal part of opercularis are
of interest. Furthermore, although several studies have looked at the IFG-STN tract, they often use FA as an exclusive measure of tract strength. However, more research is needed on other diffusional parameters, such as MD. Based on the reviewed literature, the following hypotheses are made:

1) Due to the rIFG’s involvement in the response inhibition network, it is expected that one or more sub-regions will show structural connections to the preSMA/SMA region, insula, caudate, putamen and STN.

2) Recent evidence suggested that the dorsal and ventral part of opercularis is involved in motor execution and inhibition, respectively. Thus, it is hypothesized that the FA in the tracts seeding from the dorsal pars opercularis predicts goRT, while the ventral pars opercularis predicts SSRT.

3) Previous research has shown that the FA value in the IFG-STN tract is associated to response inhibition. Hence, it is predicted that the MD in the tracts from IFG sub-regions to the STN is positively associated with SSRT.
2 Material and methods

2.1 Participants

Twenty-four participants took part in the experiment (11 females; mean age = 25.83, SD = 3.24). Two participants were excluded from the behavioral analysis. One for not completing the second session of the experiment and the other one for violating the assumptions of the horse-race model. This led to a total of 24 participants for structural connectivity analysis and 22 participants for structure-behavior analyses. All participants were right handed, had normal or corrected to normal vision and reported no history of psychiatric or neurological disorders, migraine or loss of consciousness. The experiment was approved by the internal review board of the Department of Psychology, University of Oslo. The participants answered a questionnaire for assessment of their eligibility to participate in the study. All participants gave informed consent and received a gift card of 300 NOK for participation.

2.2 Design

All participants were measured on two separate days. Session one consisted of three MRI sequences, involving a T1 image, DWI and resting state functional MRI. The full sequence took approximately 45 minutes to complete. Session two consisted of EEG, TMS and EMG which were applied concurrently during two separate computer-based experiments; the delayed response task (DRT) and the stop signal task (SST). The total time of the experiment, including preparation of EEG and TMS, took approximately 3 ½ hours to complete. As only diffusional MRI and behavioral measures are analyzed here, the EEG and TMS procedure are not elaborated further on. Behavioral indices were extracted from the DRT and SST. The trials with TMS pulses were discarded and the results were obtained from the remaining behavioral data.

2.3 Materials

2.3.1 MRI Data acquisition. All MRI sequences were performed on a 3.0 Tesla Philips Ingenia whole-body scanner (Philips Medical Systems, Best, Netherlands) with a 32-channel head coil at the Intervention Center, Oslo University Hospital. DWI was acquired using a single-shot EPI sequence, one b0 image, and diffusion weighting was distributed across 32
non-collinear directions with a b-value = 1000s/mm², flip angle = 90 degrees, repetition time (TR) = 13.45s, echo time (TE) = 62ms, field of view (FOV) = 224 x 224 x 120, Matrix = 96 x 94 x 60. The acquired voxels of size 2.33 x 2.38 x 2.0 mm were reconstructed to 2.0 mm isotropic voxels. Scanning time of DWIs was 09.51 minutes. The T1 images were acquired with the following parameters; TE =2.3, TR = 5.1, FOV = 256 x 256 x 184, Matrix = 256 x 254 x 184, voxel size = 1.0 x 1.0 x 1.0 mm. Scanning time of T1 images was 06.29 min.

2.3.2 Tasks and setup. The experimental task was developed as an in-house MATLAB script (The MathWorks, Inc., Massachusetts, USA) using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007). Participants were seated in a chair approximately 1 meter from the monitor and responded on a bilateral response box. Screen resolution was set to 1280*1024 with a refresh rate of 60Hz.

Participants performed a delayed response task (DRT) and a cued stop signal task (SST; Figure 1). The participants performed a training session to become familiar with the experimental design before each task. During the DRT, the participants were presented with a fixation cross, randomly jittered between 1800-2800 milliseconds (ms), and a preparatory cue indicating which finger to prepare for a response. The preparatory cue was either a right or left leaning bracket indicting a right and left index finger response, respectively. The participants needed to respond as fast as possible to a go-stimulus appearing next to the bracket. Nine percent of the trials were catch trials, where a go signal was omitted. Those were included to make sure the participants did not respond prematurely and would need to wait until the go-stimulus appeared. The dependent measures were reaction time to the go-stimuli and accuracy. The DRT consisted of 3 blocks of 5 minutes and took approximately 15 minutes to complete.

Subsequently, the participants performed a cued SST across 12 blocks, with pauses of self-determined duration in between. The design of the study was similar to the DRT, but with an additional stop signal presented in 33% of the trials. During the stop trials, the participants were instructed to withhold their response if the go stimuli changed color, which corresponded to the stop signal. The stop signal was presented at a variable stop signal delay (SSD). The SSD was initially set at 250ms for both hands and was subsequently adjusted based on a tracking procedure for each hand separately. The SSD was increased by 33ms if the previous stop signal trial was successful and decreased by 33ms after unsuccessful stop
The minimum and maximum SSD were set to 80ms and 800ms, respectively. The SST took approximately 1 hour to complete. The dependent variables from the DRT and SST were averaged across hands. Due to the low difficulty of DRT, it was expected that it measured a pure motoric process. In contrast, the SST relies on a different task context and is thought to recruit more cognitive control.

Participants received feedback after each block. If the average go-RT was above 600ms, the participants were instructed to be faster. However, if the average accuracy was below 45%, they were instructed to be more accurate. If the participants did not violate the abovementioned thresholds, they were presented with the feedback “Well done”. The color of the go and stop stimuli were counterbalanced between orange and blue across participants. The color of the go-stimuli was the same in both tasks for each participant. The task consisted of 432 non-TMS pulse trials with 288 go-trials and 144 stop trials. The participants had 800ms to respond in all trials. If the participant did not respond within the response window in go trials, it was counted as an incorrect response.

Figure 1. A, a go trial for both DRT and SST. A fixation cross was jittered between 1800-2300ms across trials, the left leaning bracket indicated which finger to prepare for a response (i.e. left index finger), a response should be made within 800ms after the ball appeared. B, a stop-trial in the SST. The participants should withhold their initiated movement when the ball changed color, indicating a stop-signal.

**ITI** = inter-trial interval, **ms** = milliseconds, **SSD** = stop signal delay.
2.4 Analyses

2.4.1 Behavioral measures. All behavioral variables were extracted from trials without TMS pulses. For both DRT and SST, goRT were calculated as the latency between the onset of the go-signal and the correct response. Mean goRT were calculated for each participant. Go accuracy was estimated based on the percentage of correct go-trials. For the SST, false alarm RT was calculated from the latency between go-signal and a response during failed stop trials. Finally, the SSRT was estimated using the integration method and the average SSD obtained from the tracking procedure (Verbruggen & Logan, 2009). All the obtained dependent variables were based on participants’ individual performance and were averaged across all blocks.

2.4.2 DWI analysis. The raw MR files were converted into NiFTI format with MRicroGL (http://www.cabiatl.com/mricrogl/; Figure 2A). The converted DWI images were processed in ExploreDTI v.4.8.6 (Leemans, Jeurissen, Sijbers, & Jones, 2009; Figure 2B). All images were inspected for artifacts and excessive head movements, corrected for eddy current-induced distortions and head motions with a non-diffusion weighted image as reference. Each participant’s high-resolution T1-weighted image was used for EPI correction (Figure 2C) and the DWIs were transformed into 1mm isotropic voxels (Figure 2D) for diffusion tractography (Figure 2E).

Figure 2. Visualized processing steps. A, DWIs along 32 non-collinear directions are obtained from each participant. B, DWIs are transformed to a map of the first eigenvectors scaled by fractional anisotropy (FEFA) in native space. C, DWIs are corrected for head movements and eddy-current induced geometrical distortions using the T1 and b0 image. D, the correction procedure resulted in a corrected FEFA image. E, the preprocessed images are used for deterministic tractography. Color coding: blue = inferior-superior, red = left-right, green = anterior-posterior.
Brain atlas. The regions of interest (ROI) in the rIFG were defined by a standardized brain atlas to reduce user-bias. The AAL atlas (Tzourio-Mazoyer et al., 2002), including an additional implementation of a binarized ROI of STN bilaterally (Forstmann et al., 2012), was used for extraction of fiber tracts seeding from pars opercularis, pars triangularis and pars orbitalis (Figure 3A). Due to the unclear boundaries between preSMA and SMA (see Mayka, Corcos, Leurgans, & Vaillancourt, 2006 for a meta-analysis) and terminating fiber tracts in the border between preSMA and SMA (Vergani et al., 2014), the preSMA was not anatomically separated from the SMA region, but was included in the region of SMA obtained from the AAL atlas. This area will be denoted as the preSMA/SMA region for further reference. This resulted in 92 regions (46 in each hemisphere, excluding cerebellum) for further analysis.

Tractography. A whole brain deterministic tractography procedure with every voxel as seed point was completed and utilized to map the connectivity of the sub-regions of the rIFG (Figure 3B). Seed point resolution was set at 1mm isotropic, FA threshold = 0.2 and angle threshold = 45 degrees. That is, the tract was terminated if it reached a voxel with an FA value below 0.2 or made a high angular turn exceeding 45 degrees. Furthermore, a connectivity analysis was generated based on the abovementioned AAL atlas and the whole brain fiber tracts. This resulted in separate 92*92 symmetric connectivity matrices of pass and end tracts, which specified the average value along each of the identified tracts for each diffusion parameter (i.e. FA, MD, RD and AD; Figure 3C). In the connectivity matrices, the seeding region corresponded to column i, while the target region corresponded to row j. In the matrix for ending tracts, the (i,j)th element corresponds to termination of fiber tracts in region i and j. For passing tracts, the (i,j)th element represents a passing tract through j seeding from i. The pass and end tracts seeding from the same region are differentiated and are non-overlapping. The FA and MD values were extracted from areas connecting to the three sub-regions of rIFG. There is no consensus in the literature on the inclusion criteria of a tract, but there is a tendency to use high thresholds (e.g., Leh, Ptito, Chakravarty, & Strafella, 2007; Vik et al., 2015; Orr, Smolker, Banich, 2015). Thus, a large effect size of 0.6 was chosen for a detection of tract in the present thesis. A priori power analysis based on t-test between means gave a total of 19 participants with effect size = 0.6, power = .80, $\alpha = .05$ for a reliable detection of a tract. 19 participants divided by total N (24) multiplied by 100 is equal to approximately 80%. That is, a fiber connection was included if it was present in at least 80% of the individuals.
Previous studies have shown that the pars opercularis could be structurally (Neubert et al., 2014, receptor-architectonically (Amunts et al., 2010) and functionally (Hartwigsen et al., 2018) segmented into a dorsal and ventral region. Thus, the AAL atlas was modified for the segmentation of pars opercularis. This region was split along the z (dorsal-ventral) axis halfway along its longest extent using an in-house Matlab script. This modification allowed for further atlas-based connectivity analysis in the dorsal pars opercularis (dOp; MNI: x = 49 y = 15 z = 30) and ventral pars opercularis (vOp; MNI: x = 52 y = 16 z = 10) based on the abovementioned procedure.

Figure 3. A, an AAL template is registered to participant’s data set. B, the data set included a corrected FA image and a corresponding tract file from diffusion tractography. C, connectivity analysis produced a structural connectivity matrix for both ending and passing tracts. The tracts seeding from rIFG sub-regions were extracted. D, passing and ending tracts, present in 80% of the participants, were visualized and used for further brain-behavior analyses.

2.4.3 Structure – behavior analysis.

The dependent variables from the behavioral measures and independent variables from the structural connectivity analysis were extracted and exported to IBM SPSS Statistics for Windows, Version 25.0, for further analysis. The dependent variables were goRT obtained from both DRT and SST, as well as the SSRT. The goRT refers to the measure from the SST, unless stated otherwise. The number of participants used in the analyses (n) are included in the results.
To investigate if the participants slowed down their responses in go-trials in the SST compared to the DRT, a paired sample t-test between mean DRT goRT and SST goRT were conducted. Additionally, a two-tailed bivariate correlation is conducted to investigate if they are indeed related or separated measures of goRT.

The independent variables from the connectivity analysis included both the FA and MD measures between two regions of interest. For FA, the tracts included in the analysis were the dOp-preSMA/SMA, vOp-preSMA/SMA, vOp-insula, orbitalis-putamen, orbitalis-caudate and opercularis-M1 (i.e. precentral gyrus) tract. For MD, the tract between orbitalis-STN, orbitalis-caudate, orbitalis-putamen and opercularis-M1 were extracted. Whenever possible, the terminating tracts were used in the analysis. The ending tracts includes all connections to the preSMA/SMA and the orbitalis-putamen tract. The vOp-insula, orbitalis-STN, orbitalis-caudate and opercularis-M1 connections were passing tracts.

To test hypothesis 2, the differential connectivity patterns of the dOp and vOp were inspected with respect to regions involved in response inhibition. Both the dOp and vOp showed ending and passing tracts to preSMA/SMA, while the vOp also showed passing tract to insula. Multiple regression analyses with the ending tracts between vOp-preSMA/SMA and dOp-preSMA/SMA as predictors were conducted to test if tract strength predicted SST goRT and SSRT. The same predictors were used for DRT goRT to investigate if the dOp-preSMA/SMA tract strength were specific for measures of SST goRT or if it was also associated with DRT goRT. To test for multicollinearity in the regression analysis, the predictors were correlated and inspected for their variance inflation factor and tolerance. Additionally, a one-tailed bivariate correlation between FA values of the vOp-Insula tract and SSRT were conducted due to their involvement in response inhibition.

To test hypothesis 3, a one-tailed bivariate correlation between the MD value of the orbitalis-STN tract and the SSRT was computed due to its putative role in the hyperdirect pathway. None of the other rIFG sub-regions showed projections to the STN, hence this particular tract was chosen.

Additionally, exploratory analyses were conducted with the use of both FA and MD values for tracts thought to be involved in motoric processes, including the opercularis-M1, orbitalis-caudate, and orbitalis-putamen connections. The opercularis-M1 tract was chosen because it is highly understudied and has been suggested to bypass the basal ganglia (Mars et
al., 2009; Buch et al., 2010). The connections to the striatum were chosen as they are critical input structures of the basal ganglia (Mink, 1996; Zandbelt & Vink, 2010). The connectivity analysis showed that both triangularis and orbitalis showed terminating projections to the putamen. However, the orbitalis-putamen were chosen since it exhibited tracts to both regions in the striatum (i.e. putamen and caudate). Two-tailed bivariate correlations were conducted between opercularis-M1, orbitalis-caudate, orbitalis-putamen. This led to a total of 2 (FA and MD) x 3(opercularis-M1, orbitalis-caudate and orbitalis-putamen) = 6 correlations. All the 6 p-values in the exploratory analyses were adjusted for multiple testing following the false discovery rate (FDR) procedure.
3 Results

3.1 Behavior

One participant violated the assumptions of the horse-race model and was excluded from further analysis. The remaining participants showed faster false alarm RT compared to goRT, in line with the horse-race model assumptions. Additionally, they also exhibited an average accuracy in stop trials close to 50%, indicating successful SSD tracking. A summary of the behavioral measures is presented in Table 1.

It has been suggested that participants slow down their responses when there is a probability of a stop-signal. Thus, investigation of a potential difference between DRT and SST goRT was warranted. A paired sample t-test between DRT goRT (mean = 311.29) and SST goRT (mean = 508.08) showed a significant difference between means (p = .001), while a two-tailed bivariate correlation showed a non-significant association between DRT and SST goRT (r = .197, p = .380). The results indicate that the two behavioral goRT indices measure two different mechanisms. Thus, for further investigation of the association between the rIFG and inhibitory control, goRT from the SST will be used in the subsequent analysis if not stated otherwise.

Table 1. Behavioral data

<table>
<thead>
<tr>
<th></th>
<th>DRT</th>
<th>SST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go accuracy (%)</td>
<td>97 (5)</td>
<td>95 (3)</td>
</tr>
<tr>
<td>Stop accuracy (%)</td>
<td></td>
<td>50 (4)</td>
</tr>
<tr>
<td>GoRT (ms)</td>
<td>311 (49)</td>
<td>508 (75)</td>
</tr>
<tr>
<td>False alarm RT (ms)</td>
<td>412 (74)</td>
<td></td>
</tr>
<tr>
<td>Stop signal delay (ms)</td>
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<td></td>
</tr>
<tr>
<td>Stop signal reaction time (ms)</td>
<td>192 (21)</td>
<td></td>
</tr>
</tbody>
</table>

Note. Mean values for behavioral data with standard deviations presented in the parenthesis, excluding decimals. DRT = Delayed response task, SST = stop signal task, RT = reaction time, ms = milliseconds
3.2 Connectivity analyses

The connectivity analysis for sub-regions of rIFG is presented in Table 2, including both terminating and passing tracts identified in at least 80% of the participants. Corresponding tracts are also visualized in Figure 4. All the connections presented are seeded from one of the sub-regions of the rIFG. With ending tracts, the connectivity analysis exhibits the average diffusional parameter across the tract that seeds from one rIFG subregion (e.g., orbitalis) and terminates in the target region (e.g., putamen), while passing tracts are averaged across the tract that seed from one sub-region and passes through the target region.

3.2.1 Hypothesis 1. In line with the predictions, rIFG sub-regions showed tracts to the preSMA/SMA region, insula, caudate, putamen and STN. These are target regions that have all showed increased activity during inhibitory control tasks (Cai et al., 2014; Levy & Wagner, 2011; Li et al., 2008). Both the opercularis and triangularis showed passing tracts to the preSMA/SMA region. However, only the opercularis was associated with an ending tract to the preSMA/SMA region, possibly identifying the frontal aslant tract. All rIFG sub-regions were associated with tracts passing through insula. The triangularis and orbitalis exhibited passing and terminating tracts to putamen. However, only the orbitalis showed a reliable passing projection to caudate and STN.
Table 2. FA value of the fiber tracts seeding from sub-regions of the rIFG

<table>
<thead>
<tr>
<th>Region</th>
<th>Pars Opercularis Pass</th>
<th>Pars Opercularis End</th>
<th>Pars Triangularis Pass</th>
<th>Pars Triangularis End</th>
<th>Pars Orbitalis Pass</th>
<th>Pars Orbitalis End</th>
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<td>.38 (.03)</td>
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<td></td>
</tr>
<tr>
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<td>.40 (.02)</td>
<td>.38 (.02)</td>
<td>.38 (.03)</td>
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<td></td>
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<tr>
<td>Frontal Sup Orb</td>
<td></td>
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<td>.44 (.03)</td>
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<td></td>
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<tr>
<td>Frontal Mid</td>
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<td>.38 (.02)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal Mid Orb</td>
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<td>.45 (.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>.40 (.03)</td>
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<td></td>
<td></td>
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<tr>
<td>Pars Triangularis</td>
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<td>.41 (.02)</td>
<td>.41 (.02)</td>
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<td></td>
<td></td>
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<tr>
<td>Pars Orbitalis</td>
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<td></td>
</tr>
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<td>.38 (.02)</td>
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<td>.39 (.02)</td>
<td>.41 (.02)</td>
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<td>.39 (.02)</td>
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<td>.38 (.02)</td>
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<td>.40 (.02)</td>
<td>.40 (.02)</td>
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</tr>
<tr>
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<td>.46 (.03)</td>
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<td>.46 (.03)</td>
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<td>.41 (.03)</td>
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<td>.41 (.03)</td>
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<tr>
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</tbody>
</table>

*Note. Average FA value across participants seeding from rIFG sub-regions to the target regions in the left column. Standard deviations are presented in parenthesis. All the tracts are detected in the right hemisphere. Sup = superior, Mid = middle, Orb = orbitalis part.*
Figure 4. Structural projections from the rIFG sub-regions. The visualization does not differentiate between passing and terminating tracts. Node size increases relative to connections from the rIFG sub-regions. Magenta = pars opercularis, cyan = pars triangularis, green = pars orbitalis, Sup = superior, Mid = middle, Orb = orbitalis part.
When parcellating the opercularis into a dorsal and ventral part, the connectivity analyses revealed some marked differences. White matter pathways that passes through the rolandic operculum, insula and postcentral gyrus were only reliably found seeding from vOp, while projections to the middle frontal gyrus were unique to dOp. Interestingly, both the the dorsal and ventral region showed ending and terminating projections to the preSMA/SMA region and superior frontal gyrus. For further structure-function analysis, the FA values of the white matter projections ending in the preSMA/SMA region and passes through the insula were extracted. Results from the segmentation are presented in Table 3 with a corresponding visualization in Figure 5.

Table 3. *FA values of fiber tracts seeding from the dorsal and ventral pars opercularis*

<table>
<thead>
<tr>
<th></th>
<th>Ventral Pars Opercularis</th>
<th>Dorsal Pars Opercularis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pass</td>
<td>End</td>
</tr>
<tr>
<td>Precentral</td>
<td>.39 (.03)</td>
<td></td>
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<tr>
<td>Frontal Sup</td>
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<tr>
<td>Frontal Mid</td>
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<td>.38 (.02)</td>
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<tr>
<td>vOp</td>
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<td>Pars Triangularis</td>
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<td>preSMA/SMA</td>
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<td></td>
</tr>
<tr>
<td>Postcentral</td>
<td>.41 (.03)</td>
<td></td>
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</tbody>
</table>

*Note.* Average FA value across participants seeding from the ventral and dorsal pars opercularis to the target regions in the left column. Standard deviations are presented in parenthesis. All the tracts are detected in the right hemisphere. Sup = superior, Mid = middle.
Figure 5. Structural projections from the dorsal and ventral opercularis. The visualization does not differentiate between passing and terminating tracts. Node size increases relative to connections from the dorsal and ventral pars opercularis. Magenta = dorsal pars opercularis, cyan = ventral pars opercularis, Sup = superior, Mid = middle.
3.3 Structure – function associations

3.3.1 Hypothesis 2. It was predicted in hypothesis 2 that the tracts from the dOp should be associated with goRT, while the vOp should be associated with SSRT. Both the dOp and vOp showed a reliable ending tract to the preSMA/SMA region. The FA values for the dOp-preSMA/SMA and vOp-preSMA/SMA tracts were extracted and implemented into the same model. To test this hypothesis 2, a multiple regression analysis with the ending tracts between dOp-preSMA/SMA and vOp-preSMA/SMA as predictors was conducted with goRT and SSRT as dependent variables. The results indicate that the model explained 50% of the variance and was a significant model for goRT (F (2, 15) = 8.64, p = .005), with significant predictors of dOp-preSMA/SMA (β = 1.291, p < .01; Figure 6A) and vOp-preSMA/SMA (β = - .818, p < .05; Figure 6B). However, it was not a significant model of SSRT (F (2, 15) = .124, p = .885), explaining only 1.6% of the variance. Neither dOp-preSMA/SMA (β = .006, p > .05) nor vOp-preSMA/SMA (β = - .132, p > .05) were significant independent predictors of SSRT.

To investigate the specific role in motoric cognitive control, the goRT obtained from the DRT was used as the dependent variable in the model. The model explained 11% of the variance, but was not significant (F (2, 15) = .905, p > .05) with dOp-preSMA/SMA (β = .660, p > .05) and vOp-PreSMA/SMA (β = -.589, p > .05) as predictors. Collinearity statistics indicated no evidence of multicollinearity in the presented models with all predictors showing tolerance >.1, variance inflation factor < 5 and r < .9. A summary of the models are presented in Table 4.

Additionally, since the vOp was the only region in opercularis that showed a reliable tract to insula. The FA values of the vOp-Insula tract were extracted and were correlated with SSRT. Thus, a one-tailed bivariate correlation between vOp-Insula and SSRT was conducted and revealed a significant negative correlation (r = -.530, p < .01, n = 22; Figure 7A).
Table 4. Summary of Multiple Regression Analyses (N = 17)

<table>
<thead>
<tr>
<th>SST go reaction time</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>180.781</td>
<td>.832</td>
<td>.418</td>
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<tr>
<td>dOp-PreSMA/SMA</td>
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<td>824.558</td>
<td>1.291</td>
<td>3.519</td>
<td>.003</td>
</tr>
<tr>
<td>vOp-PreSMA/SMA</td>
<td>-1933.714</td>
<td>867.151</td>
<td>-.818</td>
<td>-2.230</td>
<td>.041</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SST stop signal reaction time</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>232.730</td>
<td>87.258</td>
<td>2.667</td>
<td>.018</td>
<td></td>
</tr>
<tr>
<td>dOp-PreSMA/SMA</td>
<td>4.387</td>
<td>397.991</td>
<td>.006</td>
<td>.011</td>
<td>.991</td>
</tr>
<tr>
<td>vOp-PreSMA/SMA</td>
<td>-107.337</td>
<td>418.549</td>
<td>-.132</td>
<td>-.256</td>
<td>.801</td>
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</tbody>
</table>

<table>
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<tr>
<th>DRT go reaction time</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>299.664</td>
<td>213.469</td>
<td>1.404</td>
<td>.181</td>
<td></td>
</tr>
<tr>
<td>dOp-PreSMA/SMA</td>
<td>1308.531</td>
<td>973.650</td>
<td>.660</td>
<td>1.344</td>
<td>.199</td>
</tr>
<tr>
<td>vOp-PreSMA/SMA</td>
<td>-1227.450</td>
<td>1023.944</td>
<td>-.589</td>
<td>-1.199</td>
<td>.249</td>
</tr>
</tbody>
</table>

Note. SST = stop signal task; DRT = delayed response task;
SST go reaction time: R² = .502, adjusted R² = .436, F = 7.570;
SST stop signal reaction time: R² = .016, adjusted R² = -.115, F = .124;
DRT go reaction time: R² = .108, adjusted R² = -.011, F = .905.
Dop and Vop-preSMA/SMA are ending tracts

Figure 6. Partial regression plot of FA values between A) dOp-PreSMA/SMA and B) vOp-PreSMA/SMA predicting SST goRT. Residuals are plotted.
3.3.2 **Hypothesis 3.** To further investigate the prediction stated in hypothesis 3, the MD values of the orbitalis-STN tract were extracted and used as a predictor of SSRT. A one-tailed bivariate correlation between orbitalis-STN and SSRT was computed and showed a significant positive association (r = .427, p < .05, n = 20; Figure 7B), indicating that lower mean diffusivity is related to better inhibitory control. None of the other rIFG sub-regions showed a reliable tract to STN, thus the putative hyperdirect pathway could not be examined further.

![Figure 7. A, FA values for the vOp-Insula tract predicting SSRT; B, MD values for the orbitalis-STN tract predicting SSRT.](image)

3.3.3 **Exploratory analyses.** The connectivity analyses exhibited multiple tracts that are worth further exploration. In this case, the terminating tract to putamen seeding from orbitalis, the passing tract through caudate seeding from orbitalis and the passing tract through M1 seeding from opercularis. The putamen, caudate and M1 have all been associated with motor processes.

Two-tailed bivariate correlations between orbitalis-caudate, orbitalis-putamen, opercularis-M1 and goRT were computed to further explore possible associations to slowing of responses. The FA and MD values of the tracts of interest were used as predictors of goRT. Due to multiple comparisons, all p-values were FDR corrected. No association between goRT and orbitalis-caudate (MD: r = -.076, p > .05, FA = r = .256, p > .05, n = 21) or the MD values of the opercularis-M1 (r = -.336, p > .05, n = 22, top-right Figure 8A) and orbitalis-putamen (r = -.300, p > .05, n = 21, bottom-right Figure 8B) tracts were found. However, when the correlations were conducted with FA values, the goRT was significantly predicted by the
opercularis-M1 \( (r = .706, p < .01; \text{top-left Figure 8A}) \) and orbitalis-putamen \( (r = .554, p < .05; \text{bottom-left Figure 8B}) \) tracts, indicating that increased tract coherence in these regions are related to increased slowing of responses.

**Figure 8.** FA values for the opercularis-M1 (A, top-left) and orbitalis-putamen (B, bottom-left) tracts predicting SST goRT. MD values for the opercularis-M1 (A, top-right) and orbitalis-putamen (B, bottom-right) predicting SST goRT.
To the best of my knowledge, this is the first study to investigate white matter pathways in sub-regions of the rIFG. The pars opercularis, pars triangularis and pars orbitalis were used as seed regions to investigate differences in passing and terminating tracts. Furthermore, a similar procedure was used to investigate differential connectivity patterns of the ventral and dorsal part of the opercularis. The connectivity analyses revealed some notable differences between the rIFG sub-regions. The opercularis and triangularis showed high overlap in their connectivity patterns, while the orbitalis was found to project to multiple regions across the right hemisphere. The dorsal and ventral part of the pars opercularis also differed in their connectivity patterns. Notably, both dOp and vOp showed passing and ending tracts to the preSMA/SMA region, while only the latter region was associated with a passing tract through insula. The FA values of the dOp-preSMA/SMA ending tract were positively associated with goRT, while the vOp-preSMA/SMA tract was negatively associated with goRT. Increased FA in the vOp-Insula tract was associated with lower SSRT, while increased MD in the orbitalis-STN tract predicted prolonged SSRT. Finally, exploratory analysis revealed goRT was predicted by FA values of the orbitalis-putamen and opercularis-M1 tracts.

4.1 Structural connections of the rIFG

In line with hypothesis 1, the sub-regions showed tracts to preSMA/SMA region, insula, caudate, putamen and STN. Furthermore, the present thesis complements previous research that has used the rIFG or rIFC as a seed region. The connectivity analyses revealed which of the sub-regions of the rIFG that were associated with tracts detected from earlier connectivity studies. For instance, ample evidence has identified a structural connection from rIFG to preSMA (e.g., Aron et al., 2007; King et al., 2012; Swann et al., 2012), while the present results suggest that this tract is detected when seeding from opercularis and triangularis. Moreover, the opercularis was the only sub-region that showed a terminating projection to the preSMA/SMA region, possibly identifying the frontal aslant tract (Catani et al., 2012; Vergani et al., 2014). In line with previous research, all sub-regions showed structural connections to insula (Cloutman et al., 2012). However, parcellation of the pars opercularis suggested that only the ventral part was associated with a passing tract through the insula. A connection between rIFG and STN has been highly investigated in previous studies, due to its
putative role in the response inhibition network (Aron et al., 2007; Forstmann et al., 2012; Hinton et al., 2018). Interestingly, the present results identified passing projections through the STN when seeding from the orbitalis. This is surprising, as previous research has identified projections to the STN seeding from the opercularis (King et al., 2012) and triangularis (Isaacs et al., 2018) as well. Xu and colleagues (2016) found fiber pathways from pars opercularis/triangularis to striatum and pallidum. The present connectivity analyses indicate that fiber tracts pass through and terminate in the putamen when seeding from the triangularis and orbitalis. However, no connections were found between the opercularis and striatum, indicating that the results from Xu and colleagues could be driven by the connections from the triangularis. Moreover, the connections to caudate seem to be unique to pars orbitalis, while passing fiber tracts through pallidum were demonstrated seeding from the orbitalis and triangularis.

Previous research has identified fiber tracts from rIFG to the middle and superior temporal gyrus (Glasser & Rilling, 2008; Loui, Li & Schlaug, 2011), which was identified as a passing tract seeding from orbitalis in the present results. Additionally, the pars opercularis and triangularis have been found to connect to dorsolateral and superior frontal gyrus (Li et al., 2013). Although, these connections were replicated in the present thesis, it was also found that the connection includes projections that both pass through and terminates in the superior frontal gyrus. In addition, the inferior fronto-occipital fasciculus (IFOF) has been found to connect the occipital cortex to the IFG (Forkel et al., 2014). The connections to the occipital lobe was unique to the pars orbitalis in the present thesis. Noteworthy, the pars orbitalis also showed passing and terminating tracts to the superior and middle occipital gyrus.

The opercularis was structurally connected to the dorsomedial prefrontal cortex, which has been associated with social cognition and executive control in adolescents (Sherman et al., 2014), while the orbitalis showed passing projections to ventromedial prefrontal cortex, a region that has been found to show increased activity during interference in a cognitive control task (Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015). Furthermore, the orbitalis exhibited multiple structural connections to posterior regions. It demonstrated terminating and passing fiber tracts to the occipital lobe, regions that typically have increased activation during inhibition of automatic saccadic movements (Brown, Goltz, Vilis, Ford, & Everling, 2006).
From a broader perspective, it is notable that the rIFG sub-regions showed projections to the insula, middle frontal gyrus, M1, superior temporal gyrus, precuneus, caudate, thalamus, preSMA/SMA and middle occipital gyrus. It is interesting because these regions are significantly active during inhibition tasks (see Swick, Ashley, & Turken, 2011 for a meta-analysis). The reason as to why these widely distributed regions are active during inhibition tasks remains unclear. However, the present results might indicate that their shared function underlies a shared structural network. Indeed, the connectivity analyses showed structural connections from rIFG sub-regions to nearly all of the regions that are active in the right hemisphere during inhibition tasks (Levy & Wagner, 2011).

4.2 Structure and function

Hypothesis 2 stated that the tracts from dOp and vOp should be related to goRT and SSRT, respectively. However, the results suggested a more complex picture. The multiple regression analysis indicated that FA values of the dOp-preSMA/SMA and vOp-preSMA/SMA ending tracts predicted goRT in the SST. The dOp-preSMA/SMA tract showed a positive association to goRT, demonstrating that increased tract strength between these regions is associated with prolonged goRT. Strikingly, the vOp-preSMA/SMA tract showed a negative association to goRT, demonstrating that increased tract strength was related to faster goRT. However, neither the dOp-preSMA/SMA nor vOp-preSMA/SMA tracts were significant predictors of DRT goRT.

The averaged DRT goRT was significantly lower than the SST goRT, but they did not correlate. This indicates that the task context of the SST slows down responses compared to RT obtained in the DRT, which do not include stop-signals. Furthermore, it might be that the slowing of responses observed in SST are due to a recruitment of proactive inhibition. If this is indeed the case, it could be that the dOp is involved in proactive inhibition, as increased tract strength to preSMA/SMA predicts prolonged SST goRT. However, the negative association between vOp-preSMA/SMA tract and SST goRT is puzzling. One possible explanation could be that dorsal and ventral tract to preSMA/SMA are involved in speed-accuracy balancing, as prolonged goRT in the SST would likely result in increased accuracy. Thus, it might be that the activity in preSMA/SMA is mediated by efficient signal transfer that underlies white matter integrity. To speculate, the vOp could mediate the activation in preSMA/SMA region, consequently lowering the threshold for motor initiation during
proactive inhibition. This is in line with previous research, showing that the rIFG modulates the excitatory influence of preSMA on STN during response inhibition (Rae, Hughes, Anderson, & Rowe, 2015). Additionally, increased activity in the preSMA has been found when the participants slow down their responses (Sharp et al., 2010). Furthermore, the results also partly overlap with the recent functional model proposed by Hartwigsen and colleagues (2018). They suggested that the posterior part of rIFG could be segmented into a dorsal and ventral region corresponding to motor execution and inhibition, respectively. However, it is still unclear whether this relates to pure motor execution or is influenced by the difficulty of the task. The results support a distinction between the dorsal and ventral opercularis, but extends the theoretical framework to suggest the dOp as a hub for proactive inhibition and not pure motor execution.

In line with hypothesis 3, a positive association was found between orbitalis-STN and SSRT, indicating that increased tract coherence is associated with better inhibitory control. This might suggests that the hyperdirect pathway partly consists of a passing tract through the STN from orbitalis. Surprisingly, neither the opercularis nor triangularis showed reliable connections to the STN. However, it does not rule out the possibility that opercularis and triangularis projects to other regions that could be part of the hyperdirect pathway or even a broader inhibition network influencing STN activity. On that note, previous research has shown that the STN is active during both successful and unsuccessful stop trials, but successful stopping seems to be driven by STN’s influence on GPi (Schmidt et al., 2013). Thus, it might be plausible that the STN receives information from multiple projections and it is the net influx of signals that determine its excitatory or inhibitory effect on GPi. Further investigation of the structural and functional role of STN and GPi is warranted.

4.2.1 Exploratory analyses. The exploratory analysis revealed a significant positive association between the passing tract of opercularis-M1 and goRT. This is interesting due to the involvement of the basal ganglia in motoric function, which seem to suggest that all motoric functions loop through the basal ganglia. However, previous results have demonstrated that the rIFG and preSMA could bypass the basal ganglia (Mars et al., 2009; Buch, Mars, Boorman, & Rushworth, 2010). To speculate, it might be that rIFG could restrain the motor output from M1, thus require more excitatory signals from the basal ganglia to produce a movement. Furthermore, a significant positive association between the ending orbitalis-putamen tract and goRT was found. This is also in line with previous research
suggesting a role of the striatum and rIFG in proactive inhibition (Zandbelt & Vink, 2010). As increased tract strength between the abovementioned connections is related to increased goRT, it seems plausible that they are involved in motor control, possibly restraining the motor output of M1. This restriction could be due to increased recruitment of proactive inhibition in SST. However, even though they were involved in proactive inhibition, this mechanism is still poorly understood and more research is needed to investigate the potential functional role of these tracts.

4.3 Implications

The present brain graph provides a simple model of the underlying structural connections of sub-regions of the rIFG and complements previous functional data. While it is still unclear why highly distributed regions are involved in response inhibition, the present results suggest that they underlie a common structural network. Not only does this have an implication for understanding the structure and function of the healthy brain, it also exhibits promising preliminary data for a deeper understanding of pathological conditions. For instance, it has been suggested that insight into functional and structural connectivity of the brain could be used to elucidate potential causes and treatments for psychiatric disorders (Hulshoff Pol & Bullmore, 2013). Altered rIFG white matter integrity has also been associated with autism (Mengotti et al., 2011), post-stroke psychosis (Devine et al., 2014), schizophrenia (Shin et al., 2006) and ADHD (Casey et al., 2007). However, it still unclear how this relates to white matter pathways of rIFG sub-regions. Future research of rIFG connectivity should aim to investigate potential disturbances in the structural network of rIFG sub-regions.

The complexity of the white matter pathways seeding from sub-regions of the rIFG suggest that it should not be treated as a homogenous region. Firstly, it exhibits several unique connections to multiple regions. Secondly, the rIFG sub-regions show both passing and ending tracts to the same region, which is a distinction that is generally not made in the literature. Finally, even unique tracts from one sub-region could be differentially associated with behavioral measures.

The differences in goRT obtained from DRT and SST, suggest that the latter involves a task context that slow individuals responses in go-trials. This might indicate the goRT obtained from SSTs is not a measure of pure motoric processes, but might recruit other cognitive mechanisms such as proactive inhibition. This would suggest different
interpretations of correlations and neural correlates of motor execution in go-trials during inhibitory tasks. More research is highly needed to isolate the cognitive mechanisms underlying motor inhibition, preparation and execution processes.

4.4 Limitations and future directions

The present study was part of a larger research project investigating inhibitory control using several additional neuroimaging techniques during acquisition of the behavioral data that were not discussed in the thesis (i.e. EEG, EMG, TMS). It might be that the application of TMS during the inhibitory task could influence the behavioral measures. In the present thesis, the behavioral measures were based on non-pulse trials and the descriptive results are similar to what is normally obtained during inhibitory tasks. In addition, the results agree largely with previous evidence and models of inhibitory control and were generally in line with the hypotheses. Nevertheless, future research should aim to replicate this finding based on other cognitive control tasks, without the implementation of simultaneous neuroimaging techniques.

Deterministic tractography has some limitations that need to be addressed. For instance, voxels could consist of several tracts with multiple directions, making the overall tensor appear isotropic and could end the reconstruction of an actual continuous fiber tract (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). In addition, the reconstruction assumes one predominant orientation in each voxel, ignoring the complex structural architecture of the brain. This crossover problem illustrates why interpretation of the reconstructed fiber pathways should be made with extreme caution. However, other tractography approaches could be used to cope with the limitations of the present method, such as diffusion spectrum MRI (Wedeen et al., 2008).

The lack of connection between pars opercularis and STN is somewhat surprising. However, there might be several reasons for the absence of this tract in the present thesis. Firstly, the dMRI sequence might not be sensitive enough to identify the tract. Secondly, the present STN mask might be too small to detect actual tracts with the present parameters. Other studies have created a 10mm3 box mask for the segmentation of the STN (Aron & Poldrack, 2006; Neubert, Mars, Buch, Olivier, & Rushworth, 2010). Similar segmentation of the STN was used by King and colleagues (2012) who found structural connections between pars opercularis and STN with somewhat similar DWI parameters as in the present thesis.
However, the presence of the orbitalis-STN tract could also include tracts projecting adjacent to STN, as the present thesis exploits an atlas based binarized version of a probability map of STN (Forstmann et al., 2012). Manual segmentation of the STN could cope with this caveat, however this would require images obtained from ultra-high field MRI and with the expense of increased risk of user-bias. Finally, the parameter of the angle threshold for identification of a tract could be too conservative and “break” the connections between pars opercularis and STN prematurely. However, one should be cautious with increasing the angle threshold as it might reconstruct a continuous tract that is not anatomically possible.

Finally, although the present results show multiple anatomical connections seeding from rIFG, the tracts underlying functional role remains elusive. In addition, the present results are based on a rather strict detection threshold of 80% and the parameters used for tractography might be too conservative for detection of tracts. Thus, it is important to note that several tracts could indeed project from rIFG but were not detected with the current parameters and detection threshold. Future studies should increase our understanding of white matter tracts with an increased sample size and acquiring images with increased independent directions and resolution.

4.5 Concluding remarks

The present study provides the first parcellation-based connectivity investigation of sub-regions in the rIFG. Pars opercularis, triangularis and orbitalis exhibited structural heterogeneity with projections to different regions thought to underlie different cognitive functions. Most prominently, it showed structural end and passing white matter tracts to the putative response inhibition network. Surprisingly, the tracts were predominately identified seeding from pars triangularis and orbitalis. The segmentation of the opercularis into a dorsal and ventral region provided some marked differences, where the dOp showed passing projections through the middle frontal gyrus, while vOp projected through rolandic operculum, insula and postcentral gyrus. Both dOp and vOp had passing and terminating projections to the preSMA/SMA region. Furthermore, the results showed that FA values of the dOp-preSMA/SMA and vOp-preSMA/SMA ending tracts significantly predicted goRT, but did so in opposite directions. This might suggest that distinct properties of the opercularis-preSMA/SMA tract are involved in different mechanisms, such as speed-accuracy balancing.
Nevertheless, further examination of the opercularis-preSMA/SMA tract following a 2 (ventral/dorsal) x 2 (pass/end) procedure is warranted.

Although, the vOp-preSMA/SMA tract was not related to SSRT, the FA value of of vOp-Insula were negatively associated with SSRT. The results partly supports a role of opercularis in response inhibition, but emphasizes the role of its underlying white matter pathways. It leaves the possibility that the vOp is not only important for outright stopping, but also motor execution. Furthermore, the MD of the orbitalis-STN tract was positively correlated with SSRT, suggesting that this connection could be part of the hyperdirect pathway. However, the results did not reveal any reliable projections to or through the STN when the opercularis and triangularis were used as seed regions. The exploratory analyses provided some noteworthy results. Increased FA value of the ending orbitalis-putamen tract and the passing opercularis-M1 tract predicted prolonged goRT. The results might indicate that individuals with increased tract strength between those regions recruits more proactive inhibition.

Altogether, the present results suggest that the rIFG is a highly heterogeneous region in terms of its underlying fiber structure. It also exhibits structural connections to the widely distributed response inhibition network and its white matter integrity predicts measures of inhibitory control. More research is highly needed to elucidate the functional role of rIFG sub-regions and its associated white matter pathways.
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