An exploration of the effects of tDCS to Supplementary Motor Complex on measures of

inhibitory control: Implications for Tourette's syndrome

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Abstract

Inhibitory control (IC) depends on a cortico-subcortical network, with downstream effects on the primary motor cortex (M1). Hyperexcitability in M1 has been proposed to impair IC, a state associated with tics in patients with Tourette's syndrome (TS). Anodal Transcranial Direct Current Stimulation (tDCS) applied over the Supplementary Motor Complex (SMC) in order to decrease M1 excitability has improved IC in healthy subjects, while increased tics in patients. In parallel, cathodal tDCS to increase M1 excitability have reduced tics, but impaired IC in healthy adults. Aiming to explore these contradictory findings, we analyzed the effects of anodal, cathodal, and sham tDCS applied to the SMC on measures of IC in young, healthy adults. M1 excitability was monitored with Transcranial Magnetic Stimulation (TMS) and IC was measured from performance on the Anticipatory Response Inhibition Task. The results revealed no change in IC following tDCS. However, we observed a tDCS-induced change in M1 excitability. This suggest that tDCS applied to SMC mainly affects M1 excitability via the cortico-cortical pathway, without engaging the subcortical network important for IC. We also observed an individual response variability to tDCS, showing unreliable directions in excitatory shifts. Overall, we suggest that the puzzling effect on tics following tDCS to SMC could result from direct cortical effects from SMC, not from the involvement of the inhibitory subcortical network. Without undermining the effect of tDCS, we highlight the response variability limiting the methods reliability in the investigation of cognitive abilities and clinical symptoms.

Key words: Transcranial direct current stimulation, tDCS, supplementary motor complex, supplementary motor area, presupplementary motor area, inhibitory control, response inhibition, anticipatory response inhibition task, ARIT, Tourette's syndrome, tics

Sammendrag

Inhibitorisk kontroll (IC) avhenger av et cortico-subcortikalt nettverk, med nedstrømseffekter på primære motoriske cortex (M1). Hypereksitabilitet i M1 har vært antatt å svekke IC, en tilstand assosiert med tics hos pasienter med Tourettes syndrom (TS). Transkraniell likestrømsstimulering (tDCS) påført over det supplementære motoriske kompleks (SMC) for å redusere M1-eksitabilitet har forbedret IC hos friske forsøkspersoner, med økt alvorlighetsgrad av tics hos pasienter. Samtidig, katodal tDCS for å øke M1-eksitabilitet har svekket IC, men redusert utrykket av tics. Med sikte på å utforske disse motstridende funnene, analyserte vi effekten av anodal, katodal og sham tDCS over SMC på mål av IC og M1 eksitabilitet hos unge, friske voksne. M1-eksitabilitet ble målt med transkraniell magnetisk stimulering (TMS) og IC ble beregnet fra utførelsen av «Anticipatory Response Inhibition Task». Resultatene viste ingen endring i IC etter tDCS. Imidlertid observerte vi en tDCS-indusert endring i M1-eksitabilitet. Dette antyder at tDCS over SMC hovedsakelig påvirker M1 eksitabilitet via den cortiko-cortikale nervebanen, uten å engasjere det subcortikale nettverket som er viktig for IC. Vi observerte også en individuell responsvariabilitet til tDCS, med upålitelige retninger i eksitatoriske skift. Vi foreslår at de motstridende effektene på tics etter tDCS til SMC kan skyldes direkte cortikale effekter fra SMC, uten involvering av det inhibitoriske subcortikale nettverket. Uten å undergrave effekten av tDCS, understreker vi responsvariabiliteten som begrenser metodens reliabilitet i undersøkelsen av kognitive evner og kliniske symptomer.

Nøkkelord: Transkraniell likestrømstimulering, tDCS, supplerende motorisk kompleks, supplerende motorisk område, presupplementære motorisk område, inhibitorisk kontroll, respons inhibisjon, ARIT, Tourettes syndrom, tics

Acknowledgements

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List of abbreviations

BG – Basal Ganglia

CCM – Corticomotor excitability

EMG – Electro

GABA – Gamma-Aminobutyric Acid

Go RT – Go Reaction Time

GP – Globus Pallidus

GPe – Globus Pallidus externa

GPi – Globus Pallidus interna

IFG – Inferior Frontal Gyrus

M1 – Primary Motor Cortex

OCD – Obsessive Compulsive Disorder

PMU – Premonitory Urge

RI – Response Inhibition

sEMG – Surface Electro

SMA – Supplementary Motor Area

SMC – Supplementary Motor Complex

SN – Substantia Nigra

SNc – Substantia Nigra compacta

SNr – Substantia Nigra reticulata

SSD – Stop Signal Delay

SSRT – Stop Signal Reaction Time

SST – Stop Signal Task

STN – Subthalamic Nuclei

tDCS – Transcranial Direct Current Stimulation

TMS – Transcranial Magnetic Stimulations

TS – Tourette's Syndrome

1. Summary

Inhibitory control (IC) refers to the voluntary countermanding of ongoing motor actions (Tiego et al., 2018). In order to adapt to an ever-changing environment, the capacity to efficiently suppress unnecessary and non-rewarding behaviour is crusial. Based on the behaviour patterns of young children and adolescents, the ability to inhibit initiated motor responses increases with age (Welsh et al., 2006; Williams et al., 1999a). Insufficient IC persisting into adulthood are associated with several neurological and psychiatric disorders, e.g. Attentional Deficit Disorder (ADHD), Obsessive Compulsive disorder (OCD) and Tourette's syndrome (TS) (Bannon et al., 2002; Lanciego et al., 2012; Morand-Beaulieu et al., 2017; Schachar et al., 2000; Schachar et al., 1995; Verbruggen & Logan, 2008).

IC is frequently investigated within the framework of the Stop Signal Paradigm, an experimental approach in which the ability to cancel ongoing responses can be objectively measured (Cirillo et al., 2018; Verbruggen et al., 2008). The time it takes to process a signal to stop and inhibit the response is calculated as the stop signal reaction time (SSRT). SSRT is thought to reflect the integrity of individual inhibitory mechanisms with faster relative to slower SSRTs possibly corresponding to specific pathways in the brain. These theoretical developments have highlighted the existence of a neural inhibitory network, engaging a right lateralized cortico-basal ganglia-thalamocortical circuit (Aron & Poldrack, 2006; Coxon et al., 2009; Zandbelt et al., 2013; Zandbelt & Vink, 2010b)

The Supplementary Motor Complex (SMC) is considered an "starting point" in the inhibitory network. The SMC is thought to influence IC by affecting more deep-seated subthalamic regions, ultimately causing excitability changes in the Primary Motor Cortex (M1). Imbalance within the inhibitory network has been linked to hyperexcitability of M1 and neurological disorders, including Tourette's Syndrome (TS) (Bronfeld et al., 2013; Morand-Beaulieu et al., 2017). The inhibitory network, specifically the SMC has therefore appealed to researcher investigating IC and TS.

TS is a neurological disorder that frequently presents itself in childhood, accompanied by tics, i.e. partially involuntary phonic and motor actions. Parallel to the increase in IC as children mature into young adults, TS patients have shown a decline in symptomatic

presentation during adolescence (Cohen et al., 2013; Ferguson et al., 2021; Muller, 2007). For this reason, several studies suggest that inhibitory deficits are associated with tic-behaviour, although the underlying cause of TS is still unclear (Morand-Beaulieu et al., 2017, see review).

To date, TS cannot be cured completely (Augustine & Singer, 2018). Efforts to alleviate symptoms have included medical and behavioural interventions, proving to work for some but not for others (Kious et al., 2016b). Therefore, researchers have aimed towards developing alternative treatments for TS.

Previous work has investigated the effects of non-invasive brain stimulation (NIBS) techniques on measures of IC in healthy subjects and tics in TS patients. By applying transcranial direct current stimulation (tDCS) to the SMC, attempts have been made to temporally modulate cortical excitability and improve or restore the inhibitory imbalance suggested to underlie tic-behaviour (Dyke et al., 2022). However, stimulation protocols proving to increase IC in healthy participants, do not decrease tics in TS patients. This raises questions regarding the involvement of inhibitory deficits in the processes that contribute to tic development.

Importantly, the contradictory behavioural outcomes following tDCS in patients and healthy adults could result from general uncertainty of the neural correlates of TS, response variability to stimulation or methodological shortcomings. Specifically, previous reports have been inconsistent in assessing changes to corticomotor excitability following tDCS. Without monitoring excitability changes, one cannot establish that stimulation has had the desired effect (Dyke et al., 2022).

The present introduction attempts to highlight the current understanding of IC, by thoroughly featuring its definitions, theoretical frameworks, objective measurements, and neurobiological underpinnings. It aims to evaluate the growing research on the therapeutic benefits of NIBS techniques as a treatment for tics, and further corroborate the neurological association between inhibitory deficits and TS. The current study aims to investigate the effect of tDCS on SMC on objective measures of IC in young, healthy adults. By obtaining both baseline and post-measures of corticomotor excitability following both real and sham tDCS, the study seeks to provide complementary sham-controlled evidence to the literature on current TDCS protocols, and further contribute to the future establishment of tDCS as a therapeutic tool for TS patients.

1.1. Inhibitory Control

Inhibitory control, i.e., response inhibition, is a multifaceted term that involves the voluntary control of stimuli, cognitions and motor actions that appear goal-irrelevant to the individual (Diamond, 2013; Nigg, 2000). A distinction is often made between two inhibitory processes; (1) Motor inhibition, or Response Inhibition (RI), and (2) Attentional Inhibition (Tiego et al., 2018). RI refers to the executive ability to inhibit an ongoing motor response (Verbruggen & Logan, 2008) while attentional inhibition is the ability to avoid or inhibit the interference of salient yet irrelevant external stimuli (Howard et al., 2014; Tiego et al., 2018) . This thesis considers the process of RI as its main focus.

Early reports have suggested that the ability to suppress less goal-directed solutions first emerged in late childhood. However, the current understanding suggest that RI is in fact present in the first year of life, although in its most basic form (Welsh et al., 2006). The ability then increases in dramatic developmental leaps, ultimately reaching a sophisticated level in early adulthood (Houde & Borst, 2014; Petersen et al., 2016). Inhibitory deficits are often observed in neurological and psychiatric disorders, including OCD, ADHD, and TS (Bannon et al., 2002; Lanciego et al., 2012; Morand-Beaulieu et al., 2017; Schachar et al., 2000; Schachar et al., 1995; Verbruggen & Logan, 2008). RI is regularly investigated via the Stop Signal Paradigm, where performance on Stop Signal Tasks (SST) can be explained within a theoretical framework developed on the basis of race finish times (Schall et al., 2017).

1.1.1. Measures of Response Inhibition

The Stop Signal Paradigm, first developed by Vince (1948) provides an objective measure of RI (Coxon et al., 2007; Hall et al., 2022; MacDonald et al., 2014; Verbruggen & Logan, 2008). The paradigm has later been refined as the Stop Signal Task (SST) by Lappin and Eriksen (2014), and most recently by Logan and colleges (2008). The SST is currently available as an open-source STOP-IT software (Verbruggen et al., 2019; Verbruggen et al., 2008). The SST involves participants performing a primary task, i.e., the "go-task", establishing it as their default response. The task is sporadically interrupted by a stop signal, telling the participant to cancel the ongoing action initiated by the go-task (Logan & Cowan, 1984; Verbruggen & Logan, 2008). The time it takes to process a stop signal and cancel the tendency to «go» is referred to as Stop Signal Reaction Time (SSRT). SSRT is thought to reflect the integrity of the inhibitory mechanisms underlying RI, and is therefore often used as the primary outcome measure to reflect inhibitory control during RI behavioural tasks (Eagle et al., 2008).

1.1.2. The Independent Horse Race Model.

According to the "independent horse race model", the internal mechanisms activated by performing SSTs have been described as a «race» between the tendency to «go» and the tendency to «stop» (Logan & Cowan, 1984). A "go process" is initiated by the presentation of the "go stimulus", i.e., the primary task. A "stop process" is initiated by the presentation of the "stop signal", i.e., a cue prompting the subject to cancel the response. If the "stop process" finishes before the "go process", the "go process", i.e., the primary task is blocked, and RI can occur. In the opposite case, when the "go process" finishes before the "stop process", the planned response of «going» is completed and inhibition fails to occur (Logan & Cowan, 1984). This model has significantly influenced the field of RI over the past decades, estimating stopping latencies and analysing RI efficiency across different age groups and clinical populations (Kramer et al., 1994; Oosterlaan & Sergeant, 1998; Schachar & Logan, 1990; Schachar et al., 2000; Williams et al., 1999b). Moreover, based on the notion that inhibition relies on the time it takes the "stop process" and the "primary process" to finish, the model has described the probability of both inhibiting and completing the pre-planned response when the stop signal is presented (Logan & Cowan, 1984).

Calculating the probability of responding on a stop-signal trial and the probability of inhibiting the primary task primarily depend on SSRT, stop signal delay (SSD), and go reaction time (Go RT). SSD refers to the time elapsed between the presentation of the go stimulus, i.e., the primary task, and the presentation of the stop signal (see figure 1). Go RT refers to the time elapsed between presentation of the go stimulus and the participant's reaction to it (see figure 1). When SSD is increased, the "stop process" both starts and finishes later, relative to the "go process". Increasing SSD, and thus increasing the probability that the stop process ends later, results in slower Go RT. Finally, for every SSD, and the following increased probability of the stop process finishing after the go process, the SSRT is increased (Hall et al., 2022; Matzke et al., 2013; Verbruggen & Logan, 2008). Consequently, "the independent horse race model" have provided a mathematical equation to calculate individual mean SSRT (see figure 1) (Matzke et al., 2013).

Figure 1.

Visual representation of the horse race model.
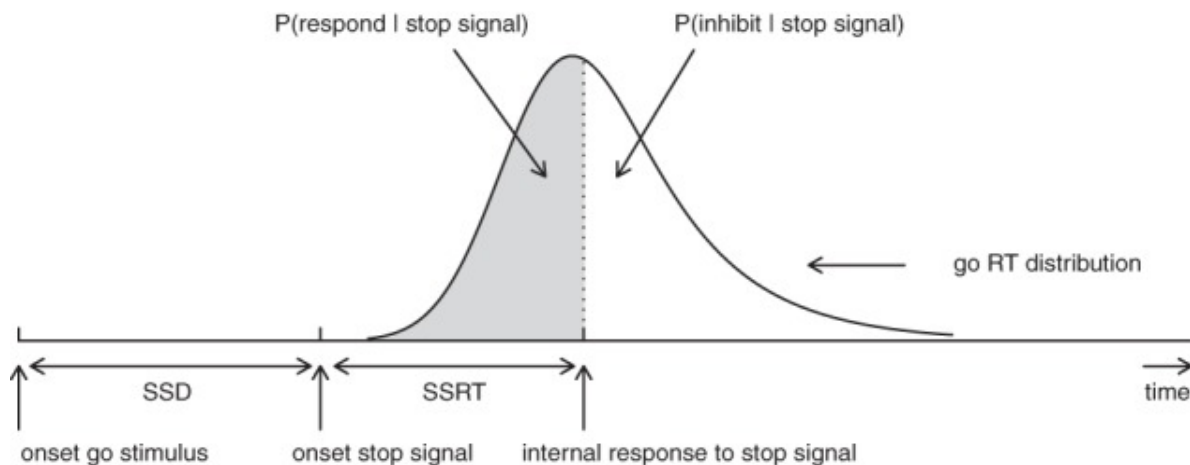
Figure 1. illustrates the idea by Logan and Cowan (1984), showing how the probability of responding to the stop signal [p(respond| stop signal)] and the probability of inhibiting the prepared response [p(inhibit| stop signal)] depend on the distribution of go reaction times, stop-signal delay (SSD) and SSRT (Matzke et al., 2013).

1.1.3.   The Anticipatory Response Inhibition Task (ARIT).

Following the same theoretical "horse race" approach, an anticipatory version of the SST has been frequently used to obtain objective measures of RI. First developed by Slater-Hammel (1960), the anticipatory response inhibition task (ARIT) involves two vertical columns rising for 1000 ms when two corresponding keys on a keyboard are depressed simultaneously (Coxon et al., 2016; Coxon et al., 2007, 2009; Gilbert et al., 2019; Macdonald et al., 2012; MacDonald et al., 2016; Zandbelt & Vink, 2010b). On go trials (GO), participants will release both keys when the columns are intercepting a stationary target (i.e., the GO stimulus) at 800 ms. On stop both (SS) trials, both columns stop prematurely (i.e., the stop signal), requiring the participants to inhibit their lift response by continuing to depress both keys. The time it takes to process the columns stopping prior to the target and cancel the lifting response is reflected in the SSRT (Hall et al., 2022).

On selective stop trials (SL/SR), only one of the columns will stop prematurely, while the other will keep rising against the target line. Participants are required to depress the key corresponding to the column that stopped, while lifting the key corresponding to the column that is still rising, attempting to intercept the target (Hall et al., 2022). SL/SR trials activate selective behavioral response cancelation, rather than a non-selective neural level cancelation (Coxon et al., 2009; MacDonald et al., 2014; Macdonald et al., 2012; Wadsley et al., 2019).

Anticipatory SSTs hold some advantages over the more traditional versions. Contrary to conventional SSTs (e.g., "choice-reaction stop-signal tasks"), requiring an "as fast as possible" response to the stop signal, ARIT involve participants making anticipated, more internally generated responses, aiming to stop the rising columns to intercept the predefined stationary target. The stationary target creates consistency in movement preparation and initiation, making it possible to avoid the occurrence of «strategic slowing» (Verbruggen et al., 2013) typically observed in traditional SSTs. «Strategic slowing» involves the tendency to intentionally slow down responses on GO trials in order to respond successfully to an upcoming stop signal. This can influence GO RT distributions, resulting in invalid SSRT calculations (Verbruggen et al., 2013). By restricting the range of RTs on GO trials around the stationary target, "strategic slowing" is substantially reduced, making it one of ARITs major benefits (Dambacher et al., 2014; He et al., 2022; Leunissen et al., 2017).

Neuroscientific approaches investigating the efficiency of "going" and "stopping" have focused on locating these processes in a structural framework in the brain. Specifically, responses on STOP and GO trials completing SSTs have been found to engage different GABAergic and glutaminergic pathways within Basal ganglia (BG). Therefore, measures on SSTs have been thought to reflect the efficiency of a neural inhibitory network (Allen et al. 2018; Aron et al. 2003; Aron and Poldrack 2006; Chen et al. 2020; Coxon et al. 2009; Dunovan et al. 2015; Li et al. 2008; Maizey et al. 2020; Ray et al. 2012, in Hall et al., 2022).

1.2. The Neurobiology of Response Inhibition

On an implementational level, neural inhibition is initiated by the transmitting of chemical signalling substances from one area of brain to another (Aron, 2007). Gamma-aminobutyric acid (GABA) is recognized as the main inhibitory neurotransmitter in the brain. By releasing GABA across the synaptic cleft, inhibition is induced in the target neuron, creating an inhibitory postsynaptic potential (Sheffler et al., 2023). Inhibitory projections help suppress or cancel further neural signalling by decreasing excitability and preventing action potentials to fire. On the other hand, glutamate is the main excitatory neurotransmitter in the

brain, having an excitatory effect on receiving neurons, when released to the extracellular fluid. Excitatory projections facilitate neural communication by promoting the firing of action potentials (Zhou & Danbolt, 2014).

RI depends on GABAergic and glutaminergic projections within a right-lateralized cortico-subcortical circuit, with downstream effects on the primary motor cortex (M1). The circuit has been referred to as an inhibitory network, and engages Supplementary Motor Complex (SMC), Inferior Frontal Gyrus (IFG), pathways within the BG, and Primary Motor Cortex (M1) (Aron & Poldrack, 2006; Coxon et al., 2009; Zandbelt et al., 2013; Zandbelt & Vink, 2010b). Movement and movement inhibition is regulated and expressed appropriately by activation travelling via distinct pathways within the network (further described in section 1.2.3.: "The Basal Ganglia"). Of most importance to this study is the SMC, the BG and the M1. A brief description of their anatomical features, functions and connectivity will be presented below.

1.2.1. The Primary Motor Cortex (M1).

Located in the precentral gyrus of the frontal lobe, the Primary Motor Cortex (M1) plays an important role in overall motor decisions (Barnes, 2014, p. 174; Bhattacharjee et al., 2021; Hooks et al., 2013; Yu & Zuo, 2011). Specific locations on the M1 contralaterally regulate distinct muscle groups, and a topographic representation of various parts of the body called the motor homunculus descends along the precentral gyrus. The degree of control M1 holds over the area corresponds to the size of the muscle representation (see figure 2).

Figure 2.

The Motor Homunculus.
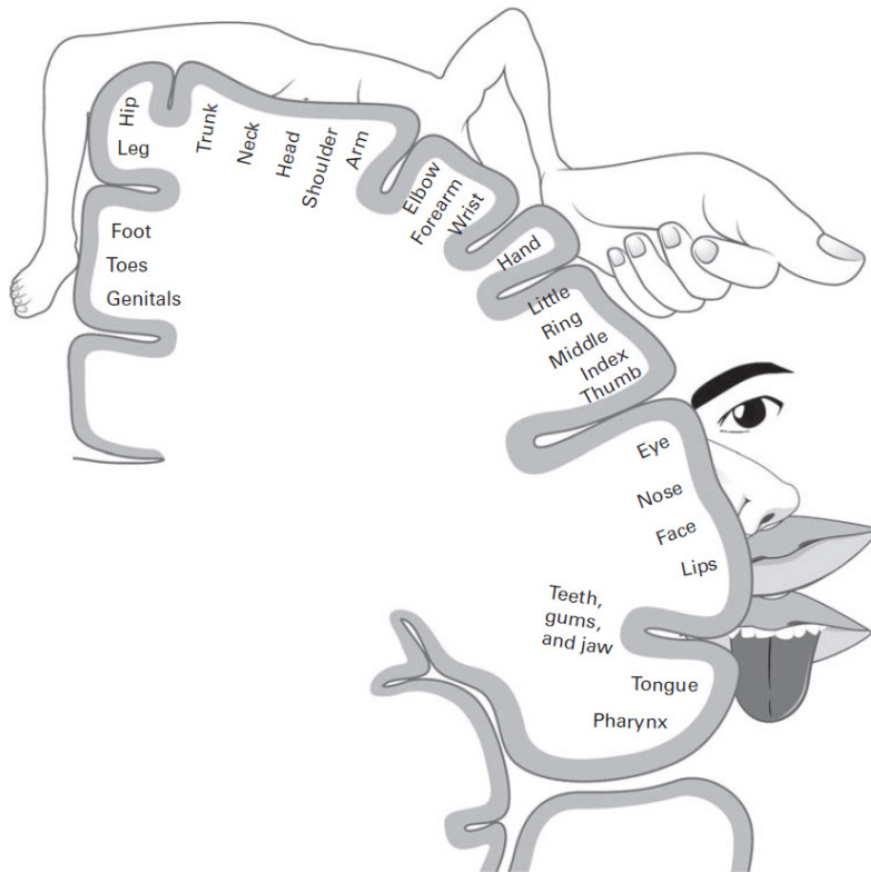
Figure 2. shows the Motor homunculus, a visual representation of the topographic body map located in the M1 (De Brigard & Sinnott-Armstrong, 2022).

For specific voluntary movements to be executed, pyramidal cells in the motor cortex as part of the corticospinal tract activate alpha motor neurons in the spinal cord. Activation then travels through the peripheral nerve system, before terminating in the target contralateral muscle inducing an action potential, causing it to contract (Doyal et al., 2022). Previous studies have revealed that stimulating specific motor representations in the motor cortex will cause the target muscle to contract.

To control movement, the M1 depends on input from various areas of the brain. These inputs are divided into thalamocortical and cortico-cortical projections (see figure 3). The thalamocortical connection involves thalamic neurons projecting to M1 with information from other more integrated parts of the brain like cerebellum and the BG (Middleton & Strick,

2000). Cortico-cortical connections involves direct input from other cortical areas including the SMC (Lee et al., 2022). Depending on the GABAergic (inhibitory) or glutamatergic (excitatory) nature of the M1 input, movement is initiated or inhibited. Excitatory signals will excite M1 and cause movement, whereas inhibitory signals will decrease M1 excitability and facilitate response inhibition. When the corticocortical-subthalamic network is disrupted, the clinical state of hyperexcitability of M1 can occur. M1 hyperexcitability has been associated with involuntary motor actions often observed in movements disorders such as TS (Thomalla et al., 2014, in Morand-Beaulieu et al., 2017). While previous research has failed to identify cause of hyperexcitability, deficit within the BG have been suggested (Albin et al., 2003; Bloch et al., 2005; Kalanithi et al., 2005; Peterson et al., 2003; Wang et al., 2011, in Bronfeld et al., 2013) (described in further detail in section 1.3.1.: "The Neurobiology of Tourette's syndrome").

Figure 3.

Simplified model of connections from the SMC to M1.
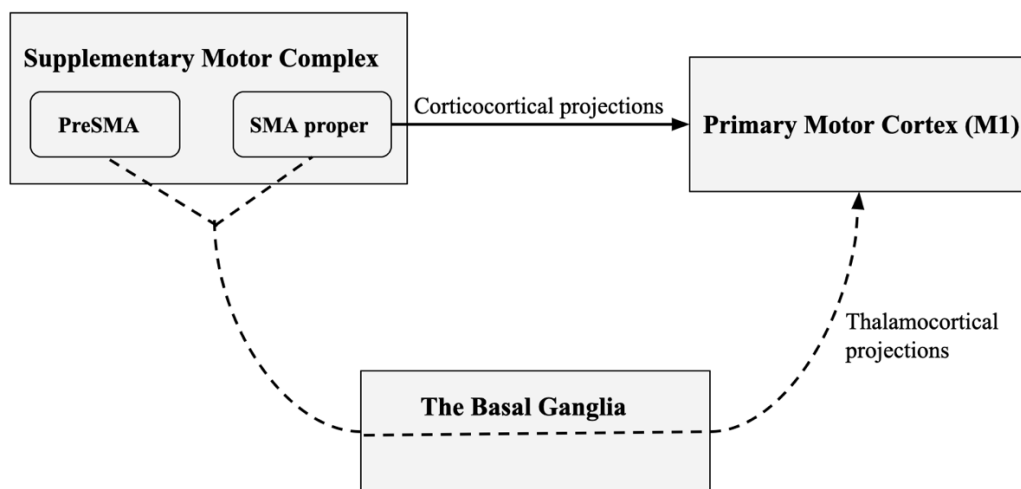
Figure 3. shows a simplified model of the connections from the Supplementary Motor Complex (SMC) to the Primary Motor Cortex (M1). The SMC can affect the M1 directly via corticocortical projections, and indirectly via thalamocortical projections via Basal Ganglia pathways.

1.2.2. The Supplementary Motor Complex.

The supplementary motor complex (SMC) is located in the dorso-medial frontal cortex (Nachev et al., 2008), serving important functions for voluntary and involuntary movement

regulation (Brugger et al., 2015). The SMC is functionally divided into the Pre-supplementary Motor Area (preSMA) and the Supplementary Motor Area (SMA proper) (Nachev et al., 2008). Neuroimaging studies have revealed significant activation of the preSMA in subjects with faster SSRTs, i.e., more efficient inhibitory mechanisms, compared to slower ones (Li et al., 2008). This has implied that the preSMA plays an important role in inhibition. Furthermore, PreSMA has been associated with movement selection, preparation, and sequencing, while the SMA proper has been related to movement execution (Akkal et al., 2007). The two structures also differ in their connectivity to other areas of the brain. While the SMA proper has direct corticocortical projections to M1, preSMA does not. Nevertheless, both structures have been considered important targets of BG output (Hiroshima et al., 2014), indirectly effecting M1 via thalamocortical projections (see figure 3). However, separating the the preSMA and SMA proper using techniques such as tDCS has proven challenging, as the large electrodes commonly used lack focality. For this reason, both structures will hereafter be collectively referred to as the SMC.

When RI is initiated, the SMC is thought to affect M1 indirectly by projecting GABAergic (inhibitory) signals onto downstream BG and thalamic areas, leading to decreased M1 excitability and the cancelation motor actions (Aron & Poldrack, 2006; Coxon et al., 2009; Zandbelt et al., 2013; Zandbelt & Vink, 2010b). Conversely, increased M1 excitability has been associated with unregulated motor activity, impaired RI and tics (Thomalla et al., 2014, in Morand-Beaulieu et al., 2017). Theoretically, a way to rectify the excess M1 activity would be to increase activity in the SMC, resulting in increased inhibition of the inhibitory components controlling the thalamus, reducing the thalamocortical drive and ultimately reduce excitability in M1. Accordingly, decreasing activity in the SMC would increase thalamocortical drive, hence increasing M1 excitability. Indeed, this pattern has been observed when non-invasive brain stimulation has been applied to young healthy adults to increase or decrease SMC activity (discussed in section 1.4.1.1.: "The effect of tDCS on RI in healthy adults").

As illustrated in figure 3, the SMC also affects the M1 directly via glutaminergic cortico-cortical connections (Hiroshima et al., 2014). Therefore, exciting the SMC could directly excite motor neurons in the M1, increasing tonic excitability and impairing inhibitory mechanisms. Likewise, decreasing SMC could also decrease activity in M1, ultimately improving RI. It remains to be investigated whether excitability of M1, and hence the reinforcement or reduction of RI, is predominantly affected by subcortical or corticocortical

pathways resulting from SMC modulation. Imbalance to the pathways affecting M1 excitability and the potential to result in M1 hyperexcitability, has been associated with several clinical conditions, including TS (Bronfeld et al., 2013; Lanciego et al., 2012; Morand-Beaulieu et al., 2017).

1.2.3. The Basal Ganglia.

The BG is a collection of interconnected subcortical structures, important for coordinating motor activity. In the strictest sense, its main components include Nucleus Caudate and Putamen (collectively referred to as the Striatum), and the Globus Pallidus (GP). GP is divided into the internal (GPi) and the external (GPe) segment. The thalamus, subthalamus (STN), and the substantia nigra (SN) are referred to as related nuclei (Javed & Cascella, 2023; Lanciego et al., 2012) on the basis of their contribution to optimal BG function. SN is divided into SN pars reticulata (SNr) and pars compacta (SNc). When stimuli are registered, the striatum i.e., the main input nuclei, receives and processes information from cortical and thalamic areas. BG output nuclei (GPi and SNr) project information back to the thalamus, which in turn projects to cortical areas, closing the neural circuit (Lanciego et al., 2012; Milardi et al., 2019).

By ultimately effecting M1 excitability, information travelling via specific pathways within the BG have shown to produce opposite effects on motor control. These functionally contrasting pathways include the "direct pathway", involved in movement initiation, the "indirect pathway" involved in movement inhibition, and the "hyper direct pathway", involved in fast inhibition. "Direct" activation initiates movement by glutaminergic projections from the cortex stimulating striatal neurons to release GABA onto GPi and SNr. In order to prevent excess thalamic activation of motor neurons in the cortex and the initiation of unwanted movement, GPi and SNr exert a continuously inhibitory control over thalamic nuclei. When GPi and SNr are inhibited, their inhibition of thalamus is "lifted", resulting in thalamic disinhibition. Consequently, thalamocortical drive is increased and movement is initiated (see figure 4) (Lanciego et al., 2012; Milardi et al., 2019). Importantly, the SNc contributes to the direct pathway with its release of dopamine onto striatum via the nigrostriatal tract. The transmitted dopamine synapse on two distinct types of dopamine receptive striatal neurons; D1 and D2 receptor neurons. D1 receptor neurons have inhibitory projections to GPi, contributing to the disinhibition of thalamic nuclei to excite motor neurons in the cortex and facilitate the direct pathwa. On the other hand, D2 receptor neurons assist with movement inhibition via the indirect pathway detailed below (Barnes, 2014, p. 333-334).

The "indirect" pathway inhibits movement via glutaminergic projecting from the cortex causing GABAergic neurons in the striatum to activate. Striatal GABAergic neurons inhibit the GPe, resulting in pallidal disinhibition and the cessation of its inhibitory effect on the STN. Therefore, STN stimulates GABAergic neurons in the GPi and SNr, causing an increased inhibition of thalamus. In turn, thalamocortical drive is reduced, and movement is inhibited (see figure 4) (Lanciego et al., 2012; Milardi et al., 2019). The synapse of nigrostriatal dopamine on D2 receptor neurons facilitates the indirect pathway. D2 receptor neurons have excitatory projections to the GPe, contributing to the area's inhibition of STN, blocking its activation of the cortex (Barnes, 2014, p. 333-334).

The main difference between the "direct" and the "indirect" pathway depends on whether SNr and GPi are inhibited or excited. As SNr/GPi sends inhibitory projections onto thalamic neurons, they have an indirect inhibitory control over motor neurons in the cortex. When the inhibitory effect on thalamus from SN is inhibited, or «turned off», the thalamus has increased drive to the cortex and initiate movement. When SN is excited, its inhibitory effects on thalamus will be increased, and thalamus drive back to the cortex will decrease, contributing to RI.

Later research has introduced a third BG pathway, operating faster than both the "direct" and "indirect" route. The "hyper direct" pathway involves direct projections from the cortex onto STN, causing it to excite the GPi/SNr without involving the striatum. This results in GPi/SNr inhibiting thalamic activity onto motor neurons in the cortex. The "hyper direct" cortical activation of STN is thought to block the "direct" pathway (frontal cortex - striatum - GP) in its movement initiation and contribute to fast and efficient RI (see figure 4) (Aron & Poldrack, 2006; Dunovan et al., 2015; Li et al., 2008; Zandbelt & Vink, 2010a).

Figure 4.

The cortico-basal ganglia pathways.
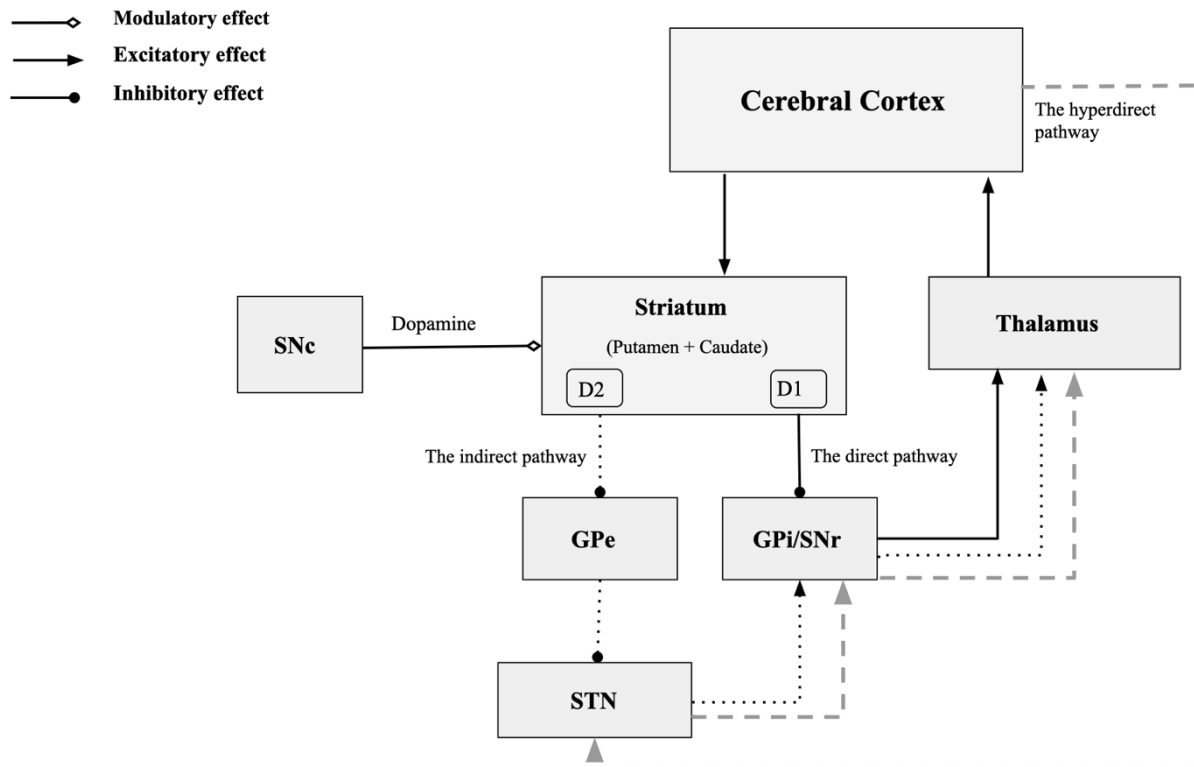
Figure 4. shows the three fundamental cortico-basal ganglia pathways. Solid line in black: the direct pathway with cortical and dopaminergic (D1) projections onto striatum, extending onto GPi and SNc, activating thalamic stimulation of motor neurons in the cortex. Dotted line in black: the indirect pathway with cortical dopaminergic (D2) projections to striatum inhibiting GPe from inhibiting STN, freeing the area to activate GPi and inhibit thalamic projections to motor neurons in the cortex. Stippled line in grey: the hyper direct pathway with direct cortical activation of STN (from where it follows the direction of the indirect pathway), resulting in activation of GPi and the following increased inhibition of thalamic activation of motor neurons in the cortex.

The integrity of the inhibitory network (i.e., the indirect and the hyper direct pathway) is thought to be reflected by the SSRTs derived from performance on SSTs. Furthermore, the speed of "go" and "stop" processes has been suggested to correlate with the relative activation of the direct, indirect and hyperdirect neural pathways within BG (Aron & Poldrack, 2006; Hall et al., 2022; Slater-Hammel, 1960; Welford, 1967; White et al., 1962).

1.2.4. The inhibitory network during Stop Signal Tasks

A distinct association between BG pathways and the relative performance on SSTs have been observed. Responses to go trials have showed significant activation in areas involved in the "direct" BG pathway. On the other hand, response to stop trials have been observed to activate a right lateralized inhibitory network, taking one of the two inhibitory roads: the "indirect" or the "hyperdirect" pathway. As previously illustrated, cortical (hyper direct) or pallidal (indirect) projections to STN contribute to the area's suppression of thalamocortical output, resulting prevention of the direct activation of "going" (Aron & Poldrack, 2006; Dunovan et al., 2015; Hall et al., 2022; Li et al., 2008; Zandbelt & Vink, 2010a). This suggests that STN plays an important role in stopping, and subsequently in RI (Aron & Poldrack, 2006). This notion is generally supported, with evidence showing that stimulation of the STN in patients with Parkinson's disease improves their SSRT (van den Wildenberg et al., 2006). Furthermore, faster inhibition times have been observed to generate greater activation patterns in IFC and STN, contrary to slower ones (Aron & Poldrack, 2006). Additionally, slower SSRT has been observed in animal models with STN lesions (Aron & Poldrack, 2006; Eagle et al., 2008). These observations emphasize the cortico-subthalamic pathway as a reflection the integrity of individual inhibitory mechanisms, measured as SSRT (Mink, 1996).

1.3. Inhibitory network imbalance: Implications for Tourette's Syndrome

For decades, imbalance within the inhibitory network has been suggested to be part of the neurobiology underlying TS. Of special interest to the present thesis that imbalance to the pathways affecting M1 excitability, and its potential to result in M1 hyperexcitability, has been associated with inhibitory deficits and several clinical conditions (Bronfeld et al., 2013; Lanciego et al., 2012; Morand-Beaulieu et al., 2017).

TS is a neurological disorder that affects 1% of 5–18-year-olds worldwide (Cohen et al., 2013). Primary symptoms include tics, i.e., repetitive, and partly involuntary vocal and motor movements (Conelea et al., 2011), often preceded by premonitory urges (PMU) described as a growing tension that subsides following tic execution (Seideman & Seideman, 2020). Some patients only experience minor tics, and the disorder does not pose any mentionable disruption to his or her well-being. For others, motor tics can be physically painful and exhausting, resulting in injury and fatigue. Consequently, TS can greatly influence patients' daily life (Conelea et al., 2011; Conelea et al., 2013; Seideman & Seideman, 2020).

TS prognoses vary between individuals. Severity and longevity of tics are highly heterogeneous, and coexisting disorders including compulsive obsessive disorder (OCD) and attention deficit disorder (ADHD) (Seideman & Seideman, 2020; Wright et al., 2012) are commonly observed. Furthermore, some patients suffer from treatment-refractory TS where treatment is not tolerated or satisfactory (Kious et al., 2016a). The heterogeneity that characterises the prognosis, comorbidity and responses to treatment challenges the understanding of the neural correlates of TS, and the specific underlying cause is still unknown.

However, TS patients generally experience a decline in symptom severity as they reach adulthood. Parallel with the decline in symptomatic presentation in patients, inhibitory control mechanisms increase with age (Welsh et al., 2006; Williams et al., 1999a). This has motivated the theory of a causative relationship between inhibitory deficits and tic behaviour. This working hypothesis has been supported by a recent meta-analysis providing evidence of impaired inhibitory control in TS patients (Morand-Beaulieu et al., 2017). Furthermore, several clinical features of TS have contributed to the characterization of TS as a disorder of inhibition (Kurvits et al., 2020). Firstly, the nature of tics is partly involuntary, with the ability to suppress, i.e., inhibit PMUs for a relative period. Secondly, increased impulsivity and reduced ability to suppress disruptive behaviors is linked to children with TS. Thirdly, although there is no cure for TS, effective approaches to alleviate tics have included cognitive and behavioral therapy Habit Reversal Training (HRT) and Exposure and Response Prevention (ERP) facilitating tic inhibition, i.e., inhibitory control (Ritter et al., 2022).

Lastly, abnormalities within the striatum, one of the major structures in the inhibitory network have been linked to TS (Bronfeld et al., 2013).

1.3.1. The neurobiology of Tourette's syndrome.

Models of TS have suggested that disruption of the cortico-basal ganglia circuit suggested to contribute to tic behaviour, is centred around deficits within the striatum (Albin et al., 2003; Bloch et al., 2005; Kalanithi et al., 2005; Peterson et al., 2003; Wang et al., 2011, in Bronfeld 2013). The main striatal neurotransmitter is GABA (Tepper et al., 2008) and dysfunction of GABAergic transmission within the striatum has been suggested as an important marker for TS (Lerner et al., 2012). This has been supported by evidence of a reduction in striatal volume in TS patients (Bloch et al., 2005; Peterson et al., 2003), attributed to a reduction of GABAergic neurons in the structure (Kalanithi et al., 2005; Kataoka et al., 2010). Animal models have further supported this notion, by demonstrating

abnormal movement patterns following disruption to the transmission of GABA within the striatum (Worbe et al., 2009). Moreover, repetitive jerking movements have been observed in rats and monkeys following the injection of GABA antagonists including picrotoxin and bicuculline (Marsden et al., 1975; Tarsy et al., 1978).

A dysfunction of GABAergic transmission in the striatum have been suggested to affect the indirect pathway in the BG, disrupting its function of inhibiting inappropriate or unintended movements. Less inhibitory effect from the striatum onto GPe increases GPe activation, resulting in stronger inhibitory effects onto STN, subsequently decreasing STN activity. When the STN is less active, excitation of Gpi/SNpr is reduced, leading to less inhibition onto thalamus. The increased thalamocortical drive results in increased cortical excitability (M1 hyperexcitability), and less inhibitory control i.e., reduced suppression of tics (Dyke et al., 2022; Milardi et al., 2019).

1.3.2. Treatment of Tourette's syndrome.

Due to prevalent comorbid disorders, uncertainty surrounding neural correlates, and heterogeneity regarding diagnosis and prognosis, treatment of TS have proven challenging (Szejko et al., 2020). Therapeutically, there is no cure for tics (Augustine & Singer, 2018). Methods attempting to alleviate symptoms are mainly pharmacological, but also include behavioural interventions and surgical deep brain stimulation (DBS) (Eddy et al., 2011). However, long-time side effects of current medications on the developing brain are not well established and behavioural interventions can be demanding for young children (Dyke et al., 2022). While DBS has showed promising results, the intervention involves invasive surgery, and does not exclude the possibility of side effects and the potential for post-operational damage (Xu et al., 2021). Moreover, the potential effects of treatment on comorbid diagnosis poses additional challenges. For some patients their diagnosis is refractory, and response to treatment interventions are not satisfactory (Kious et al., 2016a). Consequently, the need for other treatment options for TS patients is evident.

Research in recent years has explored alternative solutions, with an increasing interest in the therapeutic benefits of Non-invasive Brain Stimulation techniques (NIBS) (Dyke et al., 2022). By altering brain function momentarily and observing behavioural and clinical outcomes, NIBS techniques can provide valuable insight into how specific brain structures contribute to specific cognitive functions (Woods et al., 2016). These approaches can thereby be useful in the development of alternative treatment for neurological disorders where the neural underpinnings are still largely unknown.

1.4. Non-invasive brain stimulation (NIBS)

For centuries, the notion that external forces can be used to stimulate the brain has been well-known. However, systematic investigation started only recently, with the first practical NIBS studies conducted in the early 2000s (Zaghi et al., 2010). Explorations of the therapeutic benefits of NIBS have also become apparent in recent years, with an increasing interest in approaches such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Studies of tDCS effects on measures of RI and clinical symptoms including tics have contributed to therapeutic advances in the academic field of neurological disorders (Dyke et al., 2022). NIBS techniques have appealed to researchers as they are non-invasive, inexpensive and readily available, and with less potential side effects compared to mainstream treatment options.

1.4.1. Transcranial Direct Current Stimulation (tDCS).

In attempts to rebalance the inhibitory network and affect tics in TS patients, tDCS have been applied to areas of the cortex. As previously mentioned, tDCS is a non-invasive brain stimulation technique that temporarily modulates brain activity (Nitsche et al., 2008). The tDCS-induced excitability bypasses the active stimulation period, lasting longer or shorter depending on characteristics of electrodes (placement, size), current strength and stimulation duration (Nitsche et al., 2008; Woods et al., 2016).

By inducing a low electrical current via two electrodes placed on the scalp (either positively or negatively charged) the technique induces temporary changes to the cortical activity by affecting neural processes in the target cortical tissue underneath. The positively charged electrode is referred to as the anode, while the negatively charged electrode is referred to as the cathode (Nitsche et al., 2008; Nitsche & Paulus, 2000; Woods et al., 2016). tDCS modulates the cortical activity by either depolarizing or hyperpolarization the resting membrane potential, making the target cortical tissue underneath the anode more excitable, i.e., an increase in neuronal firing, and the tissue underneath the cathode less excitable, i. e. a decrease in neuronal firing (Nitsche et al., 2008).

tDCS has been practiced regularly over the last years, and current stimulation protocols have been considered safe by experts (Nitsche et al., 2008). This has been further supported by safety, ethical, and legal regulatory and application guidelines for low intensity transcranial electric stimulation (Antal et al., 2017) recently reaffirming that tDCS is safe for

use. Aside from very rare cases, no prolonged side effects (except itching/tingling/prickling sensations during stimulation) have been reported (Brunoni et al., 2011), making placebo trials possible and allowing for interventions to be double-blinded.

As striatal dysfunction has been associated with both impaired RI and tic-behaviour in TS (Bronfeld et al., 2013), researchers have applied tDCS to areas of the cortex to rebalance and correct striatal deficits through cortical-striatal connections. By modulating excitability within the cortico-subcortical network, effects on measures of RI in healthy participants, and on tics in TS patients have been investigated.

1.4.1.1. Effects of tDCS on RI in healthy adults. Investigations of the effect of tDCS on measures of RI in healthy adults often target the SMC. With its position as an inhibitory "starting point", the SMC is thought to recruit more deep-seated parts of the inhibitory network, ultimately effecting M1 excitability and motor regulation. Neuroimaging studies have also highlighted the SMC as important for inhibition by showing that activation in the preSMA of SMC is linked to shorter SSRTs, i.e., faster inhibition, compared to slower ones (Li et al., 2008).

Anodal tDCS applied to the SMC of healthy adults has yielded encouraging results, showing improved stopping performance on SSTs (Hsu et al., 2011; Kwon & Kwon, 2013). Previous reports have found that anodal tDCS improves efficiency of RI, while cathodal stimulation applied to SMA decreases performance on SSTs (Hsu et al., 2011). Others have reported similar results, with anodal tDCS reducing SSRT, compared to sham conditions (Kwon & Kwon, 2013). These findings have also been supported by neuroimaging studies applying tDCS to the SMC during stop trials while observing functional brain activation. Following anodal stimulation, increased activity in the SMC has been observed during efficient stopping, and the activity was linked to decreased SSRT, i.e., improved RI (Yu et al., 2015).

However, the literature also includes reports of decreased RI following identical stimulation protocols in healthy participants (Hayduk-Costa et al., 2013). These mixed results could stem from the fact that knowledge about the downstream effects in the inhibitory neural circuity is still sparse. Moreover, individual variability in response to tDCS or failure to induce the desired changes in the target tissue could cause variability on behavioural outcomes following stimulation. Results are challenged by failure to record excitability of the inhibitory network following TDCS.

Despite the mixed effects on RI following tDCS, majority of findings suggests that anodal tDCS applied to the SMC increase inhibitory performance on SSTs. Researchers have therefore suggested tDCS as a beneficial clinical intervention for patients with disorders associated with inhibitory problems such as TS (Kwon & Kwon, 2013). However, before utilizing tDCS as a therapeutic intervention for clinical use the effects on the behaviours of the healthy population is should be thoroughly investigated. Such studies can be compared to patient data, providing valuable insight into the neural mechanisms underlying inhibitory deficits, and ultimately facilitate the development of treatment alternatives for individuals experiencing inhibitory problems. Additionally, recruiting healthy participants makes it possible to avoid disrupting potential course of treatment or causing patients additional stress when participating. Although temporarily, possible changes to RI following tDCS may also negatively affect symptoms in TS patients. These effects would not cause any harm in healthy participants.

In spite of this risk, several studies investigating the effects of tDCS on tic-behaviour have been carried out. Interestingly, when comparing the effect of tDCS on RI in healthy adults with the effect of tDCS on tics in TS patients, the results are unexpected. Contrary to the working hypothesis linking inhibitory deficits to the expression of tics, anodal tDCS protocols shown to improve inhibition in healthy subjects seem to increase tic severity in patients. Moreover, cathodal stimulation shown to impair inhibition, significantly alleviate tics.

1.4.1.2. Effects of tDCS on tics in TS patients. In line with the proposed link between inhibitory deficits and tics, clinical tDCS trials have targeted the SMC in attempts to address striatal imbalance by modulating excitability within the cortico-subcortical network. Puzzlingly, while increasing excitability of the SMC can induce stronger inhibitory projections onto BG and thalamic nuclei, causing reduced activity in M1, and improve thus RI, anodal tDCS to the SMC does not reduce tics (Behler et al., 2018). Contrarily, tic reduction seems to result from cathodal tDCS to the SMC, i.e., turning the area down, supposedly increasing M1 excitability and impairing RI. Previous reports have shown that cathodal tDCS over preSMA reduced tics by 46%, a decrease still present six months later (Carvalho et al., 2015). Others have observed similar effects, with cathodal tDCS to the preSMA, SMA, pre-motor cortex and motor/inferior frontal cortex resulting in reduced tic expression and PMUs, relative to sham controls (Eapen et al., 2017; Mrakic-Sposta et al., 2008; Tajadini et al., 2019). These findings question the association between RI and tics in TS. However, as SMC also has direct connections to M1, decreasing excitatory projections

from SMC to M1 could be underlying the observed tic reduction, following cathodal protocols. However, clarifying whether tic-improvement is due to merely changing tonic inhibition within M1 (Jackson et al., 2015), or by engaging subcortical components of the inhibitory network is yet to be done.

In line with the effects of tDCS on RI, the results from patient's studies also appear mixed. Despite the promising results, previous studies have observed small differences in tic behaviour following cathodal tDCS to SMA (Behler et al., 2018; Dyke et al., 2019). Causative factors for the variability in the effect of tDCS on tics mirror those of the variability in effects on RI including, but not limited to methodological challenges related to parameters and electrode montage. Furthermore, tDCS applied to areas such as SMC are highly heterogeneous (Guo et al., 2022), with individuals responding differently to the same stimulation. The literature has also provided evidence for a potential oversimplification regarding the linear effect on excitability following anodal and cathodal tDCS. Prior studies have shown that the anode has the capacity to both excite and inhibit target brain regions (Hassanzahraee et al., 2020). In addition, there seems to be a lack of sham-controlled investigations comparing the effects of anodal and cathodal tDCS for RI.

More importantly, few studies have focused on recording the induced changes in the target brain tissue and neural circuits following tDCS. This presents a major challenge when interpreting findings, significantly limiting the strength of the literature (Dyke et al., 2022). For clinical trials, a failure to measure if the desired down-regulation of cortical excitability has been induced makes it difficult to determine the existence of any correlations between NIBS induced physiological change and tic reduction (Dyke et al., 2022). This problem could be overcome by using transcranial magnetic stimulation (TMS) as a means to measure possible changes to downstream M1 excitability following tDCS.

1.4.2. Transcranial Magnetic Stimulation.

TMS is a NIBS technique used to stimulate the brain and measure excitability in the motor cortex in both patients and healthy individuals (Barker et al., 1985; Klomjai et al., 2015; Liepert et al., 2000; Rossini et al., 1994). TMS has been used as a safe, painless and non-invasive way to assess neuromotor function since 1985 (Barker et al., 1985). The technique has been recently reviewed (Rossi et al., 2021), it has well-established guidelines, and is accompanied by minor side effects (3 of 100 experience mild headaches) (Barker et al., 1985; Rossi et al., 2021). Holding an insulated coil against the head generates a magnetic field that passes through the scalp surface (Wu et al., 2008), depolarizing and activating neurons in

underlying cortical tissue (Kobayashi & Pascual-Leone, 2003). Although applying TMS to the SMC to measure SMC excitability changes directly following tDCS would be ideal, TMS of SMC unfortunately doesn't produce easily observed measures reflecting excitability. However, when TMS is applied to M1, a stimulus travels from the stimulation site along the corticospinal tract of the spinal cord, reaching the nerve root. It then travels through the peripheral nerve system, before terminating in the target contralateral muscle inducing an action potential, causing it to contract (Doyal et al., 2022). This induced contraction is called a motor evoked potential (MEP) (see figure 5). The peak-to-peak amplitude of the recorded MEPs is routinely used as a measure of corticomotor excitability, with higher amplitude reflecting higher excitability, and smaller amplitude indicating lower excitability (Chipchase et al., 2012; Hashemirad et al., 2017).

Another fundamental unit of measurement in TMS is the resting motor threshold (RMS). RMS is obtained by determining the lowest stimulation intensity that induces MEPs of at least 50 µV amplitude in 50 % of stimulation, and functions as an additional indicator of excitability of motor cortex (Engelhardt et al., 2021; Rossini et al., 1994).

Using surface electromyography (sEMG), MEPs are recorded via a pair of bipolar electrodes placed on the target muscle. The electrodes register electric signals from active muscle fibres, to be further analysed by EMG software (see figure 5). A reference electrode is placed on a bony area (electrical inactive tissue) close to the target muscle, in order to filter out excess noise (Bordlee & Wong, 2015; Malcolm et al., 2006).

By implementing TMS, recording downstream effects on M1 resulting from SMC stimulation is made possible. When the technique is applied before and after tDCS stimulation, any changes in corticomotor excitability following tDCS compared to pre-measures would indicate that stimulation effected the target tissue.

Figure 5.

Illustration of recorded motor evoked potentials (MEP)
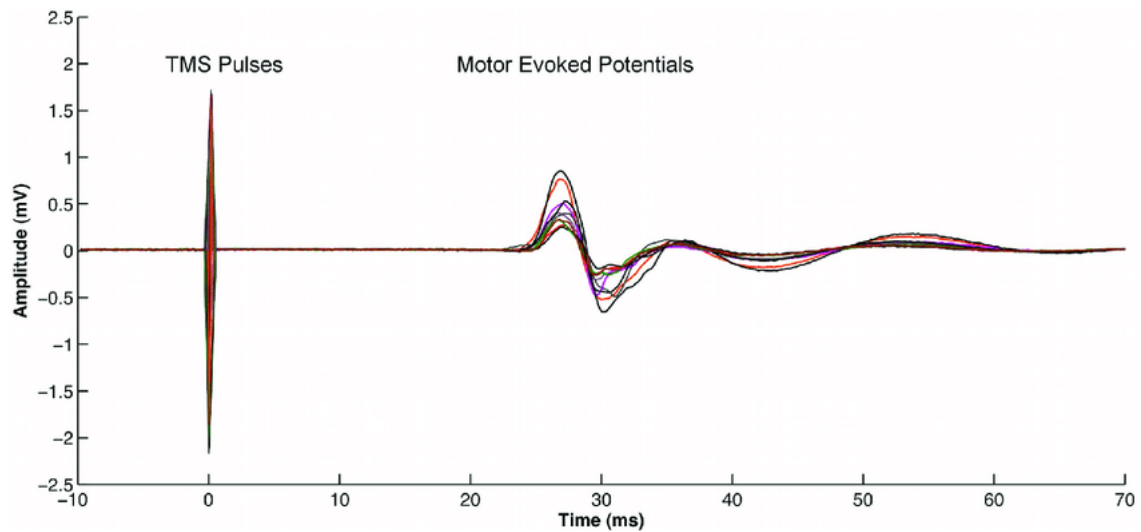
Figure 5. shows examples of motor evoked potentials (MEP). The artifact at 0 ms shows the time of stimulation (Komeilipoor et al., 2013).

1.5. Aims and objectives

The major aim of this experiment was to investigate the effects of tDCS applied to the SMC on measures of RI in healthy young adults, indexed as stop signal reaction time (SSRT). It was hypothesized that anodal tDCS applied to SMC would improve RI, indexed as decreased SSRT, resulting from reduced excitability of M1. Conversely, the study hypothesized that cathodal tDCS applied to the SMC would impair measures of RI, indexed as increased SSRT, as a result of increased excitability of M1. Finally, the study hypothesized that sham tDCS applied to the SMC would not influence M1 excitability and thus have no effect on measures of RI.

Given the puzzling effect of contrasting stimulation types in TS patients and healthy adults, the present study presumed that a sham-controlled within subject's design comparing both stimulation types would make a valuable contribution to the field. By obtaining measures of corticomotor excitability changes in M1 following both real and sham tDCS, we aimed to contribute vital sham-controlled evidence to the literature on current SMC tDCS protocols, establishing if changes to the neural circuitry are indeed induced following tDCS stimulation. Furthermore, by providing objective experimental evidence regarding the effects

of both anodal and cathodal tDCS to the SMC on measures of RI and associated neural components, we aimed to contribute to the discussion on the use of tDCS as a therapeutic tool for treating TS patients in the future, and whether improvements in tic behaviour may occur via inhibitory mechanisms. Lastly, we sought to highlight the distinction of whether modulating SMC is affecting M1 via cortical or subcortical pathways, and thereby contribute to the understanding of the neural correlates of inhibitory mechanisms.

2. Methods

2.1. Research design

The present study used a double-blind, sham-controlled, within-subject experimental design. All participants underwent three experimental sessions. Each experimental session proceeded as follows: baseline measures of RI collected via the ARIT and baseline measures of M1 excitability collected using TMS. tDCS was then applied (anodal/cathodal/sham), followed by post-tDCS measures of M1 excitability and finally RI via ARIT. The stimulation protocols (anodal/cathodal/sham) were presented in a counterbalanced order. Both anodal and cathodal stimulation were applied to prevent a possible ceiling effect that may inhibit further improvements in RI from cathodal and anodal tDCS stimulation to SMC. Stimulation mode (anodal/cathodal/sham) was the independent variable and behavioural measures and measures of M1 excitability (baseline and post-measures) were the dependent variables.

2.2. Participants

Forty-six (N= 45) participants were excluded due to not meeting the safety criteria for receiving TMS or tDCS. Individuals were excluded mostly due to prior head trauma, chronic migraines or genetic relation to individuals experiencing seizures. Eleven young, heathy subjects (n =11) (males n = 3, females n = 8) with no known neurological or psychiatric disorders were recruited. The mean age of the participants was 25,1 years (range 18-40 years). Each subject took part in three experimental sessions, with at least six days between sessions. Each session lasted approximately 3 hours. Recruitment was conducted through social media, word of mouth and by recruitment posters placed at several faculties of the University of Bergen and Haukeland University Hospital. At their first visit to the laboratory, all participants signed a form of consent.

Both participants and experimenters were naïve to the stimulation mode received in each session. Upon receiving tDCS (anodal/cathodal/sham) participants were instructed not to

disclose any details of their experience during stimulation, unless it felt uncomfortable. This was done to ensure that the study design remained double blinded. Upon completing their last session, participants received 300 NOK. None of the participants were made aware of the monetary gain before showing an interest in attending the study. The study was approved by the Regional Committees for Medical and Health Research Ethics and was conducted in line with their standardized guidelines.

2.3. Materials and stimuli.

2.3.1. Experimental documentation.

Participants were asked to answer a safety checklist in accordance with safe use of TMS and tDCS (se appendix B). Participants reported to the best of their knowledge that they did not suffer from any neurological or psychiatric disorders, had not experienced any prior seizures (neither epileptic nor fever seizure), were not directly related to individuals experiencing seizures, had not suffered any prior head trauma, did not experience any chronic headache/migraines, had no metal implemented in the upper regions of the body, had not fainted with no known cause, or lost conciseness for more than three minutes. Any chance of pregnancy or ongoing malaria treatment was also requested to be disclosed. Participants were instructed to report any ongoing medical treatment, and potential medications were investigated to ensure that the active ingredient did not pose any harm to the participant when undergoing tDCS/TMS or influence the experimental measures in any way.

Participants were then given a session-by-session safety checklist to ensure that any activities in the last 24 hours would not lead to exclusion (see Appendix C). This checklist included participants confirming that they had not consumed more than three units of alcohol in the last 24 hours, any alcohol that same day or, more than three cups of coffee in the last 12 hours, and had slept sufficiently the previous night. Participants were also asked if he or she had partaken in any other brain stimulation experiment in the last six months, and to report any potential issues or experienced side effects.

If participants responded "yes" on any of the questions in the safety questionnaire or the session by session checklist, they were either immediately excluded or the item was investigated further according to a checklist held by the experimenter (see Appendix D).

2.3.2. tDCS.

The study utilized a micro-processor controlled current source (NeuroConn DS-stimulator) to deliver stimulation. 7 x 5 cm = 35 cm2 rubber electrodes were used, placed in

dampened sponges to ensure conduction. Highly conductive electrode gel was applied to the electrodes to further facilitate the connection between the electrodes and the scalp. The active electrode was placed over the F5 region (i. e. the right SMC) and the reference electrode were placed on FP2 (i.e. the right forehead), in order to predominately target the right hemisphere (see figure 8) and the right-lateralized inhibitory network.

All participants received both active (anodal/cathodal) and sham stimulation, acting as their own control condition. To switch between active and sham stimulation mode, the study used prepared blinded codes registered to the tDCS device. Active stimulation had a duration of 1200 s. (20 min) with a constant current of 2mA. Ramping up and down was set to 15 s (see figure 6). The "sham" condition included only a small current pulse occurring every 550 ms, with the peak currents lasting for 3 ms (see figure 7). The first and last 15 s of the sham condition included similar ramping up/down as the active condition. This created sensations equivalent to the active stimulation mode, making it difficult for participants to distinguish between real and sham stimulation.

Figure 6.

Illustration of the active tDCS protocol.
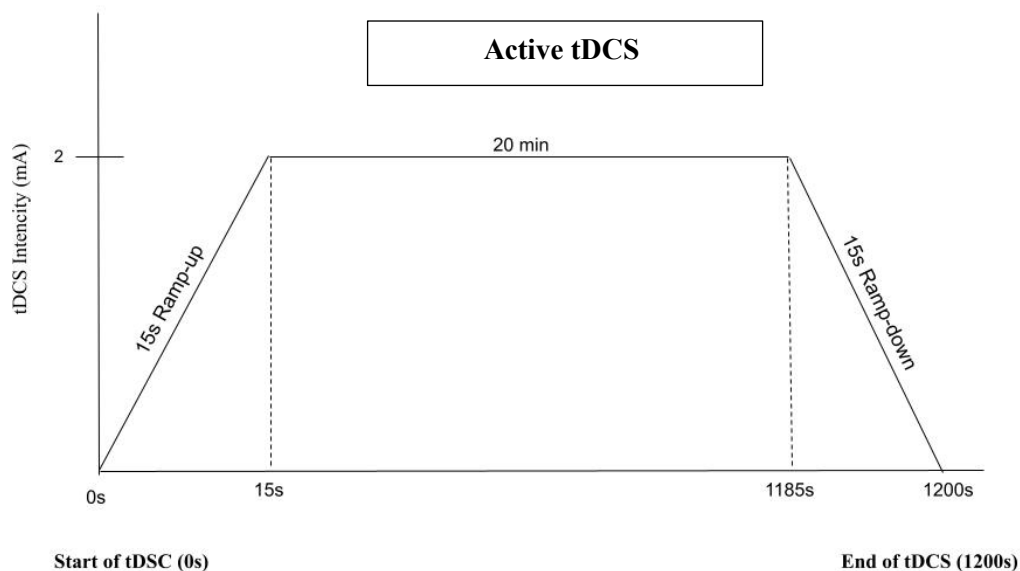
Figure 6. Shows the active tDCS protocol. Active stimulation included ramp-up to 2mA for 15 s, 2 mA stimulation applied for 20 min, then ramp-down for 15 s.

Figure 7.

Illustration of the sham tDCS protocol
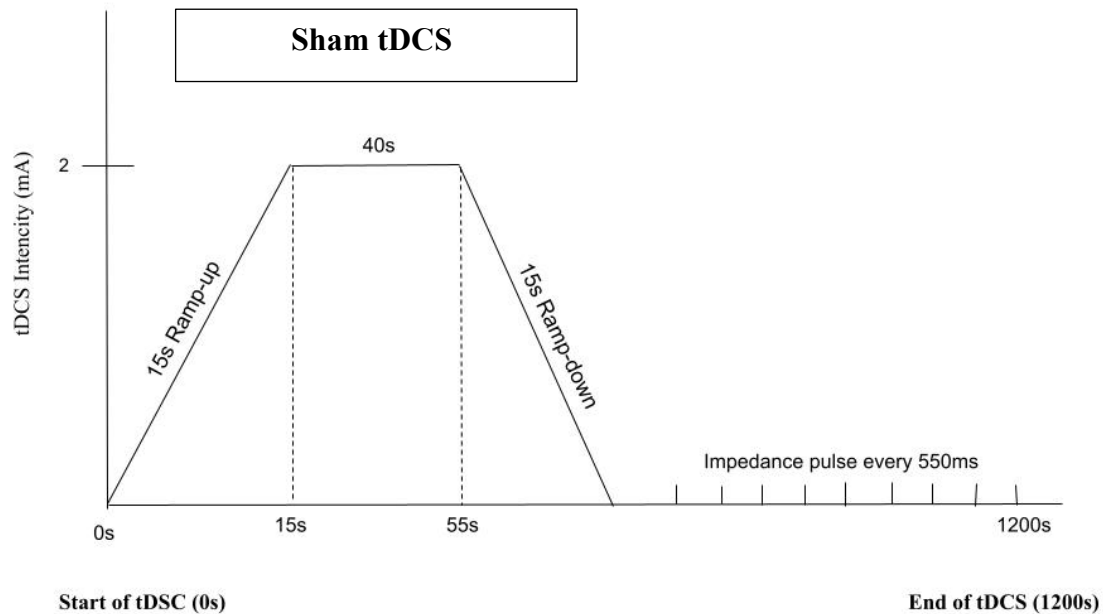
Figure 7. shows the sham tDCS protocol. Sham stimulation included ramp-up to 2mA for 15s, a duration of 40 s with 2mA applied, following a ramp-down for 15 s. The rest of the period included an impendence pulse occurring every 550 ms, with the peak currents lasting for 3 ms.

2.3.3. Electrode montage.

To ensure a standardized electrode montage, the study applied the 10-20 system for locating the SMC. The 10-20 system is an internationally recognized system for locating specific regions in the cerebral cortex, routinely used in EEG. Scull circumference was measured to identify each participant's individual cap size. With the cap on, the distance between front (naison) to back (inion) and left to right were measured, and the cap was adjusted according to centre Cz/Ref electrode. SMC (F5) was located and marked with washable pen. The active electrodes were placed on F5, and the reference electrode was placed on FP2, located on the forehead above the right eye (see figure 8).

Figure 8.

Illustration of electrode montage for tDCS stimulation.
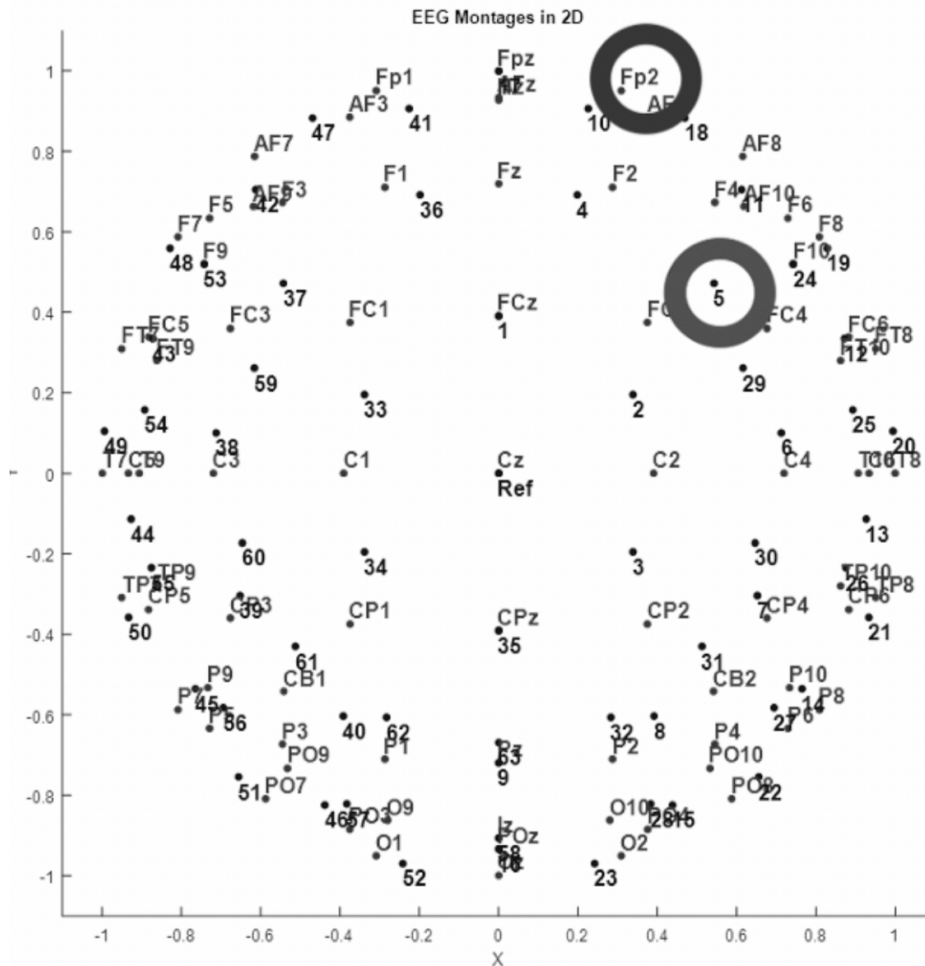
Figure 8. shows the electrode montage used in the present study. Circle over F5 is the target area, the SMC. The active electrode (anode for anodal tDCS, cathode for cathodal tDCS) was placed over F5. Circle over Fp2 refers to our reference location. Reference electrode was consistently placed over Fp2.

2.3.4. TMS.

A single pulse TMS (Medtronic MAGPRO) protocol was applied to M1 of the dominant hemisphere via a butterfly-shaped MCF-B40 coil. MEPs was recorded from two 30x22 mm electrodes placed on the contralateral first dorsal interosseous muscle (FDI), using sEMG (software Pro BSL). The ground electrode was placed on a bony, electrically inactive

area close to the FDI. Before placing the electrodes, the skin surface was prepared with exfoliating pads and alcohol wipes.

The optimal cortical location for each individual subject was determined via "hotspotting". When "hotspotting" was conducted, the coil was initially held at a 45-degree angle. It was then slowly moved around the scalp on a 1 cm grid pattern. The area that induced a posterior to anterior current perpendicular to the precentral gyrus, accompanied with the largest peak-to-peak aptitude MEPs, i.e., the «hotspot» was defined and marked with washable pen (Rossini et al., 1994). Resting motor threshold (RMT) was then determined. Thresholding involved determining the lowest stimulation intensity that induced MEPs of at least 50 µV amplitude in 50 % of stimulations. The root mean square of EMG activity (rmsEMG) within a 50 ms. window reflects the activation state of a muscle. Resting state is at rmsEMG values below 10 - 15 uV (Rossini et al., 1994).

Pre - and post RMT measures were taken to determine baseline and post intervention threshold. An additional 15 MEPs with the intensity set to 5% maximum stimulator output above pre-threshold was collected at rest before and after the intervention in order to obtain a second measure of corticomotor excitability change.

2.3.5. The Anticipatory Response Inhibition Task (ARIT).

Measures of participants performance on The Anticipatory Response Inhibition Task (ARIT) was used to obtain an objective measure of RI. The task included 250 trials, consisting of 9 blocks, lasting approximately 20 minutes. The task was administered using software written with MATLAB (version R2021a, MathWorks). Two keys on the keyboard were marked and used to monitor participants lifting and depressing according to the given trials.

Before starting the task, participants received a standardized script including general task instructions (see appendix A). After receiving the instructions, participants were given practice blocks (GO: 10, SS: 5, SL: 5, SR: 5), to ensure familiarization and comprehension of the task.

While performing the task, participants sat in front of a computer and were instructed to use their index fingers to depress the keys. The computer screen showed two columns (see figure 9), with the left corresponding to the left hand (left marked key [Z]) and the right to the right hand (right marked key [C]). Each trial started after a variable delay (400-900 ms) once participants simultaneously kept both keys depressed. Each trial involved both columns rising against a stationary target. To establish a standard behavioural response, most trials consisted

of GO trials (66%) (see figure 9, A). GO trials included both columns rising against the target, and intercepting it after 800 ms, requiring the participants to lift both fingers to intercept the columns as close to the target as possible (see figure 9). Visual feedbacks were given following each trial, with success being the release of both keys within 30 ms either side of the target line.

Stop trials had 3 variations; stop both (SS), stop left (SL) and stop right (SR), each signalling the participant to cancel their standardized lift-response if columns stopped prematurely. SS involved both columns automatically stopping, signalling the participant to continue pressing both keys down (see figure 9). SL and SR trials involved one of the columns (right/left) automatically stopping, with the opposite column still rising against the target (see figure 9C & D). This required the participant to continue pressing the index finger corresponding to the stopped column, while lifting the index finger corresponding to the rising column close to target line. Following each stop trial, visual feedback was given to inform the participant of successful or unsuccessful stopping (see figure 9).

For each type of stop trial, the stop signal delay (SSD) i.e., the time elapsed between the GO stimulus and the presentation of the stop signal was initially set to 550 ms. A staircase design with an increase/decrease of 50 ms, was then employed separately for each stop trial type (Macdonald et al., 2012), resulting in a 50% probability of success. If the stop trial was successful, the SSD would increase by 50 ms in the following trial. If the stop trial unsuccessful, the SSD would decrease by 50 ms. Implementing the staircase algorithm allowed the task to be equally challenging across participants (Hall et al., 2022; MacDonald et al., 2014).

Figure 9.

Visual presentation of trial variation in the ARIT.
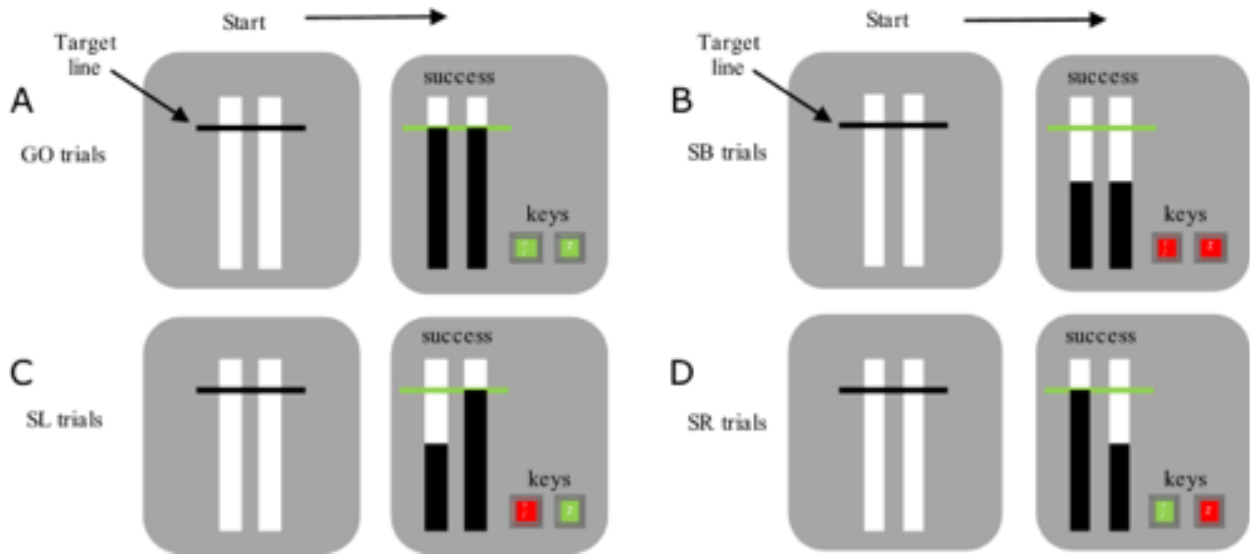
Figure 9 illustrates the four trial variations of ARIT. **A:** GO trials, **B**: Stop both, C: stop left, **D**: Stop right. Green colour coded key represents lifting of index finger, red colour coded key represents depressing of index finger (Hall et al., 2022).

SSRT was then calculated as the time participants required to process the stop signal (stopping of bar/bars) and cancel their pre-planned movement (lifting).

2.3.6. Dependent measures.

The dependent behavioural measures were individual baseline and post-tDCS SSRTs for all trials on ARIT; StopBoth SSRT, StopLeft SSRT and StopRight SSRT. The dependent neurophysiological measures were baseline and post-tDCS measures of M1 excitability; Average MEP, and average RMT. Average pre-trigger RMS EMG was also measured.

3.3.6.1. Behavioural measures. After trimming outliers (±3SD), average Reaction Time (RT) was calculated for successful Go trials, and all successful Stop trials (StopLeft, StopRight). RT was stated as the time (milliseconds) between the start of the trial and response. Individualized SSD (staircased to 50% success rate) was calculated for all stop trials (StopBoth, StopLeft, StopRight). The integration method was used to calculate SSRT for all stop trials (SSRT =nth go trial value (total go trials x probability of responding on a Stop trial) – SSD (staircased at 50% success rate) (Verbruggen et al., 2013). SSRT is the primary dependent behavioral measure and provides an index of response inhibition, with faster SSRTs indicating increased stopping efficiency.

3.3.6.2. Neurophysiological measures. Processing of TMS data was conducted using BSL Analysis (version 4.1). Peak-to-peak MEP amplitudes were calculated from the EMG data for each session over a standardized 20-ms window (20-40 ms post TMS pulse). From the evoked motor response, the root mean square (RMS) amplitude was calculated over a standardized 25-ms window prior to the TMS pulse. Trimmed averages for both MEP and RMS values were generally collected by trimming 10% of the highest and lowest values (= 4). Due to equipment issues, several RMS values exceeded the set limit of 0,01. In the case of > 3 values above 0,01, only the highest and lowest value was trimmed (= 2). In the case of < 3 values exceeding 0,01, the standardized trimming of 10% was performed (= 4).

RMS was averaged for time (pre, post) in each condition (anodal, cathodal, sham).

2.4. Data analysis.

IBM SPSS Statistics (version 27) was used to conduct all statistical analysis. A 2 X3 repeated measures (RM) Analysis of Variance (ANOVA) was run on all variables of interest [MEP average], [RMS average], [RMT average], [StopBoth SSRT], [StopLeft SSRT], [StopRight SSRT], investigating the effect of Time (pre,post) and Stimulation Type (anodal/cathodal/sham). A significance level $p < 0.05$ was accepted as statistically significant for all statistical tests. Mauchly's test checked if the assumption of sphericity had been violated [Mauchly's test of sphericity = $p > ,05$]. Greenhouse-Geiser corrected p-values were interpreted where the assumption of sphericity was violated.

3.Results

One participant withdrew after finishing 1/3 sessions due to availability issues, leaving N = 10 for the results reported below, unless otherwise indicated. There were three instances of missing data. One participant reported that he or she misunderstood the instructions during their first session of the behavioural task, which led to challenges with calculating the individual SSRT on all stop trials (Stop-Both, Stop-Left, Stop-Right). Another participant was excluded from all selective stop trials (Stop-left, Stop-Right) on all three sessions, due to challenges calculating the SSRT. Furthermore, due to technical issues excitability measures (MEP average, RMT average) were not collected for one participant in 1/3 sessions. The

missing behavioural and neurophysiological data were replaced using means of the overall group in SPSS. Descriptive values are reported as mean ± standard error below.

3.1. Response Inhibition (SSRT)

3.1.1. StopBoth SSRT.

There was no main effect of Time ($F_{1,9}$ = 0,583, p = 0,465), no main effect of Stimulation Type ($F_{2,18}$ = 1,954, p = 0,171) and no interaction effect of Time X Stimulation Type ($F_{2,18}$ = 0,929, p = 0,413, Power = 0,185) of SSRT of StopBoth. With no changes observed in the primary dependent behavioral measure StopBoth SSRT, the results suggest that none of the Stimulation Types (anodal, cathodal, sham) effected general stopping ability, i.e., response inhibition.

3.1.2. Selective stop SSRT (stop-left/stop-right).

There was no main effect of Time for StopLeft ($F_{1,8}$ = 0,038, p = 0,849) or StopRight ($F_{1,8}$ =0,082, p =0,781), and no main effect of Stimulation Type for StopLeft ($F_{2,16}$ = 0,246, p = 0,785) or StopRight ($F_{2,16}$ =2,051, p = 0,161). There was no interaction effect for StopLeft ($F_{2,16}$ = 1,184, p = 0,331). However, there was an interaction effect of Time X Stimulation Type for StopRight ($F_{2,16}$ = 7,047, p = 0,006). With no additional main effects or interaction effects observed for both types of selective stopping, the significant interaction is likely due to practice effects. Therefore, the results suggests neither Stimulation Type (Anodal, Cathodal, Sham) effected response inhibition during the process of selective stopping.

3.2. Excitability of M1 (MEP, RMT, RMS)

3.2.1. Average MEP amplitude.

There was a main effect of Time ($F_{1,9}$ = 6,508, p = 0,031, Power = 0,623; Figure 10). This arose because average MEP amplitude increased from Pre Stimulation (0,195 ± 0,030 mV) to Post Stimulation (0,347 ± 0 ,072 mV). Of note, although the Time X Stimulation Type interaction did not reach significance ($F_{2,18}$ = 1,000, p = 0,387, Power = 0,197), average MEP amplitude did not change for Sham Stimulation Type (0,192 ± 0,043 mV) to (0,204 ± 0,040 mV), but it went up for both Anodal Stimulation Type, from (0,170 ± 0,44 mV) to (0,469 ± 0,184 mV), and Cathodal Stimulation type from (0,223 ± 0,047 mV) to (0,368 ± 0,117 mV) (see Figure 11). There was however no main effect of Stimulation Type ($F_{2,18}$ = 1,014, p = 0.383). The main effect of Time combined with observed changes in interaction effect suggests that active tDCS did in fact effect M1 excitability as this was not observed for sham

condition, however not in a stable direction as interpreted from the non-significant interaction effect.

Figure 10.

Main effect of Time for MEP average.
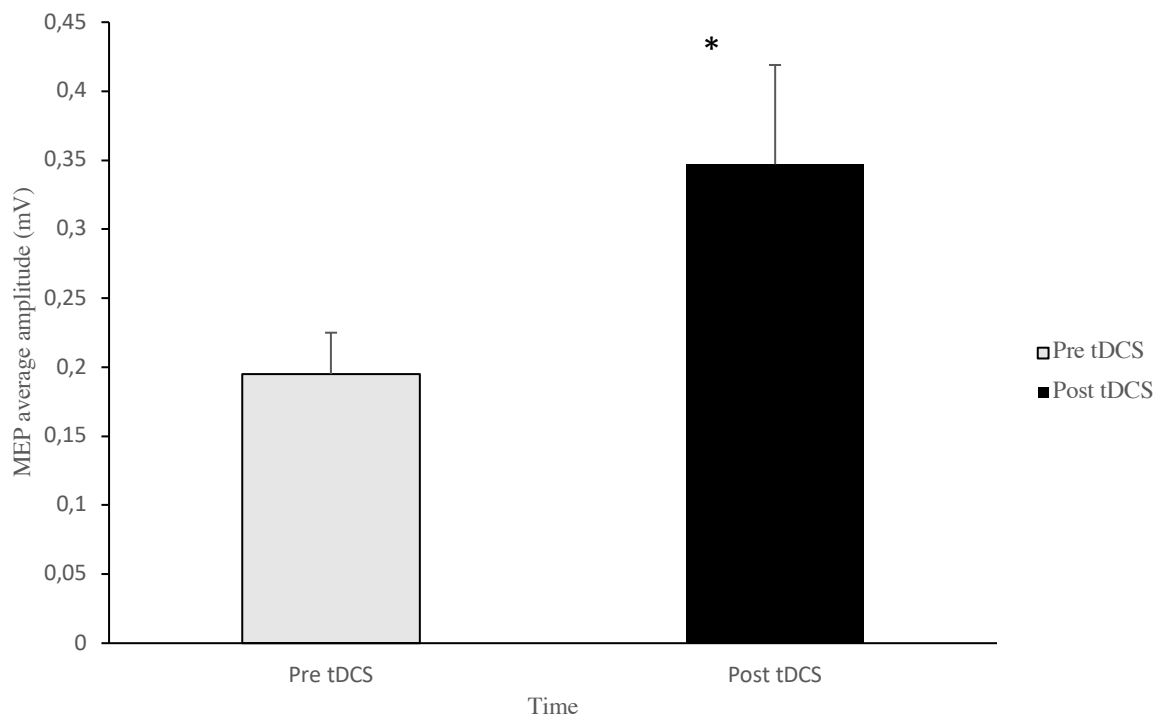
Figure 10. shows the significant main effect of Time on MEP average amplitude, resulting from average MEP amplitude increasing from the pre tDCS condition to post stimulation condition.

Figure 11.

Non-significant interaction effect between Time and Stimulation type.
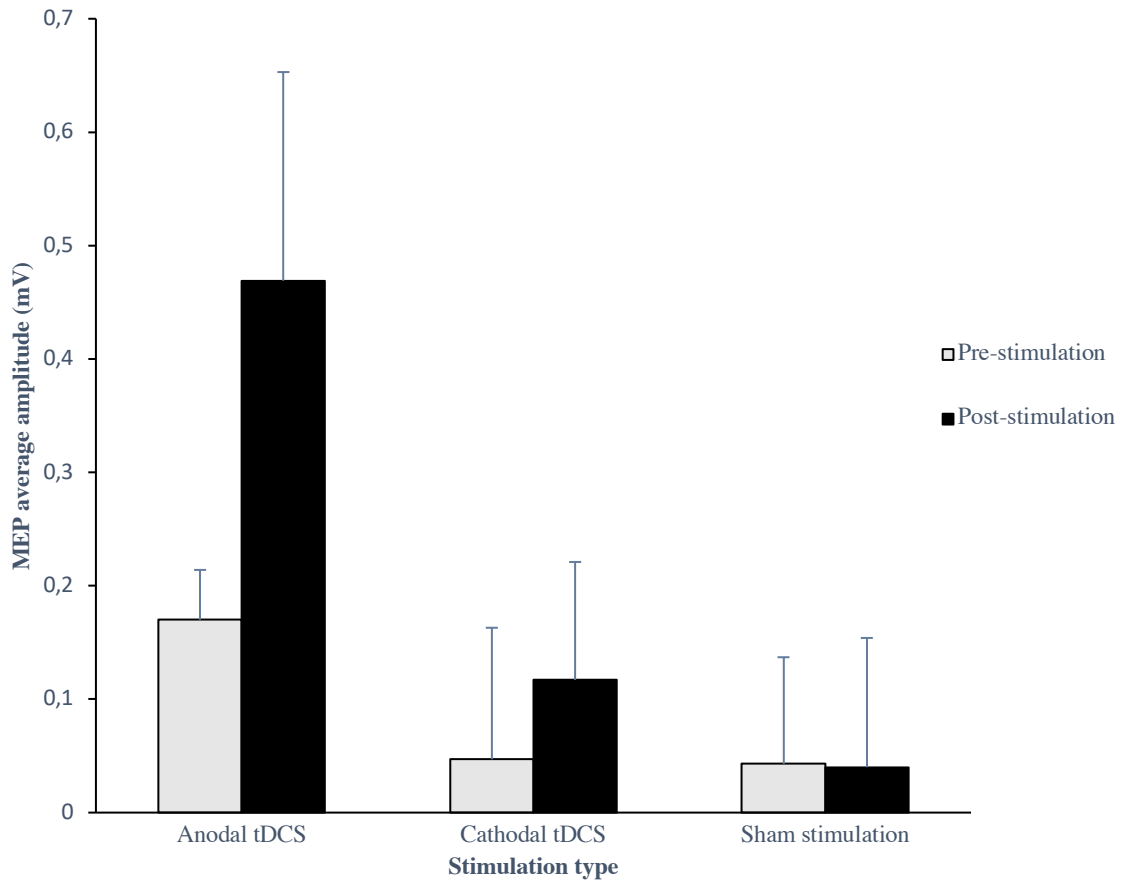
 Figure 11. shows the non-significant Time X Stimulation type interaction effect for average MEP amplitude. Although the interaction effect did not reach significance, visually M1 excitability, indexed as MEP average amplitude (mV) seemed to be modulated following active tDCS, compared to no visible change in sham condition. Unexpectedly, MEP average amplitude appeared to increase following both Stimulation Types. However, as expected a slight increase following Cathodal Stimulation Type was observed, although the main increase was apparent following anodal tDCS.

3.2.2. Average RMT.

There was a main effect of Time ($F_{1,9} = 9{,}166$, $p = 0{,}014$), as RMT changed from pre ($0{,}604 \pm 0{,}025$) to post ($0{,}570 \pm 0{,}030$). There was no main effect of Stimulation Type ($F_{2,18} = 0{,}552$, $p = 0{,}585$), or significant interaction effect of the Time X Stimulation Type interaction ($F_{2,18} = 1{,}991$, $p = 0{,}165$). With RMT being an additional measurement of M1 excitability, the main effect of Time of RMT equal to the effect observed for MEP average and similar pattern for the (non-significant) interaction effect, supports the assumption of active tDCS effecting M1 excitability compared to sham condition.

3.2.3 Average RMS.

There was no significant main effect of Time ($F_{1,9} = 0{,}179$, $p = 0{,}682$), Stimulation Type ($F_{2,18} = 3.179$, $p = 0.066$) or interaction effects ($F_{2,18} = 0.205$, $p = 0.817$) on average RMS. The lack of main effects or interactions observed for RMS data allows the significant effect of Time observed for MEP and RMS to be attributed to excitability, and not to the FDI being activated prior to the MEPs being evoked.

3. 3. Descriptive analysis

Descriptive analysis of the neurophysiological data revealed a mentionable degree of response variability between subjects following both active Stimulation Types (anodal, cathodal). Depending on the Stimulation Type, visually some participants showed no to minor response, while others showed a reversed shift in the direction excitability was modulated (Figure 12,13). These results suggests a certain degree of response variability following active tDCS, in addition to unreliable shifts in excitability following both Anodal and Cathodal Stimulation type.

Figure 12.

Individual response to anodal tDCS
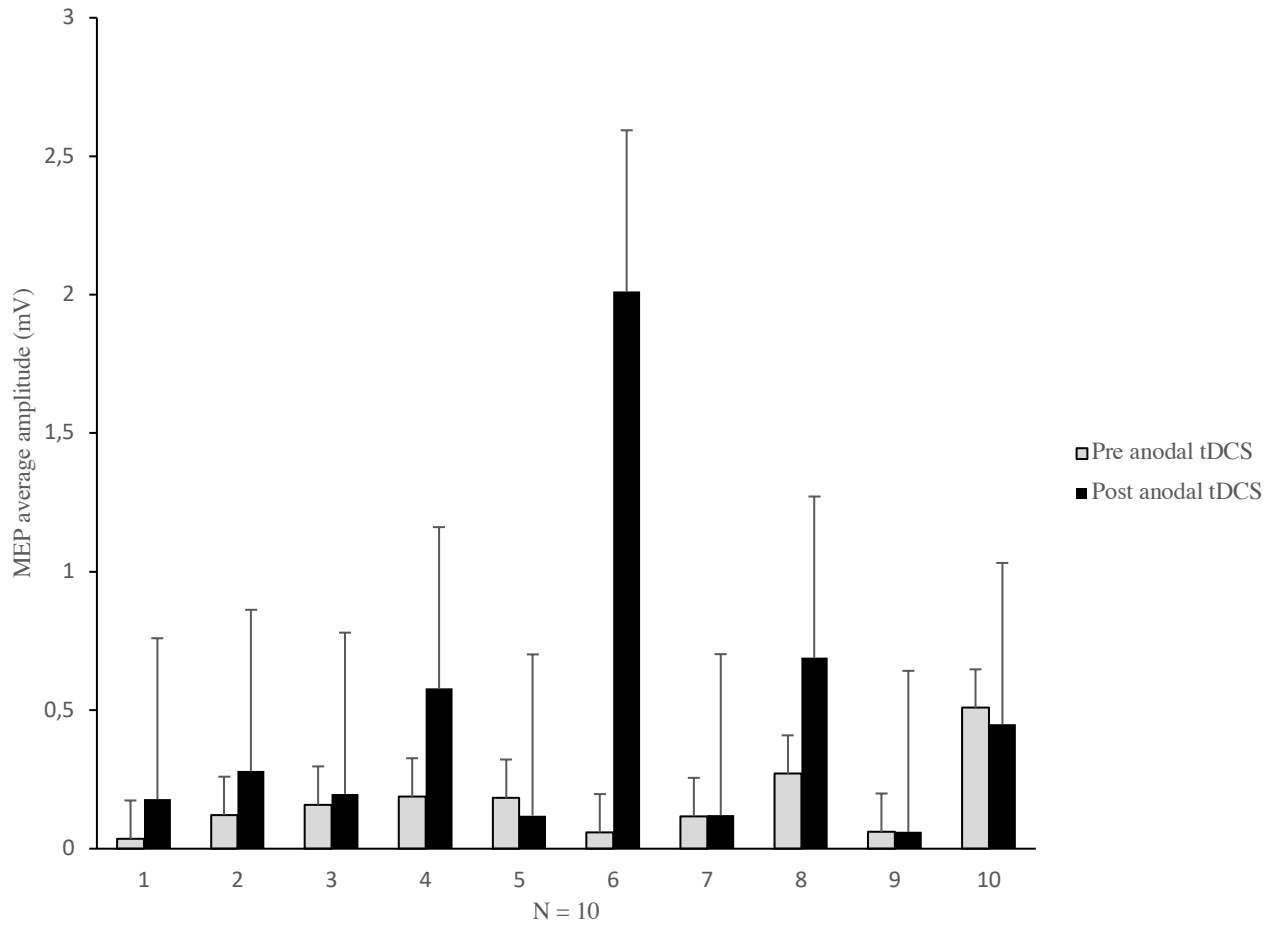
Figure 12. illustrates individual changes to M1 indexed as MEP average amplitude (mV) following anodal tDCS. As illustrated, individual response to anodal tDCS visually appeared to increase. However, six responders showed the hypothised decrease in M1 excitability, while two showed no response at all.

Figure 13.

Individual response to cathodal tDCS
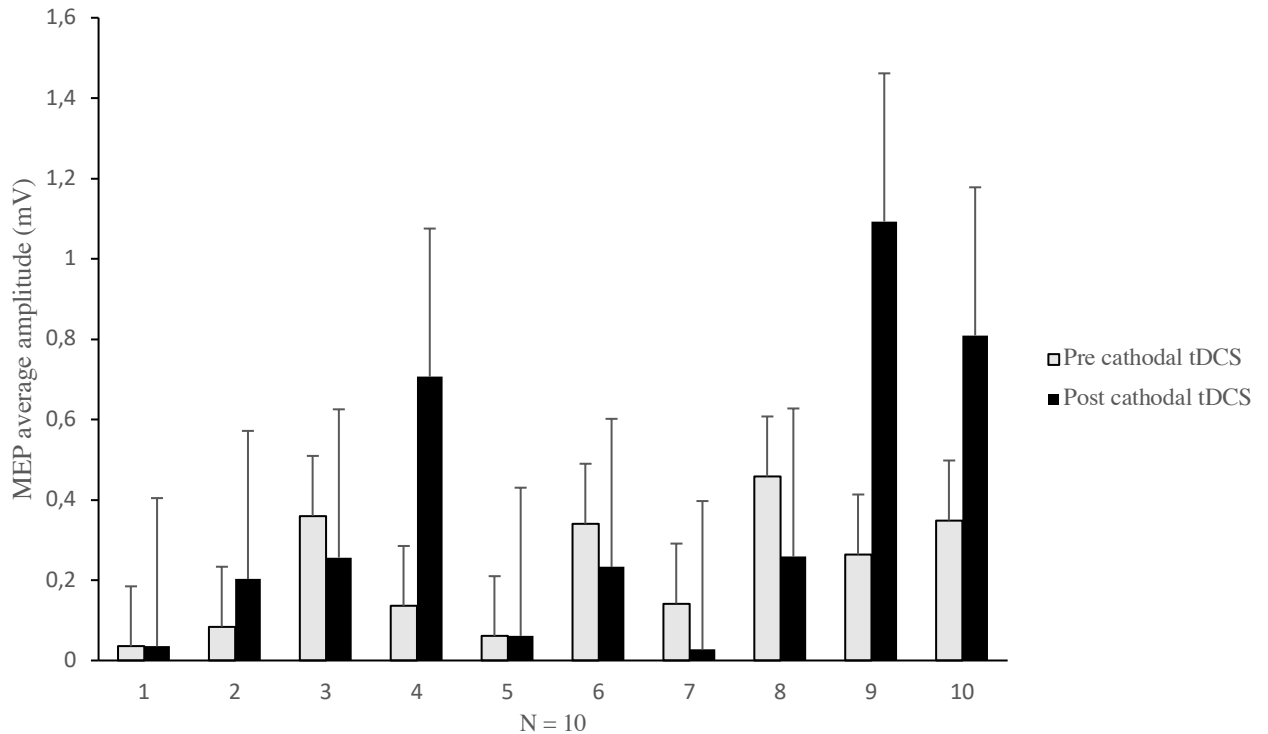
Figure 13 illustrates individual changes to M1 indexed as MEP average amplitude (mV) following cathodal tDCS. Unexpectedly, individual response to cathodal tDCS visually appeared to increase. However, four responders showed an decrese in M1 excitability, while two showed no response at all.

4. Discussion

The present study aimed to elaborate on the current understanding of the effect of tDCS on M1 excitability and RI. Contrary to our hypothesis, SSRT did not change for any behavioral measures across time or stimulation type. Of note, the interaction of time and stimulation for the right selective stop trial showed an effect. However, no additional interactions or direct effects of stimulation type or time was observed for either type of selective stopping. Therefore, the effect is likely due to mere practice effects and will not be further addressed. Overall, the lack of change in behavioral outcomes suggest that tDCS

stimulation applied to the SMC does not effect RI during stop trials when performing the ARIT.

As hypothesized, active stimulation effected M1 excitability across time, compared to sham condition. Interestingly, although the interaction did not reach significance, we observed a pattern of results that partially supported the hypothesis of a change to M1 excitability across time following active tDCS, compared to sham condition. These findings suggest that the overall change in M1 excitability following tDCS might be attributed to active stimulation, not to general arousal from performing the task or mere experimental participation. This assumption was supported by our observations of no main or interaction effects for measures of RMS, as this suggests that the changes observed for M1 excitability could be attributed to changes in excitability of the corticospinal tract, i. e., changes above the level of the muscle within the overall corticomotor pathway. As expected, our results therefore suggest that the change in MEPs result from changes to excitability, and not purely from changes in activity within the contralateral first dorsal interosseous muscle at time of stimulation. This was underlined by the results for average RMT corresponding to the change in MEP average, as our study collected RMT as an additional index of M1 excitability. Taken together, although the effects did not reach significance, visually M1 excitability appeared to be modulated following both anodal and cathodal TDCS applied to SMC, compared to no modulation following sham stimulation.

Moreover, contrary to our hypothesized polarity in the modulatory direction following anodal and cathodal tDCS, M1 excitability visually appeared to increase following both stimulation types. A pattern of slight increase in M1 excitability following cathodal tDCS was interpreted as partly supporting our hypothesis, however an additional unexpected increase following anodal stimulation was observed. In addition, modulation of M1 excitability following anodal tDCS was more pronounced, compared to the increase following cathodal stimulation type. These findings suggest that while it can be assumed that active tDCS has effected excitability to some degree, it is not done in a reliable direction. The visually apparent, but non-significant interaction could be due to the standard deviation, indicating a high response variability within stimulation types. This could possibly explain our failure to observe significant effects. The idea of response variability within and between subjects was supported by conduction of an additional descriptive analysis, revealing that individual response to both stimulation types varied in both strength and direction. Despite being underpowered to enable the interpretation of robust final effects, the results from this study suggest that the effect of tDCS on excitability can be observed in unexpected directions.

The main contributions of the present thesis can be summarized as follows: While in a small sample, we have provided sham-controlled experimental evidence indicating that tDCS applied to the SMC does not affect measures of response inhibition. Additionally, our findings have partly replicated previous literature in that active tDCS applied to the SMC does modulate M1 excitability across time, although not in a stable direction, which suggest a high degree of variability in response to tDCS. Taken together, our findings suggest that tDCS to the SMC directly effects M1 excitability via the corticocortical pathway, without engaging the basal ganglia circuits involved in response inhibition. These results have implications both i) for the use of tDCS in healthy subjects when investigating its effects on cognitive functions and ii) for therapeutic purposes in patient trials when investigating its effects on clinical symptoms.

4.1. No change in RI following tDCS to SMC

tDCS stimulation applied to the SMC did not affect objective measures of response inhibition (RI) in healthy adults, indexed as stop signal reaction time (SSRT) on the Anticipatory Response Inhibition Task (ARIT). Previous reports exploring RI in healthy participants have observed that anodal tDCS applied to the SMC reduced SSRT, thus indicating an improvement in inhibitory efficiency (Hsu et al., 2011; Kwon & Kwon, 2013; Yu et al., 2015). Additionally, cathodal stimulation to the SMC have been shown to impair RI (Hsu et al., 2011). Our failure to replicate previous reports may have several explanations. Factors including the current behavioral task, electrode montage and response to tDCS being dependent on current intensity, stimulation duration and individual physiological differences will be explored below.

4.1.1. Traditional versus Anticipatory Stop Signal Tasks.

The present study used an anticipatory version of the stop signal task (SST) when collecting measures of RI. The Anticipatory response inhibition task (ARIT) is primary targeted to BG pathways and internally generated responses. As no change in RI was observed following stimulation, we suggest that tDCS to the SMC mainly effected M1 excitability via the corticocortical pathway, failing to modulate subcortical BG pathways. Based on our interpretation, we assume that the task used was not fitted for the function of the pathway actually targeted, i.e., the corticocortical pathway. Previous reports of change to RI following the same tDCS protocol have in fact used more conventional behavioural tasks

(Hsu et al., 2011; Kwon & Kwon, 2013; Yu et al., 2015). Classical SSTs are more externally cued, possibly creating a better fit between task and targeted neural pathway. Furthermore, conventional SSTs have shown an increased response variability for response times, and challenges with obtaining baseline measures have been prevalent (Wadsley et al., 2023). Therefore, the observed change to SSRT reported in previous studies could primarily stem from changes to response time, not changes to stop times. This suggests that their protocols have influenced movement execution, rather than RI. Therefore, our use of an anticipatory version, rather than a classical SST, could possibly explain why previous studies have produced more solid behavioural outcomes, compared to our findings.

4.1.2. Limitations of Current Electrode Montages.

The present study used moderately sized electrodes (7 x 5 cm = 35 cm2), targeting a wide area on the scalp. A challenge with using large electrodes is the reduced focality of stimulation, with the potential of modulating neural activity in areas beyond the target tissue. The electrode montage used in our study aimed to specifically stimulate the SMC. In accordance with tDCS protocols of previous clinical TS trials, active and reference electrodes were placed relatively close together, using larger pad electrodes. This can lead to current traveling through the brain between electrodes (Prehn & Floel, 2015) affecting neighbouring anatomical areas (de Berker et al., 2013). As a result, any effects to RI, or the lack thereof cannot uncritically be attributed to focal stimulation of the SMC. By altering neural activity beyond the SMC, our intended modulation could have been disturbed and unmonitored cognitive effects could have been induced. This could ultimately have affected our measures of RI.

The preSMA and the SMA proper are located within the superior frontal gyrus (SFG). In line with the role of SMC for inhibition, neuroimaging studies have associated activation of the right SFG with more efficient RI (Hu et al., 2016). Inferior to the SFG is the middle frontal gyrus (MFG). However, the functional properties of the MFG do not appear to interfere with inhibitory mechanisms, as it has mainly been associated with literacy and numeracy (Koyama et al., 2017). Still, the reduced focality of commonly used tDCS electrodes poses challenges when using the method in both general experimental research and clinical trials. While the effects of modulating neural activity in multiple areas are unclear, they could potentially have interfered with our measures of SSRT.

The present study did not account for tDCS modulation of cortical areas beyond the SMC. However, the reduced focality was partly addressed in our design by the

implementation of both the preSMA and SMA proper within the collective Supplementary Motor Complex (SMC). By referring to the SMC as a collective term we intended to avoid attributing effects or lack thereof, to focal stimulation of preSMA or SMA proper. This would be incorrect considering the reduced spatial precision of stimulation and our lack of implementing additional measures to monitor current flow.

However, the collapsing of several structures within one collective area also causes limitations. As preSMA and SMA proper differ in both function and connectivity, potentially targeting one of the two structures could have affected on our measures of RI. As previously mentioned, the preSMA has been associated with aspects of movement selection and preparation while SMA proper has been linked to movement execution (Akkal et al., 2007). Importantly, improved inhibition has specifically been associated with the preSMA, with faster SSRTs being linked to increased preSMA activation (Li et al., 2008). Based on this, we speculate that tDCS stimulation applied in our study mainly targeted the SMA proper, hence, failing to sufficiently target the preSMA. This could potentially explain the lack of effects on SSRT following tDCS in our study.

This assumption is further supported by our results suggesting that M1 excitability changes across time following stimulation, without resulting in the expected change in RI. Although time and stimulation type did not interact sufficiently, there was a pattern of results that partially supported the hypothesis of change to M1 excitability across time following active tDCS, compared to sham condition. Importantly, while the SMA proper has direct corticocortical projections to M1, preSMA does not (Hiroshima et al., 2014). Taken together, this suggest that modulating the SMC might not be influencing M1 excitability mainly through subcortical BG pathways, important for RI. Rather, it suggests that M1 excitability was affected via direct corticocortical connections between the SMA proper and M1. Considering a corticocortical activation pattern, changes to RI would not be expected. On the other hand, previous findings that have observed changes to RI following modulation of the SMC implies that stimulation did indirectly affect subcortical BG pathways. Thus, the improvement following anodal tDCS to SMC indicates a facilitation of the indirect and hyper direct pathway involved in inhibition. Similarly, impaired RI following cathodal tDCS applied to the SMC indicates that stimulation indirectly facilitated the direct pathway important for movement initiation. By observing measures of RI while monitoring changes to excitability in M1 via TMS-induced MEP amplitude, the present study can establish that we failed to replicate these neurophysiological effects on subcortical BG pathways. This highlights the importance of monitoring the induced neurophysiological changes following tDCS

stimulation, ensuring that any behavioral effects are correctly attributed to its neurophysiological cause.

Importantly, while our results at least hint towards tDCS mainly effecting the SMA proper, the preSMA indirectly effects M1 via its strong connections to SMA proper. Hence, changes to M1 excitability can occur from stimulation of both structures within the SMC, without indirectly effecting subcortical structures. The assumption that our study mainly targeted the SMA proper is therefore not to be taken as a definite conclusion, rather a speculatory suggestion. Moreover, correlating activation patterns between preSMA and SSRT are not sufficient to form absolute conclusions regarding the neural basis of faster SSRTs, i.e., RI (Poldrack, 2000; Rushworth et al., 2002). Methods observing neural activation are categorized by weak functional resolution. Suggesting causative relationships between observed activation and movement generation/inhibition is therefore challenging. In fact, the activation could simply be unrelated to inhibition all together. Reports have indicated that the mere aspect on attending to unexpected stop stimuli generates activation in areas such as the IFG (Inferior Frontal Gyrus), traditionally considered a stopping related area. This indicates a challenge in distinguishing between areas specifically involved in successful stopping on SSTs versus attending to the stopping event (Sharp et al., 2010). Still, the association between activation and reduced SSRT provides strong evidence for the importance of preSMA in RI.

In summary, we propose that the reduced focality of tDCS, leading to uncertainty surrounding the affected neural activity could have contributed to our lack of effects on RI. Further measures to combat these difficulties are encouraged, and smaller electrodes to increase focality of tDCS are needed in future studies. Additionally, including structural scans would determine current flow, allowing researchers to establish whether the electrodes target the intended cortical structure. Alternatively, implementing High-Definition tDCS (HD-tDCS) would be a viable option to increase the spatial precision. HD-tDCS share technical similarities with tDCS, but its focal ability and modulating effects are thought to be superior to the more conventional protocols (Parlikar et al., 2021). This is accomplished using an electrode array of smaller, more focal electrodes (Villamar et al., 2013). Compared to tDCS, HD-tDCS is proven to induce greater effect on behavior and neurophysiological measures (Kuo et al., 2013; Sehatpour et al., 2021 in Guo et al., 2022). Previous investigations have already established HD-tDCS as an effective method for increasing RI, by observing significant changes to SSRT following stimulation of preSMA and the right inferior frontal gyrus (rIFG) (DeLaRosa et al., 2020; Guo et al., 2022). Possibly, using HD-tDCS could be better suited to investigate both cognitive functions and clinical symptoms.

4.1.3. Response variability to tDCS.

As previously discussed, our results suggest that M1 excitability changed following active tDCS, compared to sham condition. This effect was not paralleled by stimulation type or interaction of time and stimulation type. However, group response in excitability visually appeared to increase following both stimulation types, suggesting a high degree of variability in the direction tDCS effected excitability. This was further substantiated by descriptive analysis revealing patterns of excitability shifts in directions not polarity-specific to the anodal and cathodal stimulation. Interestingly, both anodal and cathodal tDCS visually appeared to increase and decrease excitability on an individual basis, while some participants did not respond at all. Since tDCS appear to induce unstable and variable neurophysiological effects, observable changes to inhibitory mechanisms cannot be expected. Therefore, we speculate whether this individual response variability could have contributed to our lack of observed change to SSRT. However, variability in response to tDCS has a broader line of challenges and implications. Although the general consensus has been that anodal tDCS enhances cortical excitability and cathodal tDCS decreases cortical excitability (Nitsche et al., 2008) several reports agree that more complex processes are at play (Lopez-Alonso et al., 2014; Rudroff et al., 2020). In fact, response to tDCS seems to depend on factors including current strength, duration of stimulation and hormonal fluctuations.

4.1.3.1. Current intensity. Contrary to our hypothesis, we did not observe opposite effects on M1 excitability following anodal and cathodal tDCS with a current intensity set at 2 mV. However, previous studies have observed that when tDCS is applied at 2 mA to M1, both anodal and cathodal stimulation increase excitability (Batsikadze et al., 2013). The expected decrease in excitability following cathodal stimulation was only reported when current intensity was set at 1 mA. These findings have been supported by reports of cathodal 1 mA and 3 mA stimulation applied to the M1 inducing inhibitory effects, while excitatory effects were observed when stimulation was applied at 2 mA (Mosayebi Samani et al., 2019).

Additionally, our results displayed a reversal in expected direction of excitability for one type of stimulation but not the other. Therefore, we assume an asymmetric stability of anodal and cathodal tDCS. This asymmetry has been discussed in previous literature, and results from cathodal stimulation being generally considered more controversial, i.e., c-tDCS being less effective or not sufficiently explored (Varoli et al., 2018). A reduced stability of cathodal stimulation has important implications for the use of tDCS in clinical trials for TS

patients. As most studies investigating the effect of tDCS on tics in TS patients have come from cathodal protocols, this indicates an increased likelihood of unexpected modulatory shifts in excitability. As changes to M1 excitability have been associated with the severity of tic behavior (Dyke et al., 2022**)**, unintentionally modulating excitability in opposite directions could increase tics, rather than alleviating them.

Although underpowered our results support the overall idea of modulatory direction following tDCS being somewhat current-dependent. As excitability effects appear current-dependent, the standardized current intensity of 2 mA recommended for safe use of tDCS (Bikson et al., 2016; Matsumoto & Ugawa, 2017) across stimulation types should be further discussed. Future investigations are encouraged to increase knowledge surrounding current-dependent variability, hence laying the groundwork for a standardized overview of the stimulation-specific effects following different current intensities. This would allow a customization of current intensity to the desired direction of excitability shift, hence optimizing tDCS protocols for the use for both research and therapeutic purposes.

4.1.3.2. Duration.   The present study applied 2 mA tDCS to the SMC for a duration of 20 minutes to replicate TS protocols. Previous studies have reported that modulatory direction of excitability depends on the duration of which specific current intensities are applied. For example, anodal tDCS to motor cortex applied for 26 min has been shown to induce inhibitory effects (Monte-Silva et al., 2013, in Thair et al., 2017), while cathodal tDCS applied for only 20 min has induced excitatory effects (Batsikadze et al., 2013). This further explains our findings of increased excitability following both stimulation types across time, as we applied both anodal and cathodal stimulation for a duration of 20 min. Based on the afore-mentioned studies, our protocol would have resulted in both stimulation types producing excitatory effects. Such duration-dependent effects of stimulation could explain why we did not observe any changes to the SSRT. Alternatively, the 20 min stimulation period used in our study might not have been long enough to effect RI, and implementing a longer duration might have resulted in the hypothesized effects. However, as stimulation periods of approximately 20 min are mostly used, the effects and possible risks of prolonged durations are still unclear (Prehn & Floel, 2015)**.**

Overall, our results indicate that tDCS is limited by variability linked to aspects of stimulation intensity and duration. To optimize tDCS protocols, future research is needed to address this variability, increasing knowledge surrounding parameters potentially affecting both behavioral and neurophysiological outcomes following stimulation. Such investigation

would contribute to a standardization of parameter-dependent effects. Here, we further underscore the importance of monitoring the induced neurophysiological changes with TMS following stimulation types applied with varying current intensities and durations. However, as directional shifts in excitability can occur during stimulation, measuring modulatory effects before and after tDCS will not sufficiently determine specific duration-dependent effects. Alternatively, future investigations can consider monitoring cortical excitability during tDCS via TMS, thus allowing for a more precise observation of direction shifts in excitability following specific durations.

4.1.3.3. Sex differences. Due to strict safety regulations and limited time to recruit participants, we were not able to balance our sample across sex, resulting in 70 % female and 30 % male participants. Descriptive analysis revealed a general response variability across sexes following both types of stimulation in M1 excitability. However, no stable pattern of variability between genders was observed. Interestingly, previous studies have reported significant sex-specific differences in the response to tDCS, with females reported to produce a more variable response to tDCS, compared to males. Previous reports have highlighted hormonal fluctuations linked to the menstrual phase in women affecting modulation of cortical excitability, resulting in increased response variability (Kuo et al, 2006, in Rudroff et al., 2020). During specific phases of the menstrual cycles, (e.g., the first follicular phase) levels of both progesterone and oestradiol are low, resulting in reduced response to both anodal and cathodal TDCS protocols. Progesterone remains low in the second follicular phase, whereas levels of oestradiol rise, leading to enhanced excitability and reduced inhibition. In both the first and second luteal phase progesterone increases, while oestradiol levels are moderate, leading to reduced excitability and increased inhibition (Inghilleri et al 2004; Smith et al 2002; Smith et al 1999, in Rudroff et al., 2020) This suggests that oestradiol enhances excitability, while progesterone increases inhibition. This leads to response variability in woman, while response in males remain more stable (Rudroff et al., 2020).

As the majority of our sample were female, the observed response variability and the lack of main effects for stimulation type could initially be interpreted as caused by hormonal fluctuations. However, we did not observe increased response variability in female participants, compared to males. On the contrary, a minor tendency towards males having fewer stable responses was slightly evident. However, acknowledging once more that we were strongly underpowered, we interpret these results as neither contrary to nor supporting of previous reports indicating greater variability in females. Instead, we interpret our findings

as indicative of a general response variability to tDCS, adding to the notion that the effect of tDCS is not linear, but rather a highly complex process influenced by several factors related to both the individual and the method itself. A general response variability could explain our failure to observe solid behavioral and neurophysiological results.

The present study did not account for potential hormonal fluctuations by asking female participants to state their current menstrual cycle. However, establishing specific cycles prior to stimulation would require a broad and time-consuming assessment, as knowledge of current menstrual cycles is usually not quickly assessable. Still, when investigating the effect of tDCS in female participants, hormonal levels should be established prior to stimulation in future designs. This could reduce sex-specific response variability to tDCS stimulation. A potential starting point could be to implement blood tests to assess hormone levels prior receiving tDCS. As previously illustrated, it appears that the levels of oestradiol enhances excitability, while progesterone increase inhibition (Rudroff et al., 2020). By establishing levels of progesterone and estradiol in female participants prior to receiving tDCS, current intensity and duration can be adjusted accordingly, while comparable measures can be obtained during similar hormonal states. Increasing knowledge surrounding these effects would contribute to the development of individualized tDCS protocols. The potential to taylor protocols to groups of individuals with specific characteristics would allow for tDCS to be established as a more reliable method, and behavioral results following stimulation could be interpreted with a higher degree of certainty. Importantly, an individualization of tDCS protocols would significantly increase the methods potential as an alternative treatment for clinical disorders, including TS. Of note, we speculate whether physiological states beyond the fluctuations related to woman's menstrual phases could affect the mechanisms underlying tDCS, and the response it induces in subjects. As tDCS is proven to be sensitive to physiological states, e.g., levels of progesterone and oestradiol, it is likely that additional hormonal changes occurring in both males and females have the potential to interfere with results. This assumption could be addressed in future studies.

Lastly, although not replicated by the present study, we urge future investigators to interpret the sex-specific response variability reported in the literature with caution. Historically, there had been a prevalent trend of not including female subjects in scientific research in order to reduce the risk of fetial harm and general fertility, and to avoid (Liu & Mager, 2016). This has major consequences, as medications and other therapeutical treatments developed by using experimental trials will be customized to mainly suit the male physiology. For example, it has been reported that woman are generally overmedicated as a

result of drug dosages being determined on the basis of experimental trials with mostly male subjects (Lerner, 2020). Considering the fact that a tendency to exclude females in experimental investigations of tDCS already exists (Alonzo et al., 2012 in Krause & Cohen Kadosh, 2014), we emphasize that rather than a source of added noise, the sex-specific response variability is an opportunity to explore the field further, increasing knowledge surrounding tDCS as an effective approach to modulate cognition and clinical states in both men and woman.

4.2. Implications for Tourette's syndrome.

The present study aimed to address the previous literature investigating RI and tics. From the perspective of inhibitory deficits being linked to M1 hyperexcitability and tics (Bronfeld et al., 2013; Morand-Beaulieu et al., 2017) the literature appears contradictory. While anodal stimulation is generally reported to improve RI in healthy participants, identical protocols applied to TS patients does not alleviate tics (Behler et al., 2018). Interestingly, turning down the SMC, i.e., supposedly increasing the relative activation of the direct pathway to increase M1 excitability, has shown to impair RI in healthy participants (Hsu et al., 2011) but reduce tic-behavior (Carvalho et al., 2015; Mrakic-Sposta et al., 2008; Eapen et al., 2017). Based on our results' indication that stimulating the SMC can directly modulate tonic excitability of M1, we propose an explanation for these puzzling findings. Alternatively, the tic reduction observed following cathodal tDCS to SMC could result from direct cortical effects from SMC, and not the involvement of the inhibitory BG network. Furthermore, our results suggest that in the context of the inhibitory control task used in this project, the direct cortical connections from SMC to M1 are excitatory. From this perspective, turning down the SMC logically leads to decreased M1 excitability and the reduction of tics, while turning up the SMC would lead to increased M1 excitability and finally increased tic severity, substantiating previous findings in TS patients (Carvalho et al., 2015; Mrakic-Sposta et al., 2008; Eapen et al., 2017).

Moreover, we suggest that the literature on the effects of tDCS on tics should be interpreted with the variability in modulatory effects following stimulation in mind. Here, the potential of responses being dependent on parameters and hormonal states should receive a distinct focus. For example, previous investigations of the effect of cathodal tDCS on tics applied a current intensity above 1 mA, with the majority applying current at 2 mA (Carvalho et al., 2015; Eapen et al., 2017; Mrakic-Sposta et al., 2008; Tajadini et al., 2019). This questions whether a reversed effect on excitability could have occurred. Variability in

stimulation duration was also apparent to some extent, potentially resulting in unexpected results on excitability. Importantly, the consequences of response variability significantly limit the reliability and the safety of using tDCS for treatment purposes. For the use of tDCS in clinical trials, altering excitability in unexpected directions may have major implications. As TS is linked to M1 hyperexcitability, cathodal TDCS applied to SMC in attempts to decrease M1 excitability and alleviate tic behavior, could have the opposite effect in some subjects, worsening symptoms depending on current intensity, duration, or subject-dependent factors.

Taken together, this questions the relationship between inhibitory control and tics. Although TS have been viewed a disorder of inhibition, a line of contradictory findings challenges this characterization by pointing to an opposite pattern. Reports have shown that TS patients express SSRTs comparable to healthy subjects, even surpassing them in some instances (Maigaard et al., 2019; Ritter et al., 2022). However, a distinction has been made between patients with TS only, and patients with a comorbidity of ADHD. Normal to increased performance on SSTs is mainly observed in children with TS only, while children with coexisting TS and ADHD have indeed illustrated inhibitory deficits (Openneer et al., 2021). Other studies have failed to establish inhibitory deficits in both TS and TS + ADHD all together (Sturm et al., 2021). Moreover, the neural substrates of ADHD have several similarities with the mechanisms hypothesized to be underlying TS, including reduced concentration of GABA (Edden et al., 2012) striatal deficits (Rubia, 2011; Rubia et al., 2011) and reduced BG gray matter (Nakao et al., 2011). This illustrates the well-known problem of establishing underlying causes for comorbid disorders. The existing literature linking TS and inhibitory deficits has not substantially accounted for the potential of coexisting ADHD, possibly confounding the results (Ritter et al., 2022). Our findings of tDCS to the SMC primary modulating M1 excitability via the corticocortical pathway, taken together with previous reports dividing the relationship between inhibitory deficits and tics, questions the importance of inhibitory mechanisms in the development of pure TS. We encourage future investigations to implement diagnostic differentiation when investigating TS, questioning the working hypothesis of inhibitory deficits being causative for tics.

Lastly, based on the previous literature and our own results, we suggest an alternative explanation as to why increased M1 excitability has been associated with tics, while inhibitory deficits have not been consistently observed in TS patients. To date, this relationship remains unclear. However, there has been observations of increased activation in the prefrontal cortex of TS patients during response inhibition tasks (Openneer et al, 2021).

Previous investigations have proposed the development of neuroplastic compensatory mechanisms because of long-term exposure to suppressing urges and tics (Hovik, et al 2016; (Eichele et al., 2016; Hovik, 2016). These findings do not suggest an inherent inhibitory deficit in TS patients, rather that more sophisticated inhibitory mechanisms develop as a response to prolonged exposure to suppression, while simultaneously serving as an explanation for the in some cases superior SSRTs compared to healthy controls. Possibly, the increased activation of the frontal cortex could directly affect M1 and result in hyperexcitability. In line with our results, increased activation of SMC directly increases excitability of M1, possibly contributing to an overflow of corticocortical excitation eventually leading to tics. We encourage future research to explore this further, as an alternative to the working hypothesis of imbalance to the cortico-subcortical inhibitory network.

4.3. Limitations

The present study has several limitations that could be adressed in future research. While some shortcomings have already been discussed, some additional limitations will be included below.

Firstly, the present study used a repeated measure experimental design, allowing for a smaller sample size. However, the strict exclusion criteria for participation in experiments using transcranial brain stimulation caused significant challenges with recruitment. While fifty-six (N=56) participants were initially screened, forty-six (N=46) participants were excluded due to not meeting the inclusion criteria's. This caused the final sample size (n = 10) to be substantially smaller than intended. We acknowledge that a sample of this size was likely to small for a significant difference to be detected. This assumption is supported by the results relating to our main dependent measures yielding a power below 0,8. The effect of tDCS on M1 excitability yielded a power of 0,197, and effect of tDCS on StopBoth SSRT had an observed power of 0,185. Overall, larger sample sizes are needed in future investigations of the effects of tDCS on measure of RI.

Secondly, we used a hand-held technique when applying TMS. Hence, we acknowledge the potential of variability in positioning the TMS coil across time, within and between sessions. TMS data are sensitive to small placement changes, minor changes in direction, location and position. Challenges with being consistent could potentially explain the general the response variability in M1 excitability. To overcome this issue, MRI guided neuronavigation systems could be used. This method involves a co-registration of head and

structural magnetic resonance imaging (MRI) scan from participants. Neuronavigation increases the precision of stimulation by providing instant feedback on how to position the coil, contributing to more stable results (Caulfield et al., 2022).

Thirdly, the present study used a double blinded design, with both participants and experimenters remaining naive to the stimulation mode in each session (anodal, cathodal, sham). However, we failed to test whether participants identified the correct condition following sessions. Testing the efficiency of blinding would further validate our study, and we recommend future studies to determine whether blinding was successful.

Lastly, due to filtering issues we had some issues with keeping measures of RMS consistent. While this was not a problem for all the data, it has implications for the interpretation of the significant change in MEP amplitude across time, observed following active tDCS. With this slight variability in measures of RMS and challenges with keeping overall values below the limit of 0.01, we cannot be completely sure that the muscle was at rest at the time of stimulation.

4.4. Conclusion

Our study aimed to investigate the effect of tDCS applied to the SMC on measures of response inhibition (RI) and address the implications for Tourette's syndrome (TS). Based on previous literature, we hypothesized that anodal tDCS to the SMC would improve RI by reducing M1 excitability and that cathodal tDCS would impair RI by increasing M1 excitability. We did not replicate previous findings, as no changes to RI were observed following stimulation. Still, our research has validated the design by illustrating that active, but not sham tDCS effected M1 excitability across time, compared to sham condition. As this effect was not paralleled by changes to SSRT, our study has two main implications. Firstly, we suggest that modulating the SMC primarily affects M1 excitability via the corticocortical pathway, rather than through thalamocortical connections. Secondly, we suggest that tDCS is limited by a general response variability on an individual basis. The variability is potentially caused by reduced focality of the current electrode montage, current parameters and individual hormonal factors. To optimize tDCS protocols and increase we encourage future research to address this variability. While we do not undermine the effects of tDCS for research purposes, our results suggests that we still have a long way to go before the method can be established as a safe and reliable treatment alternative for Tourette's syndrome.

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Appendix A: Script for Anticipatory Response Inhibition Task (ARIT)

Appendix a consists of the script read to the participants prior to their completion of the Anticipatory Response Inhibition Task (ARIT). Both Norwegian and English version are included below.

Norsk versjon: Manus til Anticipatory Response Inhibition Task (ARIT)

Før øvelsesrunde:

Du vil først bli gitt en øvelsesrunde med en rekke prøver. Hver runde vil ikke starte før du holder begge taster nede med fingrene slik (demonstrer). Ikke bruk for mye kraft, for å ikke slite ut fingrene. Du vil bli testet i to ulike prøver som kommer i tilfeldig rekkefølge; såkalt «Gå» og «stopp-prøver». I både «Gå» og «Stopp» vil to søyler begynne å stige mot en mållinje. «Gå» krever at du løfter tastene for å stoppe søylene så nært mållinjen som du kan. Lykkes du, vil mållinjen bli grønn. «Stopp-prøver» består av to ulike versjoner: Stopp- begge og stopp-høyre/venstre. I stopp-begge vil begge søyler stoppe automatisk. Dette er et signal om at du IKKE skal løfte fingerene fra tastene, men isteden fortsette å holde dem nede og slik avbryte løfteresponsen din. I «Stopp høyre/venstre» vil kun èn av søylene stoppe mens den andre vil forsette å stige mot mållinjen. Dette signaliserer at du IKKE skal løfte fingeren som korresponderer med søylen som stoppet, men isteden avbryte løfteresponsen din, SAMTIDIG som den andre fingeren som samsvarer med stigende søyle skal løftes så nært som mulig til mållinjen. Hele oppgaven vil ta omkring 20 minutter.
Har du noen spørsmål? Etter prøverunden vil alt være lettere å forstå.

Etter øvelsesrunde:

Nå har du gjennomgått øvelsesrunden og oppgaven der vi registerer prestasjonen din vil begynne. Hvis du syntes det var vanskelig, så er dette helt normalt. Det er krevende. Oppgaven begynner straks du holder tastene nede. Hvis du trenger det kan du ta pauser. Prestasjonen din er ikke knyttet til hvor lang tid du sammenlagt bruker. Nå kan du begynne når du er klar.

English version: Script for Anticipatory Response Inhibition Task (ARIT)

Before practice round:

You will first be given a practice round with a series of tests. Each round will not start until you hold both keys down with your fingers like this (demonstrate). Do not use too much force, so as not to tire your fingers. Your performance will be measured on two different tests that will be presented in a randomized order; so-called "Go" and "stop trials". In both "Go" and "Stop", two columns will start to rise towards a target line. "Go" requires you to lift both keys to stop the pillars as close to the target line as possible. If you succeed, the target line will turn green. "Stop trials" consist of two different versions: Stop-both and stop-right/left. In stop-both, both columns will stop automatically. This is a signal that you should NOT lift your fingers from the keys, but instead continue to hold them down, thus interrupting your lift response. In "Stop right/left", only one of the columns will stop, while the other will continue to rise towards the target line. This signals that you are NOT to lift the finger corresponding to the bar that stopped (thus cancel your lift response in this finger), WHILE the other finger corresponding to the rising bar is to be lifted as close as possible to the target line. The whole task will take about 20 minutes.

Do you have any questions? After the practice round, everything will be easier to understand.

After practice round:

Now you have gone through the practice round and the task where we register your

performance will begin. If you found it difficult, this is completely normal. It is challenging.

The task starts as soon as you hold down the keys. If you need to, you can take breaks. Your

performance is not linked to how much time you spend in total.

Now you can start when you are ready.

Appendix B: Safety questionnaire for TMS/tDCS

Appendix B consists of the safety questionnaire for Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation, answered by participants upon recruitment.

TMS/TDCS Sikkerhetsspørreskjema

Hvis du godtar å delta i denne studien, vennligst svar på følgende spørsmål. Informasjonen du oppgir er kun for screeningformål og vil bli holdt fullstendig konfidensiell.

Vennligst kryss av for følgende informasjon der det gjelder deg:

Kjønn: O   mann   O   kvinne

              O   foretrekker ikke å si   ikke-
                                     O   binær

Dominerende hånd: O   venstre   O
                                                høyre
Norsk morsmål :   O   ja   O nei

Alder (spesifiser) ___år.

	Ja	Nei
1) Har du noen gang lidd av noen nevrologiske eller psykiatriske tilstander?		
Hvis JA, vennligst oppgi detaljer (type tilstand, varighet, gjeldende medisin osv .)		

2) Har du noen gang lidd av epilepsi, feberkramper i spedbarnsalderen eller hatt tilbakevendende besvimelsesanfall?		
3) Er det noen i din nærmeste eller fjerne familie som lider av epilepsi?		
Hvis JA , vennligst oppgi forholdet ditt til det berørte familiemedlemmet.		
4) Lider du av migrene eller tilbakevendende hodepine?		
Hvis JA, vennligst oppgi detaljer (frekvens, utløsende faktorer, respons på medisiner osv .)		
5) Har du metall i hjernen, hodeskallen eller andre steder i kroppen (f.eks . kirurgiske klips, splinter, fragmenter osv .)?		
Hvis JA, vennligst oppgi detaljer (type metall, plassering osv .)		
6) Har du for øyeblikket noe av følgende tilpasset kroppen din?		
Cochleaimplantat		
Pacemaker		
Implantert nervestimulator		
Medisinpumpe		
Dyp hjernestimuleringsimplantat		
7) Har du noen gang lidd av hjerneskade eller traumer mot hodet?		
	Ja	*Nei*
8) Har du noen gang mistet bevisstheten eller besvimt?		
Hvis JA, vennligst oppgi detaljer (fra hodeskallebrudd, bevisstløshet, siste 6 måneder osv .)		
9) Lider du av noen alvorlige hudsykdommer (f.eks . nevrodermatitt, utslett)?		
Hvis JA , vennligst oppgi detaljer:		
10) Tar du for øyeblikket noen reseptfrie eller foreskrevne medisiner?		

Navn med store bokstaver:	
Signatur:	**Dato:**

Hvis JA , vennligst oppgi detaljer:		
11) Er du gravid, eller er det noen sjanse for at du kan være det?		
12) Gjennomgår du for tiden anti-malariabehandling?		
13) Har du drukket mer enn 3 enheter alkohol i løpet av det siste døgnet?		
14) Har du drukket alkohol allerede i dag?		
15) Har du drukket mer enn én kopp kaffe, te eller andre koffeinkilder den siste timen?		
16) Har du brukt rusmidler i løpet av de siste 24 timene?		
17) Har du sovet veldig lite i natt?		
18) Har du noen gang deltatt i et hjernestimuleringseksperiment før?		
Hvis JA , vennligst oppgi siste gang du deltok i en studie?		
19) Har du deltatt i mer enn 1 hjernestimuleringseksperiment i løpet av de siste 6 månedene?		
Hvis JA , vennligst oppgi hvor mange eksperimenter og om det var noen problemer.		

Jeg bekrefter at informasjonen ovenfor er nøyaktig så langt jeg vet.

Dette skjemaet er verifisert av (kun kvalifisert forsker):	**Dato:**
Utskriftsnavn:	
Signatur:	

Appendix C: Safety Questionnaire for TMS/tDCS – Session by session checklist

Appendix C includes the session by session safety questionnaire for Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation. "Session by session" refers to the checklist being answered again at each session.

TMS/TDCS Safety Questionnaire- Økt etter økt sjekkliste

DETTE SKJEMAET BØR BRUKES FOR SEKUNDÆRE ØKTER; ALLE DELTAKERE MÅ FULLFØRE DET LENGRE TMS SIKKERHETSSPØRRESKJEMAET PÅ PRIMÆRØTEN OG SIGNERE FOR Å BEKREFTE AT INGENTING ER ENDRET FOR PÅFØLGENDE ØKTER.

Vennligst svar på følgende spørsmål:

Sesjonsnummer:

Dato:

	Ja	*Nei*
12) Gjennomgår du for tiden anti-malariabehandling?		
13) Har du drukket mer enn 3 enheter alkohol i løpet av det siste døgnet?		
14) Har du drukket alkohol allerede i dag?		
15) Har du drukket mer enn én kopp kaffe, te eller andre koffeinkilder den siste timen?		
16) Har du brukt rusmidler i løpet av de siste 24 timene?		
17) Har du sovet veldig lite i natt?		
18) Har du noen gang deltatt i et hjernestimuleringseksperiment før?		

Hvis JA , vennligst angi når var siste gang du deltok i en studie?	
19) Har du deltatt i mer enn ett hjernestimuleringseksperiment i løpet av de siste 6 månedene?	
Hvis JA , vennligst oppgi hvor mange eksperimenter og om det var noen problemer.	

Jeg bekrefter at informasjonen ovenfor er nøyaktig så langt jeg vet.

Navn med store bokstaver:	
Signatur:	**Dato:**

Appendix D: Experimenter Safety checklist

Appendix D includes experimenter guidelines. According to the responses given by

participants on the safety questionnaires for TMS/tDCS, participants were either excluded,

included or the item was discussed with the main supervisor.

Sikkerhetssjekkliste – retningslinjer for forskere

Side 1 *(skal sjekkes hver gang deltaker kommer inn for å sikre at ingenting har endret seg - signer med dato og initialer på slutten av andre side for å bekrefte at alle svar er like)*

1. Hvis JA, noter detaljer. **Sjekk med PI.**
2. Hvis JA – ekskluder.
3. Hvis JA - Spør: Har noen i familien din (genetisk slektskap) epilepsi? Spør: Vet du om deres epilepsi er forårsaket av noe spesielt, for eksempel en hodeskade eller hjerneslag? Hvis de er i slekt gjennom ekteskap med noen med epilepsi, i stedet for genetisk relatert inkluder. Hvis de er genetisk beslektet med noen med epilepsi, men det var forårsaket av en spesifikk hendelse, for eksempel hodetraume, hjerneslag, hjernesvulst eller hjernekirurgi - inkluder.

   Hvis de er genetisk beslektet med noen med epilepsi, men de er ikke sikre på

   om det var forårsaket av traumer, hjerneslag, hjernesvulst eller hjernekirurgi -

   ekskluder.

   Hvis de er genetisk beslektet til noen som opplever epilepsi, uten kjent årsak -

   ekskluder. **Sjekk med PI.**

4. Hvis JA - Spør: Hvor ofte opplever du migrene? Spør: Vet du hva som utløser hodepinen din? Spør: Reagerer hodepinen på reseptfrie medisiner? Spør: Har du konsultert legen din om disse hodepinene?

   Hvis høyfrekvent migrene/hodepine eller er i tvil (f.eks. reagerer ikke på

   reseptfrie medisiner) – ekskluder.

5. Hvis JA – Spør: Var det fra et kirurgisk inngrep? Ved operasjon og usikkerhet på om noe metall implantert - ekskluder. Bortsett fra ved laserkirurgi øye, her trygt å inkludere. Spør: Hva slags metall er det? Hvis tannregulering – inkludert. Spør: Hvor

befinner den seg? Hvis noe metall i hode/hals – ekskluder. Hvis annet sted i kroppen, inkludere men **sjekk med PI.**

6. Eventuelle JA – ekskluder.

7. Hvis JA – ekskluder.

8. Hvis JA og usikker på årsak – ekskluder. Hvis forårsaket hodeskallebrudd – ekskluder. Hvis bevissthetstap var fra alvorlig hodetraume, i løpet av de siste 6 månedene, i flere minutter eller mer, eller forårsaket pågående problemer – ekskluder. Hvis klar årsak til besvimelse (f.eks. mangel på mat, varmt rom) og isolert hendelse – inkluder. **Sjekk med PI.**

9. Hvis JA – spør om bruk av antihistaminer. Se spørsmål 10. Pass på at det ikke er ødelagt hud (f.eks. akne eller eksem) på områder involvert i NIBS/EEG, EMG etc. Hvis hudbrudd – ekskluder.

10. Hvis JA, noter detaljer. Hvis p-piller – inkluderer. Ellers **sjekk med PI.**

 Hvis du tar antihistaminer (citrizin eller loratidin) - be deltakeren om å avstå

 fra medisiner over natten eller stå over morgendosen hvis den tas om morgenen.

 Hvis andre antihistaminer, **sjekk effekten med PI.** Hvis noen søvnmedisiner

 (inkludert over disk), **sjekk effekten med PI.**

11. Hvis JA – ekskluder.

 Side 2 *(fylles <u>ut</u> hver gang deltaker kommer inn – bekrefter også at informasjonen på første side er korrekt)*

 Spørsmål 12 – 17. Hvis JA – stopp økten.

 18. Hvis du har deltatt i rTMS/TDCS/TACS-eksperiment i løpet av de siste 2 dagene – stopp økten.

 19. Registrer detaljer, men du trenger ikke å stoppe økten.