AUGMENTATION OF COGNITIVE CONTROL WITH THETA BURST
STIMULATION OF THE RIGHT VENTROLATERAL PREFRONTAL CORTEX:
FIRST STEPS TOWARDS A NOVEL THERAPEUTIC APPROACH TO IMPROVE
BIPOLAR DISORDER OUTCOME

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the thesis entitled:

Augmentation of cognitive control with theta burst stimulation of the right ventrolateral prefrontal cortex: first steps towards a novel therapeutic approach to improve bipolar disorder outcome

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Abstract

Background: Bipolar disorder (BD) affects more than 1% of the population and causes deficits in response inhibition. Response inhibition involves three sub-components (interference inhibition, action withholding, and action cancellation), that can be assessed together in the Hybrid Response Inhibition (HRI) task. The right Inferior Frontal Gyrus (rIFG) is a potential target for augmentation of response inhibition. Current investigations of repetitive transcranial magnetic stimulation (rTMS) in BD remain limited. This proof-of-concept study will explore rTMS of the rIFG and its effect on response inhibition using the HRI task in BD and controls.

Methods: Within individuals with BD (n = 12) and a sex / age-matched control group (n = 12), we investigated the HRI performance scores associated with the three sub-components of response inhibition immediately before and after intermittent TMS (iTMS) and continuous TMS (cTMS) to either increase or decrease cortical excitability of the rIFG, respectively.

Results: The response inhibition sub-component ‘action withholding’ was significantly improved in the HRI task following iTMS for the BD group. While there were no other significant effects observed in the results, noticeable trends may imply that there may be other effects of TMS on response inhibition in BD that differs from controls.

Conclusions: Overall, this exploratory study successfully provided an initial evaluation of the effects of TMS on response inhibition in BD, showing trends and patterns that demonstrate the potential effectiveness of this novel intervention. Our study provides insights for further development and research of TMS over the rIFG in BD.
Lay Summary

Transcranial magnetic stimulation (TMS) of the right Inferior Frontal Gyrus may be a novel therapeutic approach to improve response inhibition deficits in bipolar disorder (BD). This study uses intermittent TMS (iTMS) and continuous TMS, as well as a hybrid response inhibition (HRI) task to assess the effects of TMS on three sub-components of response inhibition in BD. We found that individuals with BD had improved scores for the sub-component ‘action withholding’ in the HRI task following iTMS, which measures the ability to inhibit a prepotent response tendency. The results suggest the potential effectiveness of this novel intervention for response inhibition in BD that should continue to be investigated.
Preface

All of the work presented was conducted on three sites located at the University of British Columbia (UBC): the Behavioural Reward Affect and Impulsivity Neuroscience (B.R.A.I.N.) research laboratory, the UBC MRI Centre at Djavad Mowafaghian Centre for Brain Health, and Detwiller Pavilion of UBC Hospital. All projects and associated methods were approved by the University of British Columbia’s Research Ethics Board [certificate # H17-01529]. None of the text of the thesis is taken directly from previously published or collaborative articles. The HRI task programming and data extraction code, described in Section 2.3.3, was created by Dr. A. Sebastian and colleagues (Sebastian, Pohl, et al., 2013).

I, Karling, was involved in and led all methods described in this thesis. Specifically, I was responsible for all major areas of concept foundation, ethics applications and reporting, data collection and analysis, and manuscript composition. S. Todesco and G. Nie were involved in the early conceptual framework. J. Booth, A. Brar, K. Karimi and K. Yang were involved in study coordination. P. Kee, C. Sang, A. Romanchuk, K. Realina, P. Tutt, M. Khadem, and E. Sinclair were involved in data collection. L. Schmid and S. Zareyan were involved in data analysis. L. Barlow and colleagues were involved in the MRI portion of the study. F. Vila-Rodriguez, C. Feng, B Carroll and colleagues were involved in the TMS portion of the study. C. Schütz was the supervisor on this project and was involved throughout the project in concept formation and manuscript edits.
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Dedication

To Mom and Dad – your unconditional love, many sacrifices, and profound belief in my potential throughout my life is what led me to this adventure across the country to follow my passions. I love you!
1 Introduction

1.1 Bipolar Disorder

Bipolar disorder (BD) is a mental health disorder characterized by persistent, unusual shifts in mood and energy consisting of both acute major depressive episodes and acute manic episodes (Smith et al., 2012). Symptoms associated with depressive episodes include low mood, problems with appetite and sleeping, loss of energy, feelings of worthlessness, and suicidal ideation (American Psychiatric Association, 2013). Symptoms of manic episodes include elated or irritable mood, decreased need for sleep, racing thoughts, distractibility, and risky behaviors (American Psychiatric Association, 2013). The two most common subtypes of BD are BD type 1, characterized by manic episodes leading to significant social or occupational impairment; and BD type 2, characterized by hypomanic episodes, which are not associated with social or occupational impairment (Smith et al., 2012). BD has a lifetime prevalence of 2.6% in Canada and is highly comorbid with other mental health disorders and substance use disorders (Brady & Sonne, 1995; CCHS, 2012).

Although BD has a substantial impact on an individual’s everyday functioning and has the highest rate of suicide of all psychiatric conditions (Miller & Black, 2020; Smith et al., 2012), current treatment strategies for BD have substantial limitations (Harrison et al., 2018). The most common treatment options for BD are pharmacological supported with psychological treatments, however, these treatment options have limited efficacy and the pharmaceuticals can have serious adverse effects (Dean et al., 2018; Harrison et al., 2018). The most frequent adverse effects of pharmaceuticals for BD are weight gain, metabolic dysregulation, sedation/somnolence, and akathisia which in turn could negatively affect treatment adherence (Kemp, 2014). Thus, there is a need to improve treatment for BD.
1.2 Cognitive Control

1.2.1 Response Inhibition

Individuals diagnosed with BD show deficits in cognitive functions including attention, learning and memory, and executive function (Quraishi & Frangou, 2002; Savitz et al., 2005). The functional changes in the brain associated with these neurocognitive impairments are continuously being investigated (Savitz et al., 2005; Van Rheenen et al., 2020). A central process that affects changes in brain function associated with BD is cognitive control, the ability to manage thoughts and behaviours in accordance with one’s internal goals (Miller & Cohen, 2001). An example of cognitive control is being able to reverse decisions after they are made but before they are implemented, otherwise known as response inhibition (Jacobson et al., 2011). Such inhibitory control is ubiquitous in our daily routines, and thus is fundamental to everyday functioning (Sebastian, Pohl, et al., 2013). Response inhibition has been demonstrated to be disturbed in BD, with impulse control deficits as a fundamental behavioural symptom (Hummer et al., 2013; Quraishi & Frangou, 2002). Individuals with BD have been found to be more impulsive as a result of deficits in response inhibition co-occurring with strong impulses (Chan et al., 2023). Impulsivity is a prime factor in both BD type 1 and BD type 2 that causes maladaptive behaviours that lead to poor decision-making and functioning (Chan et al., 2023).

Response inhibition involves three separable cognitive sub-components, i.e. action withholding, interference inhibition, and action cancellation (Sebastian, Pohl, et al., 2013). All subcomponents share a common neural network in the prefrontal cortex but differ to the degree of regional involvement and thus all constitute different subprocesses of response inhibition (Sebastian, Pohl, et al., 2013). Investigations of response inhibition have given rise to a variety of behavioural measures, prominent among these measures are the Stop-signal-, Go / no-go- and
Simon-tasks, all requiring inhibitory control to suppress response tendencies (Chambers et al., 2009).

1.2.2 Action Withholding

Action withholding is defined as the ability to withhold a motor response (Sebastian, Baldermann, et al., 2013). The go / no-go task assesses action withholding by presenting a rare no-go-stimuli instead of the go-stimuli that frequently appears, thus requiring inhibition of a prepotent response tendency (Verbruggen & Logan, 2008). In the go / no-go task, action withholding is measured as the proportion of correctly withheld responses in comparison to incorrectly performed reactions of a no-go stimulus (i.e., commission errors) (Sebastian, Baldermann, et al., 2013). Individuals with BD perform worse on the go / no-go task compared to controls with significantly slower response times and more errors (Welander-Vatn et al., 2013).

1.2.3 Interference Inhibition

Interference inhibition is defined as the ability to suppress interfering response tendencies (Sebastian, Baldermann, et al., 2013). The Simon task assesses interference inhibition with a stimulus-response conflict by co-activating involuntarily response tendencies due to incongruent stimuli (Simon & Berbaum, 1990). The Simon task measures interference inhibition as the difference in reaction times in incongruent trials compared to congruent trials (Sebastian, Baldermann, et al., 2013). Although the Simon task has yet to be directly investigated in BD, a past study had found euthymic BD patients performed worse on a different interference task compared to controls (Strakowski et al., 2005).
1.2.4 Action Cancellation

Action cancellation is defined as the ability to inhibit an already ongoing motor response (Sebastian, Baldermann, et al., 2013). The stop-signal task assesses action cancellation with rare stop-signals occurring after the go stimuli at a variable stop-signal delay (SSD), thus requiring an inhibition of an already ongoing motor response (Verbruggen & Logan, 2008). Action cancellation in the stop-signal task is measured as the latency of the inhibition process (Sebastian, Baldermann, et al., 2013). A past study found individuals with BD had lower accuracy on the stop-signal task than controls (Weathers et al., 2012).

1.2.5 Hybrid Response Inhibition Task

The Hybrid Response Inhibition (HRI) task is a novel, validated paradigm that combines components of the Stop-signal-, Go / no-go- and Simon- tasks into one task (Sebastian, Pohl, et al., 2013). By using identical visual stimuli across conditions within the HRI task, we can make direct comparisons of interference inhibition, action withholding, and action cancellation (Sebastian, Pohl, et al., 2013). The HRI task is a promising tool to assess the three sub-components of response inhibition within BD and its association with impulse control deficits.

1.3 Right Inferior Frontal Gyrus

The neural network in the prefrontal cortex is essential for cognitive control including response inhibition (Chambers et al., 2009; Chan et al., 2023). Specifically, in the ventrolateral prefrontal cortex (VLPFC), the right Inferior Frontal Gyrus (rIFG) has a large role in stopping impulsive behaviour (Chan et al., 2023), and is thus a potential target for augmentation of response inhibition and cognitive control. Precisely, the pars opercularis (posterior sub-region of the rIFG), is found to be involved in response inhibition (Hartwigsen et al., 2019). It has been proposed the IFG modulates the excitatory influence of the pre-supplementary motor area (pre-
SMA) on the subthalamic nucleus, which consequently amplifies the inhibitory influence of the subthalamic nucleus on the motor cortex (Rae et al., 2015). Brain stimulation of the rIFG has been shown to improve response inhibition in healthy individuals (Chambers et al., 2007; Jacobson et al., 2011). The rIFG also plays an important role in BD pathophysiology (Zhang et al., 2020), and has been suggested to be a potential early neural marker for BD before any behavioural manifestations (Hajek, Cullis, et al., 2013). Reduced activation of the rIFG during response inhibition has been investigated in individuals with BD during both the euthymic (stable mood) and manic states compared to controls (Hajek, Alda, et al., 2013; Joshi et al., 2016; Townsend et al., 2012). Past studies have found cortical hyperactivations in BD in other brain regions such as the adjacent prefrontal cortex and superior temporal gyrus which may, in part, represent compensatory activity for the cognitive changes caused by the rIFG hypoactivations (Chan et al., 2023; Hajek, Alda, et al., 2013). Thus, treatments focused on stimulation of the rIFG may reduce the need for compensatory overactivity during response inhibition and improve behavioural outcomes (Chan et al., 2023).

1.4 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique used to deliver electrical stimuli to the cortex using magnetic fields generated outside of the head (Klomjai et al., 2015). Repetitive TMS (rTMS) is used to induce changes in brain activity that can last beyond the stimulation period (Klomjai et al., 2015). It involves stimulating specific deep brain regions by the production of high and low-intensity magnetic fields that modulate the cortical excitability (Mann & Malhi, 2023). This is attributed to long-term potentiation (LTP) and long-term depression (LTD) of cortical synapses which strengthens and weakens synaptic connections respectively (Thickbroom, 2007). A newer form of rTMS, known as theta-burst
stimulation (TBS) has been shown to produce lasting neurophysiological changes (Huang et al., 2005), with a reduced administration duration than standard rTMS (Chung et al., 2015). The two different patterns of TBS commonly used are intermittent TMS (iTMS) where pulses are delivered intermittently to increase cortical excitability, and continuous TMS (cTMS) where pulses are delivered continuously to reduce cortical excitability (Mix et al., 2010). rTMS has emerged as an effective treatment for major depressive disorder (MDD) and is also being investigated for other mental health disorders such as post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) (Baeken et al., 2019; Kozel, 2018). However, current investigations on the application of rTMS in BD remain limited (Konstantinou et al., 2022), and no study to date has looked at the stimulation of the rIFG in BD to assess response inhibition.

1.5 Aims

The current proof-of-concept study will explore rTMS of the rIFG and its effect on response inhibition in individuals with BD in the euthymic state and controls. The three subcomponents of response inhibition: interference inhibition, action withholding, and action cancellation will be investigated and compared using the HRI task before and after rTMS. We will use functional Magnetic Resonance Imaging (fMRI) to identify the target area for every participant prior to iTMS for transiently increasing cortical excitability and cTMS for transiently decreasing cortical excitability. The primary aim of the study is to assess the effect of iTMS and cTMS on improving response inhibition performance scores in the HRI task for individuals with BD. The secondary aim of the study is to identify any differences between individuals with BD and controls for the effect of iTMS and cTMS on the performance scores in the HRI task. We hypothesize (1) the BD group will perform worse on the HRI task at baseline prior to any TMS compared to the control group; (2) transient increase in cortical excitability or increased
activation of the rIFG following exposure to iTMS will improve HRI performance for both groups and have the largest impact on scores for the BD group; and (3) transient decrease in excitability or deactivation of the rIFG following exposure to cTMS will worsen HRI performance for both groups and have the largest impact on scores for the control group. This is an exploratory study that will contribute to our overall understanding of impulsivity and response inhibition as part of decision-making processes in individuals with BD. Identifying the efficacy of rTMS of the rIFG would constitute a first step towards developing a novel rTMS based intervention to improve outcome in individuals with BD and other mental health disorders associated with impulsivity.

2 Methods

2.1 Study Design

This clinical exploratory research study was conducted on three sites located at the University of British Columbia (UBC): the Behavioural Reward Affect and Impulsivity Neuroscience (B.R.A.I.N.) research laboratory, the UBC MRI Centre at Djavad Mowafaghian Centre for Brain Health, and Detwiller Pavilion of UBC Hospital. Ethical approval was obtained from the UBC Clinical Research Ethics Board (H17-01529). Additionally, approval was obtained by the Vancouver Coastal Health Research Institute (VCHRI) to meet Vancouver Coastal Health (VCH) operational requirements for study recruitment and conducting the study sessions at sites within VCH. This study was sponsored by the Brain and Behavior Research Foundation (formerly NARSAD) (Grant ID: 25951; UBC number: F18-02165). All participants provided written informed consent prior to study enrollment and ongoing verbal consent at the start of each study session.
2.2 Participants

The study sample consisted of 12 adults aged 19-45 years old with BD (I or II) in the euthymic state, and 12 (sex and age-matched) controls. Prior to study enrolment, a phone screener was performed to pre-screen eligibility. To be eligible to participate in the BD group, participants must have had a diagnosis of BD from a physician that is confirmed using the Mini-International Neuropsychiatric Interview (MINI; for Diagnostic and Statistical Manual of Mental Disorders (DSM) psychiatric disorders) screener diagnostic tool - section C (Sheehan et al., 1998), stable on psychotropic medications for at least two weeks, and in the euthymic state for at least two weeks at the time of the phone screener. Participants were eligible to participate if they were right-handed, fluent in English, and had no history of any substance use disorder, gambling disorder, physical illness, or any other mental health disorder (except anxiety disorders if the participants were not currently taking medication for anxiety). Individuals were excluded if they did not meet the criteria for both the TMS safety screening (e.g., personal or family history of seizures, past serious head injury) and the magnetic resonance imaging (MRI) safety screening (e.g., claustrophobia, metallic fragments in body, pregnant). 197 phonescreeners were conducted to get the n= 24 sample size. Participants were recruited through flyers, research recruitment webpages, newsletters, and social media. The BD participants were also recruited through advertisement at VCH clinics and a BD support group. Physicians and healthcare workers who advertised the study at VCH clinics gave their patients a "consent to disclose contact information" form to sign if they wished to be contacted by our research staff about their interest in the study.
2.3 Measures

2.3.1 Self-Report Questionnaires

Self-report questionnaires were used to collect demographic information and characterize the sample during the phone screener and at each session. The questionnaires were generated using the following two electronic tools: REDCap, a secure, web-based software platform hosted by UBC (Harris et al., 2009); and Qualtrics, a UBC survey tool platform (Qualtrics Version 2023, Provo, UT). During the phone screener, the following questionnaires were administered verbally: demographics (verbally asking the participant’s sex, weight, height, dominant hand); health history (verbally asking the participant’s psychiatric and substance use disorder diagnoses, medications, illnesses and injuries that affect brain function); MINI screener (sections: C-manic and hypomanic episodes, I-alcohol use disorder, J-substance use disorder) (Sheehan et al., 1998); modified gambling DSM screener (American Psychiatric Association, 2013), a TMS safety screener created by the UBC TMS team; and a MRI safety screener created by the UBC MRI team.

During Session 1 (characterization) of the study, various self-report questionnaires were administered to the participants on a computer. However, this “characterization” data was not included in the present study. For the two TMS sessions (Sessions 3 and 4), the following questionnaires were also administered for TMS safety: daily effects questionnaire (prior to TMS administration); patient adverse effects (immediately following TMS administration); comfort rating questionnaire – part A (immediately following TMS administration); and comfort rating questionnaire – part B (the morning following TMS administration).
2.3.2 Drug and Alcohol Screening

At the start of Sessions 2 (MRI), 3 (iTMS), and 4 (cTMS) of the study, an alcohol breathalyzer (BACtrack S80, KHN Solutions Inc., San Francisco, CA) was used to screen for alcohol, and a urine toxicology test (One Step Multi-Line Screen Test Device, Nova Century Scientific, Burlington, ON) was administered to screen for amphetamines, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol (THC), methadone, methamphetamine, methylenedioxymethamphetamine, morphine, oxycodone, and tricyclic antidepressants. Participants who tested positive on the drug or alcohol screening did not continue with the study session. However, the principal investigator made the final decision in certain circumstances.

2.3.3 Hybrid Response Inhibition Task

The computerized HRI task, a newly developed paradigm incorporating the Stop-signal-, Go / no-go- and Simon- tasks to measure the three components of response inhibition was performed once by the participants during Session 2 in the MRI scanner, and twice in Sessions 3 and 4 pre and post TMS administration. The HRI task was conducted by replicating the design created by Dr. A. Sebastian and colleagues (Sebastian, Pohl, et al., 2013), and programmed in the software Presentation (version 16.4, www.neurobs.com). The task consisted of four conditions: a congruent go condition (62.5%), an incongruent go condition (12.5%), a no-go condition (12.5%) and a stop condition (12.5%).

The task initiated with a visual presentation of the instructions for 5000 milliseconds (ms) followed by a rest period of 5000 ms during which a white fixation cross against a black background was presented in the center of the screen. A run consisted of 160 trials that were presented in a pseudo-randomized order. Each trial started with a white circle around the cross. After 500 ms, a white arrow appeared within the circle either on the right or left side of the
fixation cross for 1000 ms or until a button press was performed. In the congruent go condition, an arrow pointing right was presented on the right side of the cross, or an arrow pointing left was presented on the left side of the cross. In the incongruent go condition (interference inhibition), a right-pointing arrow was presented on the left side of the cross, or a left-pointing arrow was presented on the right side of the cross. No response on the go-trials is calculated as omission errors. In the no-go condition (action withholding; always a congruent condition), the circle changed its color from white to blue at the onset of the arrow. In the stop condition (action cancellation; always a congruent condition), the circle changed its color from white to blue after a variable SSD following the onset of the arrow.

The SSD was adapted to the participants' performance following a staircase procedure to yield a probability of 50% of correct inhibitions per run. In the beginning of a run, the SSD was 220 ms. If the response was not inhibited (commission error), the SSD was decreased by 50 ms with a minimum SSD of 20 ms. If a response was inhibited (correct stop), the SSD was increased by 50 ms. The length of the interstimulus interval was varied with a mean duration of 1500 ms and a standard deviation of 372 ms. The duration of the go process is directly observable through reaction time (RT), whereas the duration of the stop process (known as the stop signal reaction time- SSRT), is estimated by observing the effects of varying the SSD.

Five behavioural outcomes were outputted for each run of the HRI task: 1) mean RT of go trials; 2) Simon interference effect mean; 3) SSRT; 4) mean commission errors for no-go trials; 5) mean commission errors for stop trials. The mean RT was measured as the average time in ms between the onset of the arrow and a participant's response for correct responses on the go trials. The Simon interference effect was calculated by subtracting the mean RT of congruent trials from the mean RT of incongruent trials. The SSRT (ms) scores were computed using the
integration method to produce the most reliable and least biased non-parametric SSRT estimates by subtracting the mean SSD from the mean % RT and replacing the go omission errors with the maximum RT in order to compensate for lacking responses (Verbruggen et al., 2019).

Commission errors were measured as the % of errors made where the participant did not inhibit their response on the no-go and stop trials.

Therefore, the three components of response inhibition were measured as followed: 1) action withholding was measured with the mean RT of go trials and percent of no-go commission errors; 2) interference inhibition was measured with the Simon interference effect; 3) action cancellation was measured with the SSRT and percent of stop commission errors. A lower mean RT, Simon interference effect mean, and SSRT indicates a better / faster score on the HRI task. Additionally, a fewer number of mean commission errors for the no-go and stop trials indicates a better score on the HRI task.

2.3.4 Magnetic Resonance Imaging

MRI brain scans were performed on the participants during Session 2 of the research study using a single Philips Achieva 3.0 Tesla MRI scanner at the UBC MRI Research Centre. The MRI appointment serves to obtain an individual anatomical 3DT1 image, and three functional MRI (fMRI) scans while the participant is in the MRI scanner for 45 minutes. The fMRI scans were created while the participants completed the HRI task in the scanner to show the rIFG being activated during response inhibition. The anatomical 3DT1 brain scan was then sent to the TMS team to identify the exact location of the rIFG in the brain for targeting the TMS. Incidental findings were sent immediately to the UBC hospital’s radiologist. It was decided with the principal investigator if the participant should be excluded from the study.
2.3.5 Transcranial Magnetic Stimulation

Two types of rTMS on the rIFG were administered to the participants in the Non-Invasive Neurostimulation Therapies Lab at Detwiller Pavilion of UBC Hospital. During Session 3, iTMS was administered to increase cortical excitability and during Session 4, cTMS was administered to reduce cortical excitability. The TMS was single-blinded – the order of which type of TMS was given on which session day was not known to the participants. TMS was administered using the MagVenture MagPro X100 stimulator equipped with the MagVenture Cool-B65 coil for rIFG stimulation (MagPro, Medtronic). The TMS dose is 90% of a participant’s resting motor threshold, falling within the range of 35-65% intensity. First, the TMS technician started administering the TMS at 20-25% intensity where the participant starts to feel the stimulation, and then the intensity is worked up to the participant’s dose throughout stimulation. Stimulation parameters for the iTMS consisted of two-second trains of bursts of three pulses at 50 Hz, and bursts repeated at 5 Hz with inter-train pauses of eight seconds for 20 trains to deliver a total of 600 pulses over 3.30 minutes. Stimulation parameters for the cTMS consisted of a continuous train of bursts of three pulses at 50 Hz, and bursts repeated at 5 Hz for 40 seconds to deliver a total of 600 pulses over 40 seconds.

2.3.6 Motor Threshold Testing

Prior to the first TMS stimulation, each participant’s motor threshold was determined from TMS over the primary motor cortex. This procedure is used to establish the dose to be delivered. First, the TMS team made each participant a cap by taking measurements of their head to find the vertex and then marking the right motor cortex. The vertex of the head is found by marking the nasion and inion, and then marking the distance halfway in between the two. Then, the team measured tragus to tragus and marked halfway. The intersection of the two points is the
vertex. To then find the motor cortex, the TMS team marked one-third of the way from the vertex to the left tragus and then marked 1 cm anterior. This is the right motor cortex point stimulated for motor threshold. The motor response was measured using the MagPro X100 stimulator. The TMS team placed the coil on the right motor cortex and delivered a single pulse at a time. The TMS team then watched the participant's left hand for movement. The intensity started at 40%, delivering single pulses, with at least five seconds in between, at random. If no movement in the hand is observed after one or two pulses, the intensity is increased by 5%. This continued until movement is observed in the hand. Once movement is observed, more pulses are delivered at the determined intensity. An intensity is sufficient if movement is seen on at least 5/10 pulses. If movement is not seen on at least 5/10 pulses, the intensity is increased by 5%. If movement is seen on at least 5/10 pulses, the intensity is decreased by a small amount until the lowest intensity required to elicit movement on at least 5/10 pulses is found.

2.3.7 Neuronavigation

The method of neuronavigation for locating each participant’s rIFG was based on their neuroanatomical 3DT1 brain scan obtained in Session 2. We used a frameless stereotaxic system to target the specific area of interest. Neuronavigation proceeded using the system Localite (Version 3, www.localite.de) to position the coil for maximal field strength at the rIFG for each participant. The rIFG was specified by reverse co-registration from a stereotaxic coordinate on the standard Montreal Neurological Institute (MNI-152) template brain, onto each individual’s anatomical MRI. The TMS team calibrated the neuronavigation system by taping a tracker to the participant’s cap and marking landmarks on their face with a pointer that the neuronavigation camera picks up. The TMS team then marked internal landmarks on the MRI and entered the
coordinates of the stimulation target. The MNI coordinates for the rIFG subregion pars opercularis is x, y, z = +52, +13, +8, drawn from a prior study (Gough et al., 2005).

2.4 Study Procedures

2.4.1 Pre-Screening

When individuals emailed the research team to express interest in participating in the study, the researchers sent the individuals a breakdown of the study procedure, study materials including a ‘potential hazards risk sheet’, the consent form to read through, and a link to a ‘participant information contact sheet’ survey for the individuals to complete electronically and securely using REDCap electronic data capture tools. The contact sheet provided researchers with an individual’s demographic information (i.e., date of birth, sex, educational background), contact information (i.e., phone number, email address), and an electronic signature confirming the individual has read through the study documents and agrees to disclose the information. Once completed, the researchers booked an online phone screener to determine eligibility by verbally asking the participants over the phone questionnaires generated by Qualtrics. Following the phone screener, the graduate student (after clarifying eligibility requirements with the principal investigator if needed) made the final decision for if the participant met all the eligibility criteria as well as the TMS and MRI safety requirements to be deemed eligible to participate in the study.

2.4.2 Session 1 – Characterization

When participants arrived at the research lab at the David Strangway building of UBC, they were first asked to sign the consent form following a thorough read through of the form and the research team answering any questions the participants had. The consent form was also signed by the research assistant administering the form. The participants then completed self-
report questionnaires generated by Qualtrics on a laptop computer. Session 1 took approximately two hours to complete, and the participants were compensated $15.00 CAD for participating in the session.

2.4.3 Session 2 – Magnetic Resonance Imaging

Session 2 was generally completed on the same day as Session 1. At the start of Session 2, the participants were given an alcohol breathalyzer test and a urine drug screening test. Participants were allowed to continue with the study if their blood alcohol level read “0.00” on the breathalyzer and the urine toxicology test came back negative for all drugs screened. Participants also completed an MRI requisition form (stating date of birth, weight, and confirming the consent form had been signed), which was then emailed to the MRI research team. The participants then received a brief training session of the HRI task on a laptop computer. With their right hand on a computer mouse - index finger on the left mouse button and middle finger on the right mouse button, the participants were instructed to fixate their gaze on the cross in the middle of the circle on the computer screen. When an arrow appeared, they were told to click on the side of the mouse that correlated with the direction that the arrow is pointing. If a blue circle appeared, the participants were told to try and withhold their response. The participants were constantly reminded to respond as quickly and as accurately as possible.

Once the participants felt confident in performing the HRI task and completed the training session successfully, they were taken by the research assistants to the UBC MRI Centre. At the MRI Centre, an MRI technologist went through the participants’ screening form with them. The participants then laid down in the MRI scanner while four MRI scans were produced – three fMRI scans and one resting-state scan. Participants completed one run of the HRI task for each fMRI scan (three HRI task runs total) using a right-handed remote in the scanner. During
the resting-state scan, participants were instructed to sit still and fixate their gaze on the cross on the computer screen. Session 2 took approximately 1.5 hours to complete, and the participants were compensated $20.00 CAD and a USB flashdrive of their resting-state brain scan for participating in the session.

2.4.4 Sessions 3 and 4 – Transcranial Magnetic Stimulation

The procedures of sessions 3 and 4 were identical. The two TMS sessions were required to be at a minimum of 24 hours and a maximum of nine days apart. Participants arrived at the research lab at the David Strangway building and were given an alcohol breathalyzer test and a urine drug screening test just as performed during Session 2. The research assistants verbally asked the participants questions from the ‘daily effects questionnaire’ generated by REDCap. The participants then completed other self-report questionnaires generated by Qualtrics on a laptop computer. A quick recap of the HRI task instructions was given and then the participants were taken by the research assistants to the Detwiller Pavilion of UBC Hospital.

In a lab room, the participants completed one run of the HRI task on a laptop computer with a computer mouse pre-TMS. The participants were then taken into the TMS room with members of the TMS team. In Session 3, the TMS team made the participant a cap by taking measurements of their head to find the right motor cortex. A motor threshold test was then performed by stimulating the right motor cortex to determine the participant’s dose. The TMS team calibrated the neuronavigation system, marked internal landmarks on the MRI and entered the coordinates of the stimulation target. Participants were then informed of expectations regarding the sensations of TMS. Tingling, contractions, and tapping on the scalp may occur. The sensation can vary between individuals, with some feeling no discomfort at all and others feeling pain. The jaw muscles are also likely to be activated due to the positioning of the coil to
target the rIFG, and this may cause teeth to chatter during stimulation. Participants were also given earplugs since the coil can be loud when stimulating. The TMS team calibrated the coil and then placed it on the target on the participant's head. Stimulation started, starting at a low dose and turning the dose up throughout treatment, according to the participant's pain tolerance. In Session 3, participants were given iTMS, and in Session 4, participants were given cTMS.

Post-TMS administration, the participants completed one final run of the HRI task in the same lab room. The research assistants completed the ‘study id’ and ‘treatment confirmation’ surveys generated by REDCap with information (i.e., motor threshold, dose, stimulation intensity, any TMS interruptions) provided by the TMS team. The research assistants then verbally asked the participants questions from the ‘patient adverse effects’ and ‘comfort rating questionnaire – part A’ surveys generated by REDCap to evaluate the participants experience undergoing TMS. The survey link to the ‘comfort rating questionnaire – part B’ was emailed to the participants to complete the morning following the TMS session. Sessions 3 and 4 took approximately three hours each to complete, and the participants were compensated $30.00 CAD for participating in each session.

2.5 Statistical Analysis

2.5.1 Covariates

During recruitment, participants in the control group were matched by age and sex with the BD group. Therefore, age and sex were not included as covariates in the analyses. Covariates included in the analyses were determined using an independent samples t-test to examine differences in years of education between groups, and a chi-square test to examine associations between level of education and group. This was to control for education being significantly related to scores on behavioural measures of response inhibition (Votruba & Langenecker,
Education level was separated into three categories: 1) some post-secondary schooling; 2) college / university diploma; and 3) graduate studies. Since the assumptions of the chi-square test were not met, a Fisher-Freeman-Halton test was used instead to determine the associations between level of education and group. The software program G*Power version 3.1 was used to estimate the statistical power of the study assuming a medium effect size of 0.25, a sample size of 24 participants, and a significance level of 0.05 (Faul et al., 2009).

2.5.2 ANOVA

A 2-way mixed Analysis of Variance (ANOVA) with a repeated measures within-between interaction was used to conduct the analysis. The presence of outliers was assessed with visual inspection of boxplots. Standardized residuals (SRE) were also calculated to assess the presence of any residual outliers outside the range of +/-3. The analysis was performed for the following variables: 1) pre / post iTMS mean RT of go trials; 2) pre / post cTMS mean RT of go trials; 3) pre / post iTMS Simon interference effect; 4) pre / post cTMS Simon interference effect; 5) pre / post iTMS SSRT; and 6) pre / post cTMS SSRT.

An interaction effect was first investigated with the ‘Tests of Within-Subjects Effects’ output between time (pre / post) and group (BD / control) on the outcome variables. A significant interaction effect would mean that the effect of time on the outcome variables differ between groups. Next, the main effects of time (with the ‘Tests of Within-Subjects Effects’ output) and the main effects of group (with the ‘Tests of Between-Subjects Effects’ output) were assessed to see if group or time independent from each other had an effect on the outcome variables. The analyses were further explored by examining the pairwise comparisons of group and time based on estimated marginal means (EMM) with the Bonferroni correction (to account for multiple comparisons) for all possible pairs of categories. 95% confidence intervals. The upper bound and
lower bound 95% confidence intervals (CI) were also evaluated to indicate the range within which the true population means are estimated to lie with 95% confidence. For a statistically significant difference, \( p \leq 0.05 \).

The following assumptions were checked before conducting the analyses for each pre / post outcomes: normality, homogeneity of variances, and homogeneity of covariances. The normality assumption was assessed with the Shapiro-Wilk test and the visual inspection of histograms. The normality of residuals were also assessed. A non-significant p-value on the Shapiro-Wilk test indicates the data follows a normal distribution and therefore the normality assumption would be met. The dependent variables that did not follow a normal distribution underwent transformations until the normality assumption was met. If the dependent variables were left-skewed, the following transformations were tested to increase their values: 1) squared; or 2) cubed. If the dependent variables were right-skewed, the following transformations were tested to decrease their values: 1) natural logarithm (ln); 2) log base 10; 3) square root; 4) cube root; or 5) reciprocal transformation. The homogeneity of variances assumption was assessed with the Levene’s test. A non-significant p-value on the Levene’s test indicates the variances of the dependent variable is equal across different groups of the independent variable and therefore the assumption of equal variances would be met. The homogeneity of covariance matrices assumption was assessed with the Box’s test. A non-significant p-value on the Box’s test indicates no significant differences in covariance matrices between groups, and therefore the assumption of homogeneity of covariance matrices would be met.

2.5.3 Ordinal Logistic Regression

The distribution of the data is not normal for the percentages of the commission errors in the dataset partly because of the large concentration of zeroes, which contributes to the violation
of the normality assumption in an ANOVA test. Thus, we can confidently say the data would not be normally distributed in a general population and so an ordinal logistic regression analysis was performed instead of the ANOVA for the following variables: 1) pre / post iTMS no-go commission errors; 2) pre / post cTMS no-go commission errors; 3) pre / post iTMS stop commission errors; and 4) pre / post cTMS stop commission errors. The difference between the pre and post outcomes was calculated by subtracting the post TMS commission errors from the pre TMS commission errors and were computed into three categories: decreased (improved) = 2, no change = 1, and increased (worsened) = 0. This model determines the odds of moving up or down the ordinal scale given the predictor variables. The proportional odds assumption was checked before conducting the ordinal test to ensure that the effect of the education levels on the odds of being in a higher dependent variable category remains consistent across all levels of the education variable. The proportional odds assumption was tested with the test of parallel lines. A non-significant p-value suggests that the slopes of the ordinal regression model are parallel, indicating that the assumption is met.

The goodness of fit was the first table evaluated to determine the overall fit of the model for a population with a normal distribution. The deviance and Pearson chi-square tests in the goodness of fit table were assessed. A non-significant p-value indicates the model is a good fit. Next, the likelihood ratio (omnibus) test was assessed to compare the study’s model to the simplest possible model. A significant p-value indicates our model is a better fit. There are a total of 18 possible combinations in the data (two groups, three education levels, and three outcome ordinal levels). Thus, the number of observed combinations with zero frequencies were identified in each analysis for when considering the reliability of the model. The next test evaluated is the test of model effects to see if the predictors (group and education level) were associated with the
outcome variable. A significant $p$-value indicates the predictor has a significant effect on the outcome.

Next, the parameter estimates table was investigated to evaluate the magnitude and direction of the effect that group has on the outcome while accounting for the other predictor in the model (education level). The odds ratio- $\text{Exp}(B)$, indicates the magnitude and direction of the effect by calculating the odds of the BD group being in a higher category divided by the odds of the control group being in a higher category. Thus, a value greater than one indicated that BD is associated with a higher odds of being in a higher category; and a value greater than zero and less than one indicated that BD is associated with a higher odds of being in a lower category. Finally, we conducted a crosstabulation to view the frequency and percentages of BD participants and controls in each category of the commission errors to visualize any differences between groups.

3 Results

3.1 Study Design

The education level means but not the number of years of education means differed between the BD and control groups ($p = 0.03$). Therefore, education level was included as a covariate across all models. The power analysis indicated a power of 0.65, suggesting there is a 65% chance of detecting a true effect.

3.2 Participants

Participant demographics are shown in Table 1. The sample average age was 29.17 years old for the BD group and 29.08 years old for the control group, comprising majority female (83.33%) for both groups. More than half of the BD group identify as White (58.33%) and 50% of the control group identify as Asian. The average number of years of education is 16.67 years
for the BD group and 18.50 years for the control group. The majority of the BD group has a college or university diploma (75%), and 50% of the control group have some education in graduate studies (Table 1).

3.3 ANOVA Analysis

3.3.1 iTMS Mean RT

The ‘pre / post iTMS mean RT’ variables were initially right-skewed and were therefore transformed using the ln transformation so that the normality assumption was met. When the ANOVA was performed, although the outcome variables did not significantly deviate from normal ($p > 0.05$), the normality residual assumption was not met. This was observed after attempting different transformations. The analysis was carried on assuming that this violation is okay given that the Kolmogorov–Smirnov test showed normality, the outcome is normally distributed, and that ANOVA is robust to deviation from normality (Knief & Forstmeier, 2021; Yang & Berdine, 2021).

There were no significant interaction effects or main effects observed for the ‘pre / post iTMS mean RT’ outcome variables ($p > 0.05$). However, when examining the plot of the EMM (Figure 1), we observed the mean RT for the BD group to be decreased from the pre iTMS outcome to the post iTMS outcome. Meanwhile, we observed that the control group had a consistent mean RT for both outcomes that was higher than the BD group. Additionally, the pairwise comparisons of the pre vs post iTMS mean RT for the BD group is marginally significant (between 0.05-0.01; Pritschet et al., 2016), where $p = 0.09$. Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses revealed a decreasing pattern from pre to post TMS for the BD group’s mean RT of go trials in our sample.
3.3.2 cTMS Mean RT

The ‘pre / post cTMS mean RT’ variables were initially right-skewed and therefore underwent different transformations until the normality assumption was met. The mean RT variables were reciprocally transformed, representing the inverse of the original outcome values and changing the interpretation of the results. Thus, a higher outcome value now represents a faster (better) RT and a lower outcome value now represents a slower (worse) RT. All assumptions were then met following the transformation.

There were no significant interaction effects or main effects observed for the ‘pre / post cTMS mean RT’ outcome variables ($p > 0.05$). However, when examining the EMM plot (Figure 2), we observed an increasing trend for the reciprocal mean RT in the BD group from the pre cTMS outcome to the post cTMS outcome. Meanwhile, we observed the control group to have a consistent reciprocal mean RT at both time points. Additionally, the pairwise comparisons of the pre vs post cTMS mean RT for the BD group approaches significance ($p = 0.07$). Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses revealed a faster speed / RT pattern of go trials from pre to post TMS for the BD group in our sample.

3.3.3 iTMS Simon Interference

The ‘pre / post iTMS Simon interference’ variables met all assumptions for the ANOVA analysis. The results of the analysis showed no significant interaction effects or main effects for the Simon interference effect mean outcome variables for time or group ($p > 0.05$). However, in the EMM plot (Figure 3), we observed the BD group to have visually higher means for both the pre and post iTMS scores in comparison to the control group’s scores with similar, small decreasing slopes. These observations were also investigated in the pairwise comparisons of the
pre vs post outcome variables for the BD group (112.86 ms for pre iTMS to 104.20 ms for post iTMS) and the control group (96.74 ms for pre iTMS to 92.47 ms for post iTMS). Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses suggest there may be an effect of group and time on the Simon interference variables separately, but not an interaction between them in our sample.

3.3.4 cTMS Simon Interference

The ‘pre / post cTMS Simon interference’ variables did not meet the homogeneity of covariance matrices assumption showing a significant p-value ($p = 0.01$) on the Box’s test. All other assumptions for the ANOVA analysis were met. The violation of the assumption primarily affects the reliability of the significance tests for interaction effects. We decided to continue with the analysis of the main effects with careful consideration when interpreting the results because of the potential impact of unequal variances on the significance levels and effect sizes.

The results of the analysis showed no significant main effects for the Simon interference mean outcome variables for time or group. However, when examining the pairwise comparisons, the EMM plot (Figure 4) showed the BD and control groups’ lines cross at an intercept because the control group seems to have a steep, decreasing slope between the two time points (91.07 ms for pre cTMS to 78.31 ms for post cTMS), while the BD group appeared to have Simon interference effect means that remained consistent for the pre and post cTMS time points (86.12 ms for pre cTMS to 84.30 ms for post cTMS). Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses revealed a trend towards an effect of cTMS on the Simon interference means for the control group but not the BD group in our sample.
3.3.5 iTMS SSRT

The ‘pre / post iTMS SSRT’ variables’ distribution was originally left-skewed due to an extreme outlier found in the dataset. After careful examination, the outlier was deemed to be too low a value possible for an SSRT variable. The value was an incorrectly outputted from the HRI task computer program and was therefore removed from the dataset (n = 23). After removal of the outlier, all assumptions for the ANOVA analysis were met.

The results of the analysis showed no significant interaction effects or main effects for the SSRT outcome variables (p > 0.05). However, the pairwise comparisons EMM plot (Figure 5) visually showed the slopes differed between groups with an intersection of the lines. The SSRT scores for the BD group appeared to decrease more following iTMS (246.67 ms for pre iTMS to 227.23 ms for post iTMS), while the control group appeared to have a smaller decrease in SSRT scores (238.93 ms for pre iTMS to 232.07 ms for post iTMS). Additionally, the pairwise comparisons of the pre vs post iTMS SSRT for the BD group approaches significance (p = 0.07). Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses revealed a trend towards a larger effect of iTMS on SSRT for the BD group compared to the control group in our sample.

3.3.6 cTMS SSRT

The ‘pre / post cTMS SSRT’ variables met the normality assumption for the outcomes but not for the residuals. The distribution of the data was left-skewed and so the square transformation was performed on the variables. All other assumptions were met.

The results of the analysis showed no significant interaction effects or main effects for the SSRT outcome variables (p > 0.05). However, the EMM plot (Figure 6) visually showed the slopes of the BD group and control group lines to differ in direction. The BD group showed a
steep, increasing trend on the SSRT from pre to post cTMS while the control group showed a small, decreasing trend on the SSRT from pre to post cTMS. Therefore, although there were no significant main effects of group or time on the outcome variables, the exploratory analyses revealed a trend towards a larger effect of cTMS on SSRT for the BD group that also differed in direction compared to the control group in our sample.

3.4 Ordinal Logistic Regression Analysis

3.4.1 iTMS No-Go Commission Errors

The ‘pre / post iTMS no-go’ variables met the proportional odds assumption for the ordinal logistic regression. The model was determined a good fit based on the goodness of fit and omnibus tests. There were 7 combinations (38.9%) of predictor and outcome variables with zero frequencies in the model.

When controlled for education level, group showed a significant effect ($p = 0.01$) on the outcome variables. We found the BD group to have a strong effect on the no-go commission errors [$\text{Exp}(B) = 31.92; \text{CI} = 2.26, 450.52$]. The odds ratio indicated that the BD group has a 32 times higher odds of being in a higher category (‘no change’ or ‘improved’ category) following iTMS. This was further investigated in the crosstabulation where the BD group had 50% of their participants with improved no-go scores post iTMS compared to no change (33.3%) and worsened no-go scores (16.7%). Moreover, the majority of the control participants had no change to their scores from pre to post iTMS (58.3%) compared to worsened (25.0%) and improved (16.7%) scores. Therefore, the results showed the BD group but not the control group had a significantly higher odds of improving on the no-go outcome variables after iTMS which can thus be representative of the general population.
3.4.2 cTMS No-Go Commission Errors

The ‘pre / post cTMS no-go’ variables met the proportional odds assumption for the ordinal logistic regression. The model was determined a good fit based on the goodness of fit test. However, the omnibus test was not significant ($p = 0.52$) and therefore suggested the model does not significantly improve the fit compared to the null model. There were 7 combinations (38.9%) of predictor and outcome variables with zero frequencies in the model.

The results of the analysis showed no significant effect for group on the outcome variables ($p > 0.05$). However, the odds ratio indicated that the BD group may be associated with lower odds of being in a higher category following cTMS [$\text{Exp}(B) = 0.26; \text{CI} = 0.03, 2.24$]. This was further investigated in the crosstabulation where the BD group had 58.3% of their participants with no change, 33.3% with worsened no-go scores post cTMS, and 8.3% with improved no-go scores. This differed from the control participants who had 75.0% with no change, 16.7% with improved scores, and 8.3% with worsened scores. Therefore, although there were no significant effects of group on the ordinal outcome variables, the results showed a trend for the BD group but not the control group to have lower odds of improving on the no-go outcome variables after cTMS in our sample.

3.4.3 iTMS Stop Commission Errors

The ‘pre / post iTMS stop’ variables met the proportional odds assumption for the ordinal logistic regression. The model was determined a good fit based on the goodness of fit test. However, the omnibus test was not significant ($p = 0.62$) and therefore suggested the model does not significantly improve the fit compared to the null model. There were 4 combinations (22.2%) of predictor and outcome variables with zero frequencies in the model.
The results of the analysis showed no significant effect for group on the outcome variables [Exp(B) = 0.63; CI = 0.11, 3.74; p > 0.05]. This was further investigated in the crosstabulation where the BD group had 41.7% of their participants with no change, 33.3% with worsened stop scores post cTMS, and 25.0% with improved stop scores. The control participants had 33.3% of participants in all three ordinal categories: no change, improved scores, and worsened scores. Therefore, there were no significant effects or differences found between the BD and control groups on the ordinal outcome variables following iTMS in our sample.

3.4.4 cTMS Stop Commission Errors

The ‘pre / post cTMS stop’ variables met the proportional odds assumption for the ordinal logistic regression. The model was determined a good fit based on the goodness of fit test. However, the omnibus test was not significant (p = 0.35), and therefore suggested the model does not significantly improve the fit compared to the null model. There were 5 combinations (27.8%) of predictor and outcome variables with zero frequencies in the model.

The ordinal regression revealed no significant effects of group on the ordinal outcome variables, but the effect does approach significance (p = 0.09). The parameter estimate indicated the BD group may be associated with lower odds of being in a higher category following cTMS [Exp(B) = 0.19; CI = 0.03, 1.33]. In other words, the control group may be associated with higher odds of being in a higher category following cTMS. This was further investigated in the crosstabulation where the control participants had 41.7% for both no change and improved score categories, and 16.7% with worsened scores. This differed from the BD group who had 50.0% of their participants with no change, 33.3% with worsened stop scores post cTMS, and 16.7% with improved stop scores. Therefore, although there were no significant effects of group on the
ordinal outcome variables, the results showed a trend for the control group but not the BD group to have higher odds of improving on the stop outcome variables after cTMS in our sample.

4 Discussion

4.1 Main Findings

4.1.1 Summary of Results

The present study investigated the effects of increasing cortical excitability (iTMS) and decreasing cortical excitability (cTMS) of the rIFG on the performance scores of a computerized task measuring three sub-components of response inhibition in BD and controls. The response inhibition sub-component ‘action withholding’- measured by no-go commission errors, was significantly improved in the HRI task following iTMS for the BD group. There were no other significant effects observed in the results. However, action withholding measured by the mean RT (Figure 1), and action cancellation measured by the SSRT (Figure 5), both showed a trend approaching significance (\(p\)'s are less than 0.1 and more than 0.05) in the sample for iTMS improving the scores of BD participants. Additionally, interference inhibition measured by the Simon interference effect visually showed a trend of the controls having better scores for both sessions compared to the BD group (Figure 3). There were no observed effects of iTMS or differences between groups for action cancellation measured by the stop commission errors.

For the effect of cTMS, action withholding measured by the mean RT showed a trend approaching significance in the sample for cTMS improving the scores of BD participants (Figure 2). Conversely, action cancellation measured by the stop commission errors showed a trend for cTMS not improving the scores for BD and was approaching significance. Also, both action cancellation measured by the SSRT (Figure 6), and action withholding measured by the no-go commission errors, showed a trend for cTMS worsening and not improving the scores for
BD respectively. Lastly, interference inhibition measured by the Simon interference effect visually showed a trend in Figure 4 for the controls to have improved scores following cTMS.

4.1.2 Hypotheses

We hypothesized the BD group would perform worse than the controls on the HRI task prior to TMS. Hypothesis 1 was incorrect because there were no significant differences between the BD group and the control group at the pre iTMS session for mean RT, Simon interference, or SSRT. However, both the Simon interference and SSRT scores at pre iTMS are visually worse for the BD group with a 16.12 ms Simon interference difference and 7.74 ms SSRT difference from the controls, suggesting there may be a main effect of group at baseline on interference inhibition and action cancellation in our sample that is not being detected in our model.

We also hypothesized that iTMS will improve the HRI performance scores for both groups with a larger impact on the BD group. Our second hypothesis was partly correct. The BD group significantly improved on the HRI task following iTMS for action withholding. Although not significant, interference inhibition (Simon interference = 8.66 ms improvement) and action cancellation (SSRT = 19.44 ms improvement) also showed a trend towards improvement following iTMS in BD. The control group had no change to their HRI performance scores following iTMS for action withholding and interference inhibition. However, there appeared to be a trend towards an improvement on action cancellation post-iTMS for the control group (SSRT = 6.86 ms improvement).

Our final hypothesis was that cTMS will worsen the HRI performance scores for both groups with a larger impact on the control group. Hypothesis 3 was incorrect because there were no significant effects of cTMS on the HRI performance scores for either group. There were two trends that conflicted each other: action withholding measured by the mean RT showed a trend
for improvement in the BD group following cTMS, while action withholding measured by the no-go errors showed a trend for the BD group not improving. Also, action cancellation showed a trend towards worsened scores following cTMS in BD. There were no observed effects of cTMS on interference inhibition in BD but there was a trend towards improvement for the control group. Additionally, action cancellation measured by the stop errors had a trend towards higher odds of improving for the control group. There were no observed effects of cTMS on action withholding in controls.

4.1.3 Explanation

Even though the three subcomponents of response inhibition have mutual activation in the rIFG (Sebastian, Pohl, et al., 2013), our results show only action withholding (the ability to withhold a motor response), was significantly improved following iTMS of the rIFG in the BD group. A possible explanation for why increasing the cortical excitability of the rIFG only had a significant effect on action withholding and not interference inhibition or action cancellation is because the three subcomponents are required at different time points in the programming and generation of the response output (Sebastian, Pohl, et al., 2013). In the process of response inhibition, action withholding is positioned inbetween interference inhibition and action cancellation. Interference inhibition resembles an early subcomponent because it requires the inhibition of response tendencies that are involuntarily activated by incongruent stimuli, which are thought to arise before response initiation (Sebastian, Pohl, et al., 2013; Simon and Berbaum, 1990). In contrast, action cancellation would be considered a late subcomponent because it assesses the inhibition of an ongoing response (Verbruggen & Logan, 2008). Action withholding is an intermediate subcomponent of response inhibition because it comprises aspects of both action selection and inhibitory action (Mostofsky and Simmonds, 2008; Sebastian, Pohl, et al.,
Therefore, the rIFG may be more involved in the middle stage of the response inhibition process.

Another explanation to how action withholding differs from interference inhibition and action cancellation is that interference inhibition and action cancellation both involve a spatial response selection (left or right button press) in addition to a movement initiation, while action withholding just requires participants to decide between responding and withholding a response. Interference inhibition and action cancellation also have increased pre-SMA activation than action withholding in the HRI task (Sebastian, Pohl, et al., 2013). Therefore, stimulation of the rIFG in BD might be more involved in withholding a response and thus only improve the action withholding subcomponent. In contrast, the pre-SMA region might be more involved in downstream movement executions (e.g. initiating and retracting the movement in action cancellation and performing a button press in interference inhibition) (Sebastian, Pohl, et al., 2013). Future studies should consider investigating the differences between stimulating the rIFG and the pre-SMA, and their effects on the three response inhibition subcomponents.

4.2 Limitations

There were some limitations in this study. First, the power of the study was determined to be 0.65, which is lower than the typical desired power of $\geq 0.80$ (Hintze, 2008). This reduces the chances of detecting a true effect and therefore, the model was more likely to produce false negative results (Type II errors). Our sample size of $n = 24$ was insufficient to provide statistical power and detect meaningful results. We had a small sample size of twelve participants per group due to limited funding, recruitment challenges for finding interested participants with BD, scheduling challenges with the participant’s availability and hours of operation for the MRI and TMS centres, the COVID-19 pandemic pausing data collection and recruitment, and interested
BD participants not meeting the eligibility criteria during the phone screeners (e.g., was not currently in the euthymic state, had diagnosed comorbid mental health or substance use disorders, or did not meet the safety criteria for MRI or TMS). Therefore, the lack of significance seen for some of the results where trends were observed does not necessarily mean no difference but could be because of the low power and low sample size that the difference was not detected.

Another limitation to the study was that most of our BD participants were females (ten females, 83.33%), with only two males (16.67%) in the BD sample due to recruitment challenges. Despite efforts to recruit a sample with an equal ratio of males to females, most people with BD who were interested in participating were females. Due to the timeline of the project and slow recruitment for the study, we continued data collection with a predominantly female sample, but made sure to recruit controls that were sex and age matched to the BD participants so that there were no sex differences between groups. In Canada, studies found 0.84% of females in the population have BD and 0.77% of males; a ratio of 1.09 females to males (GBD, 2020). The gender imbalance in our sample does not represent the proportion of males and females with BD in the general population and may therefore influence the study’s external validity and restrict the extent to which the conclusions can be applied to the wider population.

An additional limitation to the study is the possibility of a practice effect that may have resulted in increased performance scores post-TMS. This would explain why the performance scores for the Simon interference effect seemed to be improved at pre-cTMS (86.12 ms for BD and 91.07 ms for controls; Figure 4) compared to pre-iTMS (112.86 ms for BD and 96.74 ms for controls; Figure 3). However, a past study on a response inhibition task revealed there was no practice effect found until a minimum of 5 training sessions were completed (Zhao et al., 2016).
By ensuring participants in both groups completed iTMS and cTMS in the same order, this reduced the chances of a practice effect influencing our results. Further investigations of the possibility of a practice effect in the three sub-component response inhibition tasks are needed before making any definite conclusions.

The final limitations to our study were regarding the TMS administration. There was a lack of double-blinding in the administration of iTMS and cTMS. The iTMS was consistently delivered during Session 3 and cTMS was delivered in Session 4. While the participants were unaware of the specific treatment order, the researchers were aware of the assigned protocols. Efforts were made to ensure Sessions 3 and 4 were completed the exact same way except for which TMS was administered. Additionally, there was a sufficient time gap between sessions, with a minimum of 24 hours to a maximum of 9 days a part. The aftereffects of a single session of rTMS are short-lived (<70 minutes; Thut & Pascual-Leone, 2010), and therefore the effect from the first TMS session is not long enough to impact the second TMS session. There was also the absence of a placebo condition to blind the participants regarding their treatment allocation. The goal of the study was to compare the HRI performance scores pre and post each TMS session and therefore a placebo condition was not feasible or necessary for this exploratory study. Additionally, active and sham rTMS differs with respect to the subjective quality of the sensation which may be easily distinguishable and therefore could have unblinded the participants (Arana et al., 2008).

4.3 Future Directions

Future investigations of iTMS on BD with a larger sample size is necessary to draw any definite conclusions about the trends and patterns observed in the present study. A larger sample size would increase the power of the study and may therefore be able to detect more significant
differences in the analyses. With a larger sample size, further analyses should also be conducted such as investigating other predictors (e.g., perceived stress scale; state, trait, and anxiety inventory; Beck’s depression inventory) and examining the differences between iTMS and cTMS.

This was also the first study to examine and compare three types of response inhibition measures in one task in BD. The effect of stimulating the rIFG on action withholding, interference inhibition, and action cancellation differed and therefore further analysis is needed to determine if the rIFG is more involved in specific sub-components of response inhibition compared to response inhibition as a whole or if other brain regions in the neural network (e.g., pre-SMA) may be better targets for some of the subcomponents. Future studies should consider all three subcomponents of response inhibition when investigating cognitive control in different populations.

Once stimulation of the rIFG is confirmed to improve response inhibition in BD, researchers could then start to investigate longer-term effects with multiple sessions of iTMS in longitudinal studies. For the progressive evaluation and development of TMS as a therapeutic target for BD, this treatment approach would need to undergo the different phases of clinical trials to further assess the safety, effectiveness, and long-term effects of TMS to obtain regulatory approvals and treatment guidelines.

5 Conclusion

Our findings indicate that TMS affects a specific subcomponent of response inhibition in BD that is not seen in controls. Specifically, iTMS of the rIFG improves action withholding in individuals with BD. Although there were no other overall differences between groups or from TMS on other subcomponents of response inhibition, there appears to be noticeable trends in the
results implying that other effects of TMS on response inhibition in BD may still be present in the general population even though it did not reach statistical significance in our analysis with a small sample size. Overall, the exploratory analyses successfully provided an initial evaluation of the effects of iTMS on response inhibition in BD, showing trends and patterns that demonstrate the potential effectiveness of this novel intervention. In summary, this proof-of-concept study was an important early step towards the ultimate goal of investigating TMS as a potential therapeutic approach for improving response inhibition and provides evidence for further development and research of TMS over the rIFG in BD.
Table 1. Summary of demographics of BD and control participants (N = 24).

<table>
<thead>
<tr>
<th></th>
<th>Bipolar Disorder Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td>N (%) or Mean ± SD</td>
<td>N (%) or Mean ± SD</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>29.17 ± 6.56</td>
<td>29.08 ± 6.80</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<tr>
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<td>10 (83.33) / 2 (16.67)</td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<td></td>
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<td>2 (16.67)</td>
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<tr>
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<td>6 (50.00)</td>
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<td>Hispanic</td>
<td>1 (8.33)</td>
<td>2 (16.67)</td>
</tr>
<tr>
<td>Black</td>
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<td>1 (8.33)</td>
</tr>
<tr>
<td>Prefer not to disclose</td>
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<td>1 (8.33)</td>
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<tr>
<td><strong>Education (years)</strong></td>
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<td>Graduate studies</td>
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<td>6 (50.00)</td>
</tr>
</tbody>
</table>
Figure 1. Line graphs of the estimated marginal means in ln(ms) (ln transformation) for the HRI performance score ‘mean RT’ of go trials at pre and post iTMS for both the BD group (n = 12) and control group (n = 12); error bars: 95% CI; p > 0.05.

Figure 2. Line graphs of the estimated marginal means in ms\(^{-1}\) (reciprocal transformation) for the HRI performance score ‘mean RT’ of go trials at pre and post cTMS for both the BD group (n = 12) and control group (n = 12); error bars: 95% CI; p > 0.05.
Figure 3. Line graphs of the estimated marginal means in ms for the HRI performance score ‘Simon interference effect’ at pre and post iTMS for both the BD group (n = 12) and control group (n = 12); error bars: 95% CI; p > 0.05.

Figure 4. Line graphs of the estimated marginal means in ms for the HRI performance score ‘Simon interference effect’ at pre and post cTMS for both the BD group (n = 12) and control group (n = 12); error bars: 95% CI; p > 0.05.
Figure 5. Line graphs of the estimated marginal means in ms for the HRI performance score ‘SSRT’ at pre and post iTMS for both the BD group (n = 11) and control group (n = 12); error bars: 95% CI; p > 0.05.

Figure 6. Line graphs of the estimated marginal means in ms² (square transformation) for the HRI performance score ‘SSRT’ at pre and post cTMS for both the BD group (n = 12) and control group (n = 12); error bars: 95% CI; p > 0.05.
Bibliography


of medial frontal cortex activation during a Go/No-go task. *Neuroscience Letters, 549*, 51-56. https://doi.org/10.1016/j.neulet.2013.06.010

