COGNITIVE DYSFUNCTION IN TREATMENT-RESISTANT DEPRESSION AND THE LONGITUDINAL BENEFITS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

by

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Abstract

Introduction: Cognitive dysfunction (CD) is a commonly reported symptom of Major Depressive Disorder (MDD) and recognized as a distinct symptom domain. Patients with treatment-resistant depression (TRD) tend to experience greater rates of CD, however cognition is not well-characterized in this population and treatment options remain scarce. Repetitive Transcranial Magnetic Stimulation (rTMS) is effective in treating affective symptoms in TRD, but its effect on CD in TRD has not been established.

Objectives: (1) To characterize CD in TRD; (2) to assess whether rTMS is associated with cognitive improvement.

Methods: This study used data from a non-inferiority clinical trial investigating two excitatory rTMS protocols to the left dorsolateral prefrontal cortex in unipolar outpatients with TRD. Cognitive testing was performed at baseline and 3 months post-treatment in patients and a demographically matched cohort of healthy volunteers (HV). A MANOVA was performed on baseline data to assess the effects of TRD on cognition using both normative and individualized adjustments. K-means clustering was performed on the patient sample to elucidate cognitive subgroups, and binomial logistic regression was subsequently performed to determine significant clinical and demographic predictors of cluster belonging. Changes in cognitive performance from baseline to post-treatment were assessed using repeated-measures ANOVA.

Results: At baseline, TRD showed selective impairment compared to HV in domains of verbal memory, speeded attention, set shifting, and inhibitory control. Relative cognitive scoring revealed greater differences in scores between TRD and HV across all cognitive domains.

Clustering revealed two cognitive subgroups in TRD, namely a global impairment (GI, 57%) and a selective executive dysfunction (SE, 43%) subgroup. Belonging to the GI subgroup was predicted by benzodiazepine use and older age. Only the GI subgroup showed meaningful changes in cognitive performance at 3 months post-treatment, with significant improvements in verbal memory. Further, improvement in verbal memory was associated with improvements in affective symptoms.

Conclusions: This research provides new insights into the cognitive heterogeneity of TRD by identifying cognitive subgroups and predictors of cognitive functioning. Furthermore, the findings suggest that rTMS to the left DLPFC may improve verbal memory in a subgroup of TRD patients.

Lay Summary

Major Depressive Disorder (MDD) is a serious psychiatric disorder that can present with significant cognitive challenges, *e.g.* difficulty remembering things, concentrating, or making decisions. Patients who do not respond to first-line treatments are at particular risk for cognitive symptoms. This study found that about half of patients with treatment-resistant depression (TRD) present with widespread cognitive dysfunction (CD) , and that this is more likely in patients who are older and taking benzodiazepines (a class of anxiolytic medications). Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurostimulation treatment, was found to improve memory functions in patients who showed widespread CD before treatment, in addition to effectively treating their mood symptoms. rTMS may be a useful multifaceted intervention for treating TRD patients who also suffer from CD.

Preface

Data used in this study were originally collected as part of two randomized clinical trials co-investigated by Dr. Vila-Rodriguez (ClinicalTrials.gov identifiers: NCT02800226 and NCT01887782) at the Non-Invasive Neurostimulation Therapies Laboratory, University of British Columbia, in collaboration with the Centre for Addictions and Mental Health (CAMH) and the Toronto Western Hospital.

Elizabeth Gregory and Dr. Fidel Vila-Rodriguez, with input of members of the thesis committee (Drs. Sophia Frangou and Ivan Torres), contributed to the hypothesis, design, and objectives of this study. Elizabeth Gregory was responsible for data preparation, statistical analysis, and the writing of this thesis.

A version of the baseline analyses presented in this thesis (Chapter 1, section 1.1 – 1.3; Chapter 2, section 2.1 – 2.3; chapter 3, section 3.1 – 3.3; chapter 4, section 4.2 – 4.3) has been previously published in the Journal of Affective Disorders.

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All trial participants provided informed consent, and ethical approval of the experimental protocol was granted from the UBC Clinical Research Ethics Board (CREB number H13-02340).

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CHAPTER 1: INTRODUCTION

1.1 Cognitive Dysfunction in Major Depressive Disorder

Major depressive disorder (MDD) is a widely prevalent mood disorder, affecting roughly one in six adults in their lifetime (World Health Organization, 2017). MDD is characterized in the DSM-5 as the presence of either persistent depressed mood or anhedonia (*i.e.* the loss of interest or pleasure in usual activities) lasting for at least a two-week period of time (American Psychiatric Association, 2013). In addition to affective symptoms, the DSM-5 conceptualizes cognitive symptoms as a key symptom domain, with one of the nine criteria for diagnosis being the presence of impaired thinking, concentration, and decision-making (American Psychiatric Association, 2013).

The definition of cognitive impairment in MDD is disputed in the literature, as MDD is not typically associated with severe, widespread impairments in cognitive functions as seen in other psychiatric disorders such as schizophrenia (Rund et al., 2006). Cognitive impairment is typically defined as performance below a certain standard deviation (SD) of a standardized age appropriate average, with definitions ranging from 0.5 to 1.5 (SD) below the population average (Douglas et al., 2018; Douglas, Milanovic, Porter, & Bowie, 2020). Using this method, rates of impairment in MDD samples are typically quite low, despite MDD showing deficits in a number of cognitive domains relative to matched healthy controls (McClintock et al., 2010).

Normative definitions of impairment fail to account for an individual's cognitive abilities prior to the onset of an illness or disorder. As longitudinal data on cognitive performance is often not available for MDD patients, performance on word reading tests, such as the North American

Adult Reading Test (NAART), can be an effective and reliable way of estimating an individual's premorbid abilities, as language functions are not typically affected by neuropsychiatric disorders (Crawford, Deary, Starr, & Whalley, 2001). Previous research on MDD samples has found that accounting for individual differences in cognition using premorbid IQ estimates allows for greater sensitivity in the detection of impairments, and that these scores are more closely aligned with the patient's subjective experience of their cognitive functioning (Douglas et al., 2018; Tran, Milanovic, Holshausen, & Bowie, 2021). In light of this, it may not be accurate to describe cognition in MDD as impaired, given that "cognitive impairment" typically refers to performance relative to the general population. As such, the term "Cognitive Dysfunction" (CD) will be instead by used throughout this paper.

Cognition, the mental process of understanding, acquiring, and applying knowledge, is widely accepted as being comprised of the following broad domains: Executive function and attention, memory, processing speed, and language abilities (Weintraub et al., 2013). MDD is associated with moderate yet broad deficits across all cognitive domains, with the exception of language functions (Douglas, Milanovic, Porter, & Bowie, 2020; Rock, Roiser, Riedel, & Blackwell, 2014).

Executive function encompasses cognitive abilities associated with frontal lobe function and responsible for the control of attention, or the allocation of limited conscious resources to a particular task (Stopford, Thompson, Richardson, Neary, & Snowden, 2010). Executive function is comprised of three separable but correlated functions: updating, shifting, and inhibition (Miyake et al., 2000). Updating functions are necessary to monitor and assess incoming information for its relevance to the task; inhibition allows for the suppression of responses or behaviours irrelevant to the task at hand; finally, shifting is required for attentional engagement

and disengagement when switching between tasks or sub-tasks (Miyake et al., 2000). Studies probing updating, shifting, and inhibition consistently find widespread, significant deficits in MDD patients (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Snyder, 2013; Stordal et al., 2004).

Memory is involved in functions of information encoding, storage, and retrieval. Tulving's monohierarchy postulates that there are three hierarchical levels of memory: procedural, semantic, and episodic (Tulving, 1985). Procedural, the most basic form of memory, involves memories for performing activities; for example, riding a bike or driving a car. Semantic memory is the ability to store and remember concepts such as object categories (*e.g.* animals, plants, furniture), allowing us to create schemas about the world. The third and most complex level is episodic memory, which encompasses memories of specific events rather than general knowledge (Radvansky & Tamplin, 2012). Episodic memory is dependent on the hippocampus, whereas procedural and semantic memory are disassociated with hippocampal functions, instead relying on cortical areas within the temporal lobes (Mishkin, 1997). MDD is associated with deficits specifically in episodic memory (MacQueen, Galway, Hay, Young, & Joffe, 2002), with moderate deficits in recall and recognition reported across studies (den Hartog, Derix, Van Bemmel, Kremer, & Jolles, 2003; Fossati, Coyette, Ergis, & Allilaire, 2002; Fossati et al., 2004; Philip Gorwood, Corruble, Falissard, & Goodwin, 2008; Rock et al., 2014).

Processing speed, also referred to as psychomotor speed, is broadly defined as the time taken to process, and react to, a specific amount of information, essentially reflecting an individual's efficiency when performing a task (Weintraub et al., 2013). Deficits in this domain are moderate in MDD (Rock et al., 2014), and some studies have even suggested that slowed processing speed may mediate the deficits demonstrated in more complex cognitive tasks, *i.e.* memory and

executive functions (den Hartog et al., 2003; Zaremba et al., 2019). However, processing speed tasks are typically impure measures, but rather involve a wider array of cognitive functions including attention and executive processes (Weintraub et al., 2013).

Finally, functions of language require the synchronization of memory functions (knowledge of words, grammatical structure and meaning), sensory input (visual, auditory, and/or tactile processing), and motor output (expressing concepts through verbal, written, or signed communication) to effectively communicate (Price, 2000). Language functions are fairly stable and appear to only be affected with significant neurological changes, such as with neurodegenerative diseases or stroke (Weintraub et al., 2013). In MDD, language does not seem to be significantly impacted, although deficits on verbal fluency tasks have been noted (*e.g.* Fossati, Guillaume, Ergis, & Allilaire, 2003). However, this is thought to be attributed to executive dysfunction, as verbal fluency is a non-specific task involving a number of cognitive domains (Aita et al., 2018; Snyder, Miyake, & Hankin, 2015; Whiteside et al., 2016).

MDD is one of the leading global causes of disability, accounting for more than 8% of global years lost to disability according to an analysis using data from the 2010 Global Burden of Disease study (Ferrari et al., 2013). However, psychosocial and occupational functioning is best predicted not by the severity of affective symptoms, but rather by cognitive functioning (Lam, Kennedy, McIntyre, & Khullar, 2014; McIntyre et al., 2013). CD persists in remitted states of Major Depressive Disorder (Conradi, Ormel, & De Jonge, 2011; Rock et al., 2014). This has been speculated to be a significant contributing factor for patients who are unable to regain premorbid levels of psychosocial functioning even with the remission of mood symptoms (Evans et al., 2013; Lam et al., 2014). Problematically, there are no standard, effective treatments to address CD in MDD (Douglas et al., 2020).

1.2 Cognitive Symptoms: State or Trait?

The origins of CD in MDD give further insight into this debilitating symptom. Thus, an important question is whether CD is a state or trait of MDD. A state characteristic is evident only during depressive symptomology and shows a relationship with symptom severity. On the other hand, a trait characteristic must be associated with the onset of an illness as well as show independence from clinical state. Historically, CD in MDD was associated with disorder state, in that these deficits were considered to be causally related to mood symptoms. Certainly, some aspects of CD in MDD appear to change with mood, the most consistent being psychomotor speed (Douglas & Porter, 2009). Improvements in memory and verbal fluency may accompany remission of mood symptoms (Douglas & Porter, 2009; Lin et al., 2014), although the likelihood of improvement with remission appears to reduce with age (Douglas & Porter, 2009). However, if CD were an epiphenomenon of low mood, a relationship between the severity of mood symptoms and CD would be expected. Interestingly, subjective, but not objective, cognitive complaints, are associated with mood symptom severity (Petersen, Porter, & Miskowiak, 2019). Instead, studies consistently report a lack of relationship between the severity of mood symptoms and CD, suggesting these symptoms may be distinct entities in MDD (McDermott & Ebmeier, 2009; Rock et al., 2014).

Instead, evidence is accruing supporting the notion that CD MDD may be a trait-like feature in MDD. Effects of deficits in psychomotor speed, executive functions, and memory are seen across first-episode patients both in acute and remitted states (Goodall et al., 2018). However, CD in remission could be associated with a multitude of other factors, such as lingering subclinical mood symptoms (Halahakoon, Lewis, Roiser, & Psychiatry, 2019), side-effects of medication (Gregory et al., 2020; S Pu, Noda, Setoyama, & Nakagome, 2018), or comorbid

disorders, such prodromal dementia, that is especially common in elderly depressed populations (Brommelhoff et al., 2009).

On the one hand, the presence of affective symptoms does appear to at least exacerbate CD (Allott, Fisher, Amminger, Goodall, & Hetrick, 2016). CD are related to disease history, with patients in first-episode MDD exhibiting substantially less impairment in comparison to patients with recurrent MDD (Basso & Bornstein, 1999). In both acute and remitted states there is a relationship between the number of past episodes and CD (P. Gorwood, Richard-Devantoy, Baylé, & Cléry-Melun, 2014; Vanderhasselt & De Raedt, 2009). In accordance, Dotson and colleagues (2008) examined cumulative effects of affective symptom severity on cognitive function over a period spanning several decades, finding that these symptoms averaged longitudinally, rather than acute symptomatology at the time of neuropsychological testing, was more closely associated with cognitive functioning.

In addition, the developmental stage during which MDD first presents seems to play an important factor: Affective symptoms in adolescence were associated with later reduced vocabulary abilities in adulthood, even with normal vocabulary abilities in adolescence (Allott, *et al*., 2016). Further, cognitive control appears to be impaired in individuals who develop MDD in adolescence, while normal cognitive control development occurs in individuals who do not develop MDD until adulthood. This suggests that MDD impairs the normal development of cognitive faculties (Allott, *et al*., 2016). Acute depressive episodes have previously been conceptualized as chronic stressors on the brain, which are associated with alterations of core gene expression in both the hippocampus and the prefrontal cortex that compromise both neuroplasticity and functionality (Belleau, Treadway, & Pizzagalli, 2019; Kobrosly, van Wijngaarden, Seplaki, Cory-Slechta, & Moynihan, 2014; Mcewen et al., 2015). Further, in

bipolar patients, chronic stress responses in the brain induced by mood episodes were associated with greater CD (Vieta et al., 2013).

Together, these findings suggest that rather than being a state or trait symptom of MDD, CD might be caused by scarring effects of mood episodes which accumulate over time. Assuming the burden of depressive symptoms is causal in the development of CD, it stands to reason that early, effective interventions for MDD are crucial in preserving cognitive function.

1.3. Cognition and Treatment-Resistant Depression

Despite the vast number of treatments available for major depressive disorder, non-response continues to be a major challenge. Specifically, 30-50% of patients do not respond to first-line treatments (Milev et al., 2016). Thus, a rather large subset of MDD can be considered to have treatment-resistant depression (TRD; Ionescu, Rosenbaum, & Alpert, 2015), which is accompanied by greater rates of disability and disease burden (Lam *et al*., 2014).

TRD is associated with more pronounced CD both during, and after remission of, depressive episodes (Maeshima et al., 2016; Reppermund, Ising, Lucae, & Zihl, 2009). TRD patients typically present with an earlier onset of symptoms (Kornstein & Schneider, 2001), so it is possible that the CD in TRD are related to scarring caused by affective symptoms during critical developmental periods. However, there is a distinct relationship between treatment response and cognition; for example, non-response to antidepressants is associated with worse baseline executive function and attention (Groves, Douglas, & Porter, 2018; Pimontel et al., 2016; M. Vicent-Gil et al., 2018). Furthermore, patients presenting with TRD perform substantially worse

on an array of cognitive tasks, including memory, psychomotor speed, and executive function, compared to patients experiencing first-episode MDD (Basso & Bornstein, 1999; Meijsen et al., 2018; Rao et al., 2019).

Proponents of the cognitive neuropsychological model of depression propose that CD is antecedent to the development of the affective symptoms of MDD, driving negative biases and maladaptive thinking patterns that maintain low mood (*e.g.* LeMoult & Gotlib, 2019). Indeed, there is evidence for CD in unaffected family members of patients (such as in twin studies), suggesting a genetic liability exists (Allott et al., 2016; Douglas & Porter, 2009). Premorbid IQ and the risk of CD are highly correlated, although it is unclear how much this is due to the effects of cognitive reserve, *i.e.* the notion that patients with a higher IQ are less susceptible to cognitive insult caused by disorders (Elgamal, Denburg, Marriott, & MacQueen, 2010). The cognitive neuropsychological model thus suggests that rather than TRD being a risk factor for CD, it would be CD that drives non-response to interventions, resulting in chronic, refractory depression.

In light of this, it is important to note there are several other factors specifically associated with TRD that further differentiate this subgroup from the general MDD population. In addition to aforementioned factors, the most consistent clinical features associated with a greater risk for TRD are the presence of a comorbid anxiety disorder, suicidal ideation, chronicity, melancholic symptoms, and overall depressive severity (Balestri et al., 2016; Bergfeld et al., 2018; Kautzky et al., 2019; Murphy, Sarris, & Byrne, 2017). Critically, these features are also associated with worse cognitive functioning, rendering the disentanglement of the relationship between treatment-resistance and CD challenging (Basso et al., 2007; Philip Gorwood et al., 2008; McDermott & Ebmeier, 2009; Shenghong Pu, Setoyama, & Noda, 2017; Zaninotto et al., 2016).

1.4 Neurobiology of Cognitive Dysfunction in Treatment-Resistant Depression

According to Menon (2011), many psychiatric and neurological disorders can be conceptualized as network-based disorders, rather than caused by the aberrant activity of discrete brain regions. There are three primary large-scale brain networks, being the default mode network (DMN), the central executive network (CEN), and the salience network (SN) (Bressler & Menon, 2010). The triple network hypothesis posits that aberrant activity within and between the three large-scale brain networks is the source of psychopathology in a number of disorders, including mood-based disorders such as MDD, as well as psychotic, anxiety, developmental and neurodegenerative disorders (Menon, 2011).

The DMN (primary nodes: the ventromedial prefrontal cortex and the posterior cingulate cortex) is active primarily during periods of rest and relaxation as well as self-referential processes and deactivates during engagement in cognitively demanding tasks (Bressler & Menon, 2010; Qin & Northoff, 2011). In contrast, the CEN (primary nodes: the dorsolateral prefrontal cortex and the posterior parietal cortex) is most active during cognitively demanding tasks involving attentional control and task monitoring (Seeley et al., 2007). The DMN and CEN typically show anticorrelated activation, in line with their opposing functions (Bressler & Menon, 2010). Finally, the SN (primary nodes: the anterior insula and the anterior cingulate cortex) is responsible for detecting and orienting towards personally salient and rewarding stimuli, essentially serving as a switch between the former two networks (Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008).

As per the triple network theory, all three large-scale networks are implicated in MDD (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). MDD may be thought of as a DMN-

dominant disorder, with hyperconnectivity thought to be a source of affective symptoms, including rumination, negative self-perception, and hopelessness (Anderson, Hoy, Daskalakis, & Fitzgerald, 2016). While the CEN and DMN are considered to be opposing networks, anti-correlation of the two is less pronounced in MDD patients, whom tend to show DMN dominance over the CEN. Furthermore, abhorrent switching between the DMN and CEN is hypothesized to contribute not only to the affective symptoms, but also to the CD associated with MDD.

The dorsolateral prefrontal cortex (DLPFC), one of the two primary CEN nodes, is of particular interest, as this brain region shows consistent hypoconnectivity during resting state in MDD (*e.g.* Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Koenigs & Grafman, 2009; Liston et al., 2014). As part of the CEN, the DLPFC plays an important role in executive functions (Miller & Cohen, 2001), and MDD have also demonstrated DLPFC hypoactivation during working memory tasks (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). It is also speculated that the DLPFC plays a role in cognitive control, which may contribute to the reduced emotional regulation associated with MDD (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011).

While relatively few studies have examined large-scale network connectivity in TRD patients, as opposed to more general MDD populations, there is evidence that TRD patients show the same aberrant connectivity patterns, albeit with a greater degree of disturbance compared to non-TRD patients (de Kwaasteniet et al., 2015). Furthermore, Ge *et al*. (2019) found evidence of hyperconnectivity between the DLPFC, amongst other CEN nodes, and the hippocampus (involved in DMN functions), which was associated with memory deficits in TRD patients. In all, this suggests that the DLPFC plays an important role in the CD associated with TRD.

1.5 Addressing Cognitive Dysfunction: Pharmacological and Non-Pharmacological Interventions

While the underlying cause of the relationship between TRD and CD is not clear-cut, successful treatment of cognitive symptoms in TRD could aid in achieving improved functionality. The burden of disease is elevated in TRD compared to MDD due to greater functional impairment, which appears to be mediated by CD (Gupta et al., 2013). Remission of cognitive symptoms may be key to achieving full remission in TRD (Bortolato et al., 2016). It is thus of high importance to investigate potential therapies for cognitive symptoms in TRD.

Currently, therapies exist for CD in MDD, although their efficacy is inconsistent across studies. Conventional pharmacological treatments for MDD, such as selective serotonin reuptake inhibitors (SSRIs), show modest effect sizes in improving cognition in MDD, although it is unclear whether cognitive changes are due to improvements in affective symptoms (Listunova et al., 2018). Of note, patients who have more pronounced CD, particularly in domains of executive function, show poor response to SSRIs; potential improvements in cognition from SSRIs may not benefit those that are most in need of treatment for these symptoms (Groves et al., 2018). Additionally, SSRIs are not infrequently accompanied by unfavourable side effects, further reducing the number of patients that may be able to seek this treatment for cognitive complaints (Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016). Novel treatments specifically for CD, such as vortioxetine, have demonstrated clinical efficacy, however these medications carry side effect profiles similar to SSRIs, and long-term safety and tolerability are unknown to date (Kelliny, Croarkin, Moore, & Bobo, 2015).

Unconventional pharmacological treatments, such as erythropoietin, insulin, and antibiotics, have been investigated as potential treatments for CD, although investigations are preliminary and inconclusive (Bortolato et al., 2016). Non-pharmacological interventions, such as physical exercise and cognitive remediation therapy (CRT), on the other hand, are not accompanied by the same tolerability issues as SSRIs, and while studies report benefits of both on cognition in MDD, these reports are inconsistent, potentially due to variability in methods and a lack of standardization of protocol across studies (Listunova et al., 2018). In the case of CRT, ecological validity is questioned, as gains made in training do not necessarily transfer to other cognitive domains or improve real-world functioning (Morimoto, Manning, Kim, & Cote, 2018). Furthermore, as both treatment options are time-intensive, treatment adherence is often low, particularly in TRD (Helgadóttir, Hallgren, Kullberg, & Forsell, 2018; Preiss, Shatil, Cermakova, Cimermannova, & Flesher, 2013).

1.6 Addressing Cognitive Dysfunction: Repetitive-Transcranial Magnetic Stimulation

Alternatively, neuromodulation techniques have been proposed in recent years as a tool to treat CD in TRD. Repetitive transcranial magnetic stimulation (rTMS) therapy is a relatively novel yet effective treatment for TRD (Leggett et al., 2015), with response and remission rates of roughly 50-60% and 30-40%, respectively (Milev et al., 2016). The underlying neurobiological mechanisms of action of rTMS are not fully elucidated but preconditioning the stimulation target and related synaptic pathways is hypothesized to induce long-term potentiation (LTP) at high frequency stimulation rates (Morimoto et al., 2018). Notably, compared to other effective stimulation therapies for TRD, such as electro-convulsive therapy (ECT), rTMS is not

accompanied by cognitive side effects (Schulze-Rauschenbach et al., 2005), and may even improve cognitive functioning in TRD (Serafini et al., 2015).

High frequency rTMS is typically delivered over the left dorsolateral prefrontal cortex (DLPFC). As the DLPFC is a node of the CEN, excitatory stimulation of this region is purported to rebalance large-scale network interactions, namely reversing the DMN dominance over the CEN typically evident in depression (Anderson et al., 2016). In healthy individuals, stimulation of the left DLPFC using rTMS has been shown to enhance working memory (Bagherzadeh, Khorrami, Zarrindast, Shariat, & Pantazis, 2016). As hypoactivity of the DLPFC is implicated in CD in TRD, stimulation of this region could alleviate cognitive symptoms in this patient population (de Kwaasteniet et al., 2015; Ge, Downar, et al., 2019; Menon, 2011).

A recent systematic review by Martin *et al*. (2016) of sham-controlled rTMS investigated left DLPFC stimulation effects on CD in depression. The authors report modest gains in performance on the trail-making test, which measures processing speed and executive functions of attentional shifting. This test is sensitive to frontal lobe dysfunction (Stuss & Levine, 2002), suggesting that rTMS may elicit beneficial functional changes related to cognition. Martin and colleagues report that cognitive gains due to rTMS were independent of improvements in mood symptoms, however it is unclear whether this is due to true lack of relationship or if gains in cognition and mood occur along different time-courses with rTMS. Further, several studies included in the review measured cognition immediately following rTMS; thus, whether rTMS can invoke long-term cognitive changes remains unclear. Lastly, because this review did not focus on TRD, but rather investigated cognitive changes due to rTMS in MDD overall, it is unclear how the findings translate to the TRD subtype.

Unfortunately, research on the use of rTMS as a treatment for CD in TRD is similarly inconclusive. A systematic review of 22 studies investigating cognitive changes after rTMS in TRD by Serafini and colleagues (2015) found that the majority reported variable cognitive gains in domains of psychomotor speed, attention, verbal fluency, executive function, and working memory from rTMS treatment. The authors, however, noted flaws in the methodology of many of the studies, such as inadequate control groups and/or statistical power, thus bringing the role of practice effects and expectation into question. Furthermore, only eight studies included in the review stimulated the left DLPFC, although six of those investigating this protocol revealed promising cognitive improvements.

Looking at individual studies of rTMS treatment and CD in TRD, a majority of those that report positive results tend to be missing control groups for which to compare cognitive gains against (*e.g.* Holtzheimer et al., 2010; Martis et al., 2003; Pallanti et al., 2012). Another important aspect of study design to consider is when cognitive assessment occurs in relation to rTMS delivery. rTMS is known to exert acute, transient effects on cognition (Luber & Lisanby, 2014), and it is thus important to determine whether measured improvements in cognition are transient or enduring. In contrast, the majority of studies report cognitive testing on the same day as the final treatment session, with only a handful of studies measuring cognitive function between 3 days to 3 months following the final treatment session (P. Holtzheimer et al., 2010; Martis et al., 2003; Nadeau et al., 2014; Schulze-Rauschenbach et al., 2005).

Variation in stimulation intensity, frequency, and number of treatments, all parameters which may alter the ability of rTMS to exert positive changes in cognition, pose a challenge when generalizing the results of individual studies (Trevizol & Blumberger, 2019). At least 20 daily sessions of rTMS stimulation of either 10Hz or intermittent theta burst stimulation (iTBS) to the left DLPFC at 120%

of an individual's motor threshold (MT), determined by the minimal stimulation intensity needed to elicit visual observation of a thumb twitch with motor cortex stimulation, has been shown to produce optimal results for MDD (Trevizol & Blumberger, 2019). Sub-optimal parameters may be responsible for negative results; for example, Nadeau and colleagues report no cognitive improvement; however, only 10 daily sessions were delivered, using 5Hz stimulation to the left DLPFC at 100% MT (2014).

Given the shortcomings of studies investigating the cognitive benefits of rTMS to date, whether or not rTMS is an efficacious treatment for CD in TRD remains an open question. Studies employing optimal rTMS parameters are necessary in order to determine whether or not an adequate course of rTMS over the left DLPFC alleviates the symptom of CD in TRD. Control groups are additionally necessary to address the issue of practice effects. Finally, understanding whether cognitive effects of rTMS are enduring, or whether improvements are due to acute, transient effects of stimulation, is essential to determining the utility of this treatment for cognitive symptoms in TRD. All studies to-date which have investigated cognitive benefits of rTMS to the left DLPFC in patients with a primary diagnosis of treatment-resistant depression are summarized in Table 1.6.1.

Table 1.6.1 Summary of studies investigating cognitive changes from rTMS to the left DLPFC in patients with treatment-resistant depression.

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Avery et al., 2006	66 unipolar TRD outpatients (33 active, 33 sham). Failed to respond to at least 2 AD.	20 daily sessions of 10 Hz stim to the left DLPFC. 110% MT.	RAVLT, WAIS intelligence, TMT A/B, COWA, GOAT (attention/goal orientation)	Baseline, treatment completion.	No significant differences in neurocognitive outcomes between the two groups	Sham-controlled.
Blumberger, 2012	74 TRD inpatients (19 left, 24 bilateral, 18 sham).	15 daily sessions of 10Hz for left DLPFC, 1Hz for right DLPFC. 100% MT for people under 60, 120% MT for people over 60.	RBANS, Hopkins verbal learning (HVLT), brief visual memory test, grooved pegboard test	At baseline and treatment completion.	No significant changes between three groups on cognitive measures. Greater improvement in remitters compared to non, but not statistically significant.	Sham-controlled.
Concerto, 2015	30 TRD outpatients (15 receiving HFL, 15 receiving sham)	20 daily sessions, 10 Hz stimulation to the left DLPFC at 120% MT.	Frontal assessment battery, Stroop colour-word test	Baseline, end of rTMS treatment, 3 months post-treatment, 6 months post-treatment	HFL group showed significantly better performance at end of treatment, but this improvement was no longer evident at 3- and 6-month follow-ups.	Sham-controlled.
Corlier 2020	77 TRD outpatients (failed at least 3 AD trials)	30 daily sessions, 10 Hz stimulation of left DLPFC at 120% MT.	Stroop task accuracy and reaction time	Not specified	Improvement in accuracy greatest for older responders.	None.

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Fiztgerald, 2009	27 TRD outpatients (16 receiving HFL, 11 receiving LFR)	15-20 daily sessions, 110% MT; HF = 10 Hz (left DLPFC), LF = 1 Hz (right DLPFC),	Brief visuospatial memory test, Hopkins verbal learning test, COWA, digit span	Baseline, week 3 (after 15 treatments), week 4 (after 20 treatments).	Improvement in immediate verbal memory, verbal fluency. Unrelated to stimulation site.	Double-blind HFL versus LFR but no differences between the groups. No sham condition.
Galletly, 2016	63 TRD patients (in/outpatient status not reported)	18-20 treatments either 3 or 5 days per week, bilateral stimulation (10Hz to left DLPFC, 1 Hz to right DLPFC), 110% MT	IntegNeuro cognitive battery (assesses sensorimotor, verbal/language, memory, executive planning, attention)	Baseline, after final rTMS treatment	Improvement in visual memory, which was no longer significant when change in depressive symptoms were added as a covariate	None.
Hausmann, 2004	41 unipolar & bipolar inpatients (12 left DLPFC; 13 left then right; 13 sham).	10 daily sessions of 20Hz to left DLPFC at 100% MT, 1Hz to the right DLPFC at 120% MT.	German equivalent of CVLT, TMT A/B, Stroop test, CO)WA.	At baseline, day 14 (following last treatment).	Improvement in Stroop, TMT A and B, in rTMS groups compared to control. Trend for COWA improvement too. Significant group by time effect for CVLT encoding. CVLT improvement was associated with mood improvement.	Sham-controlled.

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Holtzheimer, 2004	15 TRD outpatients (7 rTMS, 8 sham). failed at least 2 AD trials. Out/inpatient status not reported.	10 daily sessions 10HZ to the left DLPFC. 110% MT.	RAVLT, digit symbol, digit span, Stroop test.	Screening, baseline, and after final rTMS.	Subjects receiving rTMS showed greater improvement in RAVLT delayed recall trial compared to sham	Sham-controlled.
Holtzheimer, 2010	14 TRD inpatients (failed at least 1 AD trial).	15 sessions over the span of 2 days. 10 Hz left DLPFC	RBANS full testing battery	Before treatment, 1 day after, 3 weeks after, 6 weeks after treatment completion.	Improvement at 6 weeks in RBANS total score.	Sham-controlled.
Hoy, 2012	137 TRD failed to respond to at least 2 AD. Out/inpatient status not reported.	20-30 daily sessions to right, left, or bilateral DLPFC. 1 Hz right, 10 Hz left. 100% MT for left.	Digit span, HVLT, BVMT, COWA	Baseline, after either 2 or 3 weeks rTMS, and at end of rTMS treatment	Depression improvement associated with improvement in immediate visuo-spatial memory. Improvements in WM and verbal fluency	None.
Kedzior, 2012	10 TRD outpatients, 8 healthy volunteers.	20 daily sessions, 10 Hz stimulation of left DLPFC at 100% MT.	RBANS full testing battery, modified concept-shifting task (mCST)	Daily testing before and after rTMS (40 in total) for the mCST, before the first and after last rTMS treatment for RBANS	Improvement in RBANS immediate memory, as well as mCST	Healthy volunteers (not matched to patients)

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Loo, 2001	18 MDD (9 rTMS, 9 sham). Out/inpatient status not reported.	10 daily sessions of 10Hz rTMS to left DLPFC at 110% MT. additional 10 sessions same protocol in open-label following.	RAVLT, COWA, tower of London, autobio memory interview, digit span (forward), visual paired associates learning.	At baseline, after 10 sessions blind and after 10 sessions open label.	Trends for improvement in neuropsych performance but no different between sham and rTMS groups.	Sham-controlled.
Loo, 2003	19 TRD (9 rTMS, 10 sham) unipolar non-TRD. 4 inpatients, 15 outpatients. Excluded patients who had failed more than 2 AD trials.	20 sessions of twice daily rTMS in in blind phase. Extra 4 weeks open label phase (once daily). 10Hz stim to left DLPFC at 110% MT.	RAVLT, TMT A/B, digit span, COWA,	At baseline, weekly during blind phase, and after 4th week (2 weeks after blind phase completion).	No improvement in neuropsych test scores for active group – worsening for TMT A in active group compared to sham at 2 week; no differences at 4 week.	Sham-controlled.
Martis, 2003	15 TRD (both unipolar and bipolar). Out/inpatient status not reported.	10-12 rTMS sessions over 2-4 weeks. 10 Hz left DLPFC at 110% MT.	Information processing speed task, Stroop, COWA, letter number span, Weschler memory scale, mental alternations; NART; grooved pegboard, squire test	Day before or morning prior to first rTMS, and 3 days after last rTMS.	Improvements in working memory, objective memory, fine motor speed	None.

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
McDonald, 2006	62 outpatient TRD with severe resistance (average of 8 failed AD trials; 12 sham, 25 left then right, 25 right then left).	10 daily sessions of 10 Hz to the left DLPFC + 1 Hz to right DLPFC at 110% MT.	BVMT, RBANS, COWA	At baseline and after final treatment.	No effects related to group on cognitive performance.	Sham-controlled.
McLoughlin, 2007	46 TRD inpatients (24 = rTMS, 22 = ECT)	15 daily sessions of 10 Hz stim of left DLPFC. 110% MT.	Digit span, autobiographical memory interview, TMT A/B, symbol digit task, pegboard task	Baseline, after treatment.	No difference between rTMS and ECT on neurocognitive outcomes	ECT group
Mosimann, 2004	24 elderly (>40 years, mean age 62) outpatient TRD (15 rTMS, 9 sham) Failed to respond to at least 2 AD	10 daily sessions, 20 Hz stimulation of left DLPFC at 100% MT.	VLT, TMT A/B, Stroop, COWA	Baseline and after last rTMS session.	No differences in cognitive gains between the rTMS and sham group.	Sham-controlled.
Nadeau, 2014	48 outpatients with moderate-severe TRD (18 left, 16 right, 14 sham)	10 daily sessions, 5 Hz stimulation of left DLPFC at 100% MT	Boston naming test, block design subtest of Wechsler, Stroop, TMT B, COWA, CVLT, PASAT	Immediately post-treatment, 1 month, 3 months	Left side stimulation was not beneficial to cognition, and if anything, was associated with worse cognitive performance compared to sham.	Active right (same parameters as left), sham-controlled (right and left).

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Ozcan, 2020	30 TRD inpatients	20-30 daily sessions of 20 Hz rTMS to the left DLPFC. 100% MT.	Cambridge gambling test, stop signal test, internal/external dimensional change	Baseline and following final rTMS treatment	No significant changes in performance	None.
Padberg, 1999	18 inpatient TRD (6 in each group).	5 daily sessions of rTMS to the left DLPFC. Either 10Hz, 0.3 Hz, or sham. 90% MT.	Verbal learning and memory task.	Prior to first rTMS and on same day following last rTMS.	Improvements in verbal memory after 10Hz.	Low frequency stimulation group, sham-controlled.
Rosa, 2006	35 unipolar TRD (20 rTMS, 15 ECT). Failed to respond to at least 2 AD. Out/inpatient status not reported.	20 daily sessions of 10 Hz stimulation to the left DLPFC. 100% MT.	WAIS intelligence, digit span, rivermead behavioural memory test	Baseline, after 2 weeks Tx, after 4 weeks (Tx completion).	No significant differences in neurocognitive outcomes between the two groups.	Compared to ECT.
Schulze-Rauschenbach, 2005	30 TRD (16 rTMS, 14 ECT), 15 healthy controls. Out/inpatient status not reported.	10 daily sessions of 10Hz stim to the left DLPFC. 100% MT.	AVLT, memory for persons test, autobio memory test, four-card task (from rivermead behavioural mem test), TMT A/B, digit span, letter-number span, word fluency	Baseline, ~1 week after last treatment.	Improvement in learning and memory functions for rTMS group relative to ECT group, but not relative to controls.	ECT group.

First author, year	Sample	Stimulation Parameters	Cognitive Tests	Testing timeline	Findings	Comparator group
Tovar-Perdomo, 2017	24 TRD outpatients.	20 twice daily sessions of 10Hz to the DLPFC. 120% MT.	Iowa Gambling Task, balloon analog risk task, game of dice task, Stroop colour/word task, continuous performance task, stop-signal task	Baseline, within 1 week after last treatment	No changes in performance on any tasks.	None.
Vanderhasselt, 2009	15 TRD, inpatients and outpatients.	10 daily sessions 10 Hz stimulation of left DLPFC. 110% MT.	Task-switching paradigm (not validated)	Baseline and after the 2 week treatment course.	improvement in motor speed, task switching associated with treatment response	Crossover sham-controlled.
Wajdik, 2014	68 (35 rTMS, 33 sham) TRD. Out/inpatient status not reported.	15 daily sessions 10Hz stimulation of left DLPFC. 110% MT.	RAVLT, digit symbol, digit span, TMT A/B, COWA, logical memory (Wechsler), Stroop	Twice before rTMS; immediately following each of the 15 treatments.	No significant difference in rTMS versus sham.	Sham-controlled.

1.7 Thesis Objectives

The aims of this thesis are two-fold: firstly, to characterize CD in patients with TRD, and secondly, to determine whether an adequate course of repetitive transcranial magnetic stimulation is associated with enduring cognitive benefits in TRD. To address these goals, I used data from the THREE-D study, a clinical trial investigating the non-inferiority of two repetitive transcranial magnetic stimulation protocols (Blumberger et al., 2018a). Neuropsychological assessments were performed at baseline and at three months post-treatment follow-up for patients as well as in a sample of demographically matched healthy volunteers.

For the first aim, we hypothesized that patients would present with global CD relative to healthy controls. Further, we hypothesized that CD would present heterogeneously in patients; that is, distinct subgroups of patients could be identified based on cognitive performance.

For the second aim, we hypothesized that rTMS treatment would be associated with gains in domains of executive function. Furthermore, we hypothesized that these improvements would be independent from antidepressant response to the treatment.

CHAPTER 2: METHODS

2.1 General Methods

Participants

62 TRD patients and 43 age-, sex-, and premorbid IQ-matched HVs were recruited as part of two randomized clinical trials, in which patients with TRD were assigned to receive either intermittent theta burst stimulation (iTBS) or high frequency left (HFL) rTMS protocols to the left DLPFC (Blumberger et al., 2018a). Patient inclusion criteria included a confirmed primary diagnosis of MDD, outpatient status, and a Hamilton Rating Scale for depression score (HRSD-17; Hamilton, 1960) of ≥18. MDD diagnosis was confirmed by a trained rater using the Mini International Neuropsychiatric Interview (MINI) assessment (David V. Sheehan et al., 1998). TRD was defined as failing to achieve a clinical response to at least 1 adequate antidepressant trial in the current episode, or as being unable to tolerate at least two separate antidepressant trials.

HV were included if they had no history of Axis I or Axis II disorders as determined by the Mini International Neuropsychiatric Assessment (Sheehan et al., 1998), and excluded if they had a lifetime diagnosis of psychiatric disorder; a history of mood disorders or psychosis in first-degree relatives; a history of substance dependence within the last 3 months; had a significant neurological condition or a major unstable medical illness.

The complete inclusion and exclusion criteria for both trials are outlined in supplement Appendix A.

The trials were registered in ClinicalTrials.Gov, identifier NCT02800226 and NCT0188778229. All participants provided informed consent and both experimental protocols were approved by both the UBC Clinical Research Ethics Board as well as the Vancouver Coastal Health Research Institute.

Demographic and clinical characteristics

Demographic characteristics collected for all participants included age, sex, number of years of education, and estimated premorbid IQ.

For patients, the following additional variables were collected once at screening: length of current depressive episode, number of years with depression, anxiety disorder comorbidity, antidepressant treatment history form (ATHF) score, antidepressant equivalent dose, and benzodiazepine equivalent dose. The MINI assessment was used to identify anxiety disorder comorbidities. ATHF score provides an objective measure of antidepressant treatment trial adequacy in the current episode as described by Oquendo and colleagues (2003). Given the variability in antidepressant dosage, dose equivalence is necessary for accurate comparisons of pharmacotherapy. Escitalopram dose equivalents were calculated using previously defined ratios from the literature (Colvard, 2014; Y. Hayasaka et al., 2015; Inada & Inagaki, 2015). Use of benzodiazepines was limited to 2mg or less of lorazepam or equivalent dose as per study protocol.

Repeat psychiatric assessments were performed at baseline and at 3 months post-treatment, including the following measures: The HRSD-17 (Hamilton, 1960), the Sheehan Disability Scale (SDS; Sheehan, Harnett-Sheehan, & Raj, 1996), the Perceived Deficits Questionnaire (PDQ;

Sullivan, Edgley, & Dehoux, 1990), and the Brief Symptom Inventory anxiety subscale (BSI-A; Derogatis & Melisaratos, 1983).

Neuropsychological assessment

A neuropsychological assessment was conducted at baseline and at 12 weeks post-treatment follow-up. The assessment was performed by trained research personnel supervised by a senior clinician-researcher and registered clinical neuropsychologist (IT). All participants were required to be fluent in English, assessed using a language questionnaire. This was indicated by participants reporting English as their primary language or else reporting a preference for English language use in the majority of the items on the questionnaire.

The North American Adult Reading Test (NAART) was included as an estimate of premorbid IQ (Blair & Spreen, 1989). The Rey Verbal Learning Test (RAVLT) was administered to measure verbal learning and memory (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). An alternate version of the task was administered at follow-up to minimize practice effects (Strauss e*t al*., 2006). Four tests were used to assess domains of executive function. 1) The Size Judgment Span (SJS) task, shown to be analogous to the digit span task (Cherry, Elliott, & Reese, 2007) was administered as a measure of working memory. 2) The Trails Making Test (TMT) parts A and B were administered as measures of attentional shifting (Heaton *et al*., 2004). 3) The Controlled Oral Word Association (COWA) test, version FAS at baseline, and version CFL at follow-up, was used as a measure of verbal fluency. 4) The Stroop test was administered as a measure of executive functioning involving inhibition (Golden, 1978). All measures of executive function were selected

on the basis that they have been shown to be which impaired in depression (Snyder, 2013; Strauss et al., 2006).

As premorbid IQ is a stable trait, the NAART was only administered at baseline (Strauss *et al*., 2006). The other tests (*i.e.* RAVLT, SJS, TMT, Stroop, COWA) were delivered both at baseline and follow-up, in the same order, with alternate forms for select tests known to be most susceptible to practice effects; namely, an alternate word list was used for the RAVLT test at follow-up, and two separate versions of the COWA test were used at baseline (version FAS) and follow-up (version CFL).

Neuropsychological Scoring

All baseline and follow-up test scores, except for the SJS, were converted to z scores using normative data obtained from either *A Compendium of Neuropsychological Tests* (Strauss et al., 2006), the Heaton norms (Heaton et al., 2004), or from the appropriate test manuals (Golden, 1978). For the SJS, normative data was not available for the age group used in the study, so HV data were used as the normative data to convert raw scores into z scores. Using the Shapiro-Wilk test, the SJS data was not normally distributed for any of the groups being tested ($p<0.05$), however both patients and controls' SJS histograms showed similar distribution and groups were matched for sex, age and premorbid IQ, and thus this was judged to be an acceptable method to obtain normative group for Z score computation.

For the RAVLT test, we chose to include the total score (sum of trials 1-5) as a learning and memory indicator, and the delayed recall score (trial 7) as a delayed memory indicator, and exclude all other trials (*i.e.* trial 6, distractor list, and recognition trials). Trials 1-5 and trial 7 are

the most reliable measures whereas the other measures have low reliability, particularly when interpreting differences between scores (Strauss *et al*., 2006).

When considering only baseline scores, RAVLT subtests showed high levels of collinearity ($r>0.80$). For this reason, RAVLT trials 1-5 was the chosen subtest due to the greater reliability and external validity associated with this subtask as well as larger effect sizes previously noted in these cognitive domains in MDD samples (Strauss *et al*., 2006). RAVLT trial 7 was excluded from analysis. Six domains were thus assessed: working memory (SJS), learning and memory (RAVLT 1-5), speeded attention (TMT part A), task switching (TMT part B), verbal fluency (COWA FAS/CFL), and inhibitory control (Stroop Colour/Word Trial).

For the effects of rTMS treatment, seven domains of cognitive performance were assessed: working memory (SJS), learning and memory (RAVLT trials 1-5), delayed memory (RAVLT trial 7), speeded attention (TMT part A), task switching (TMT part B), verbal fluency (COWA FAS/CFL), and inhibitory control (Stroop Colour/Word Trial).

Cognitive performance adjusted by individual IQ

A common challenge in interpreting neurocognitive scores is that a patient's individual potential is not typically taken into account. Normative scores indicate an individual's performance relative to the general population (often stratified by factors such as age, sex, or educational attainment). However, this method fails to take into account an individual's cognitive potential, where the subject's neuropsychological performance may be considered normal with respective to normative datasets, whereas their scores are far below what would be expected when taking premorbid cognitive functioning into account (Douglas et al., 2020). For example, a patient may have a z

score of 1 on a cognitive test, which by normative standards is intact cognitive performance. However, if the individual had achieved a Z score of 2 on the test in their premorbid state, this denotes a clear deficit in their cognitive performance that would not be captured by simple normative scoring.

Longitudinal neuropsychological data, especially premorbid performance, is often not available. Instead, IQ scores derived from word-reading tests are a useful proxy measure for premorbid ability, as ability in these tasks are not typically affected by neuropsychiatric conditions (Crawford et al., 2001).

To explore the effects of normative versus individualized definitions of CD, wwe created individualized IQ-adjusted scores (iIQAS). Aall z scores created with the use of normative data (*i.e.* all scores except from the SJS task), were transformed using methods outlined by Douglas *et al*. (2018). For each subject, their premorbid IQ was subtracted from their test score. For example, a subject scoring 1 on a cognitive test, with an IQ z score of 2, would have an IQ-adjusted test score of -1 on that particular test. In contrast to normative scoring, the iIQASs ascertain how close or far a given individual is from their optimal cognitive potential. The reference point for the Z score is not the population, but rather a hypothetical distribution of likely values for each individual based around their estimated premorbid abilities.

Statistics

All statistical analyses were performed using R, version 3.5.1, unless otherwise specified.

2.2 Cognitive Dysfunction at Baseline: Normative versus Individualized Definitions of Impairment

Demographic variables for TRD and HV were compared using t-tests for continuous variables, or chi-squared tests for discrete variables, namely age, estimated premorbid IQ, highest level of education, and sex.

To compare the effects of normative (norm-adjusted scores; NAS) versus individualized (iIQAS) on differences in performance between TRD and HV, the percent change between each subject's normative and iIQAS were calculated for all tests except for the SJS, since this score was not created using normative data. To calculate percent change, scores were first converted to T scores, and the following equation was used:

$$\frac{\text{iIQAS - NAS}}{\text{NAS}} \times 100\%$$

Independent sample t-tests with FDR correction were performed to compare the mean change in these scores between TRD and HV.

Two multivariate analyses (MANOVAs) were then carried out to compare the TRD and HV groups, one using NAS, and one using iIQASs. Dependent variables were z scores on the 1) SJS, 2) COWA FAS, 3) RAVLT trials 1-5, 4) TMT part A, 5) TMT part B, and 6) Stroop colour-word trial.

All MANOVA assumptions were checked prior to the analysis. Box's M test was used as a preliminary test of the homogeneity of variance-covariance matrices. Homogeneity of variance was not rejected at significant levels ($p>0.05$). Multivariate normality was not violated according

to a Shapiro-Wilks test of normality for any of the neuropsychological measures in either testing condition, ($p>0.05$), except for the SJS, which was discussed in the section above. No multivariate outliers were identified after determining each participant's Mahalanobis distance. The assumption of linear relationships among dependent variables was tested by examining scatterplots between all pairs of DVs through SPSS PLOT. All relationships between DVs were significantly correlated except the SJS and TMT scores, with a Pearson's $r = 0.154$, and with a p value of $p=0.063$; there was not a significant linear relationship between the SJS and Trails B, but the linear assumption was not severely violated for this sample. No tolerance scores were significant ($p>0.05$), indicating that the assumption of absence of multicollinearity and singularity was not violated.

2.3 Cognitive Dysfunction at Baseline: Heterogeneity in Patient Sample

As the use of iIQAS yielded larger differences between TRD and HV, these scores were used for all further analyses (baseline cluster analysis and rTMS changes).

To determine subgroups within TRD based on cognitive performance, a K-mean cluster analysis was performed with the five cognitive z scores as the clustering variables. The optimal number of clusters for the TRD sample was found to be 2 using the Calinski-Harabasz index (maximum number of iterations set to 10), which evaluates the cluster validity based on the average between- and within-cluster sum of squares. See Figure 2.2.1 for CH index evaluation of cluster validity. Cognitive performance between the subgroups was compared using analysis of variance (ANOVA).

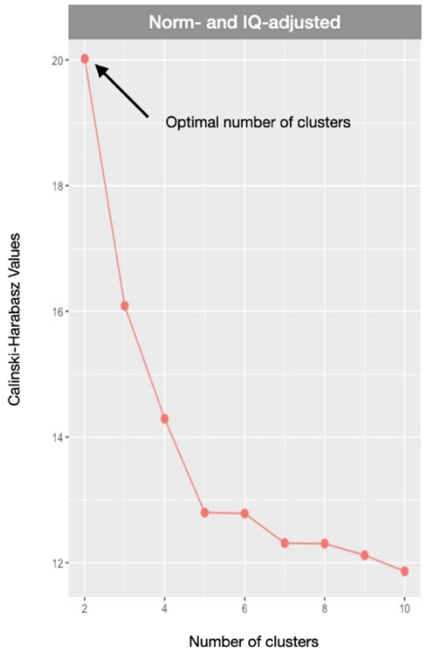

Figure 2.3.1 Calinski-Harabasz values for k number of clusters.

A binary logistic regression was performed to assess the demographic and clinical factors associated with cognitive function, using cluster membership as the dependent variable. Predictors were loaded using a forward loading likelihood ratio model as follows: age, highest level of education, estimated premorbid IQ based on NAART score, number of years with depression, length of current episode in months, ATHF score, HRSD score, SDS score, PDQ score, antidepressant dose (in mg), benzodiazepine dose (in mg), and CRP levels (in mg/L). Sex, presence of an anxiety disorder comorbidity, and lifetime diagnosis of PTSD were loaded into the model as factors. BSI-A was not included in the binary logistic model as it demonstrated a high degree of multi- collinearity with HRSD ($p = .001$). Anticonvulsant, antipsychotic, and lithium pharmacotherapy use were not included as the number of patients taking these medications were low, and counts did not differ significantly between the two clusters (see Table

2.2.1). A Box Tidwell test indicated that the relationship between continuous predictors and the log odds was linear ($p>0.05$ for all predictors).

Post-hoc path analyses (PROCESS macro for SPSS, version 3.4; Hayes, 2012) were performed to further characterize the mediation effects of significant predictors on the relationship between clinical variables that had shown an association with cognitive performance but did not load onto the logistic regression model as predictors.

Table 2.3.1 Counts of patients receiving pharmacotherapy

	IQ-adjusted clusters		
	Global impairment	Selective Executive Dysfunction	χ^2
Pharmacotherapy	(n = 34)	(n = 26)	
Benzodiazepine	13	2	**7.33****
Anticonvulsant	4	5	0.64
Antidepressant	20	18	0.69
Antidepressant combination	8	5	0.00
Antipsychotic augmentation	6	3	0.43
Lithium augmentation	3	1	0.59

2.4 Assessing the Effects of rTMS on Cognition

rTMS treatment

Treatment parameters were previously reported with clinical trial outcomes; see Blumberger et al. (2018) for a detailed description.

In brief, patients were randomized to receive either 10 Hz or intermittent theta burst (iTBS) stimulation. Patients received 20 to 30 daily treatments over the course of 6 weeks (5 daily treatments per week). For 10Hz rTMS, patients received stimulation at 120% resting motor threshold (RMT) intensity, 10 Hz frequency, with 3000 pulses delivered per session (duration: 37.5 minutes). For iTBS, patients received stimulation at 120% RMT, triplet 50Hz frequency, with 600 pulses delivered per session (duration: 3 minutes).

Missingness

13 of the 60 patients were lost to the three-month follow-up, leaving 47 patients that were measured at both timepoints. To explore factors associated with adherence, independent samples t-tests or chi-squared tests were conducted comparing adherers and non-adherers on a number of baseline variables, including clinical, cognitive, and demographic factors (See table 2.4.1). The only variable that was significantly different between the two groups was education, where adherers were more highly educated compared to those that were lost to follow-up.

To ensure that missingness was not associated with treatment outcome, we also assessed frequency of response and remission, as measured at the final rTMS treatment, of adherers and non-adherers. There was no difference in response to treatment, indicating that loss to follow-up was not related to treatment outcome.

Given that there appeared to be no systematic differences between adherers and non-adherers, a complete-case-analysis approach was used (Mukaka et al., 2016), where patients lost to follow up were excluded from analysis.

Table 2.4.1 Relationship between study completion and clinical, cognitive, and demographic variables.

Demographic or clinical characteristic	Adherers (n=47) M (SD)	Non-adherers (n=13) M (SD)	*t* or $\chi 2$
Age	42.02 (12.54)	46.85 (10.53)	-1.05
Sex (female/male)	28/19	7/6	0.34
Highest Level Education	15.49 (2.24)	13.77 (2.45)	**2.42***
Estimated Premorbid IQ	115.17 (4.94)	111.96 (6.19)	1.45
Baseline HRSD	21.77 (4.00)	23.85 (3.56)	-1.84
SJS (NAS)	0.01 (1.02)	-0.37 (0.83)	1.38
RAVLT 1-5 (iIQAS)	-1.02 (1.18)	-1.08 (1.27)	0.15
RAVLT 7 (iIQAS)	-0.94 (1.00)	-0.96 (0.92)	0.09
TMT A (iIQAS)	-1.27 (1.26)	-0.98 (0.91)	-0.76
TMT B (iIQAS)	-1.12 (0.95)	-1.54 (1.28)	1.30
COWA FAS (iIQAS)	-0.89 (1.21)	-0.91 (0.93)	0.42
Stroop C/W (iIQAS)	-0.93 (1.11)	-0.81 (0.82)	-0.34
Neurocognitive cluster (GI/SE)	21/26	5/8	0.16
AD dose (mg)	22.21 (17.68)	12.16 (17.65)	1.92
BZD dose (mg)	0.69 (1.47)	0.80 (1.54)	0.06
ATHF	7.83 (3.88)	6.92 (3.12)	0.39
Treatment type (iTBS/HFL)	25/22	5/8	0.88
Response (responder/non)	26/21	8/5	0.07
Remission (remitter/non)	19/28	6/7	0.52

Abbreviations: HRSD: Hamilton Rating Scale for Depression; SJS: Size Judgment Span; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trails Making Test; COWA FAS: Controlled Auditory Word Association, version FAS; NAS: Normative-adjusted score; iIQAS: Individualized IQ-adjusted score; GI: Global impairment; SE: Selective executive dysfunction; iTBS: Intermittent theta burst stimulation; HFL: High-frequency left.

Effect of rTMS on cognition

A repeated-measures ANOVA (package "ez") was used to determine effects of rTMS treatment on changes in cognitive score. The 7 neurocognitive test scores (SJS, RAVLT 1-5, RAVLT 7,

TMT A, TMT B, COWA, Stroop) were set as the dependent variable, with time set as a between-subjects factor. Diagnostic status (TRD versus HV) set as an additional between subjects-factor. Partial eta squared was calculated for each model. Post-hoc tests of significant effects were performed using package “emmeans”, with Tukey HSD adjustment for multiple comparisons.

As treatment may be expected to have differing benefits on cognition depending on an individual’s baseline cognitive functioning, we performed an additional repeated-measures ANOVA with clustered baseline cognitive functioning as an additional between-subjects factor rather than diagnostic status. This was based on k-means patient clusters derived from baseline test scores, which grouped patients into two distinct cognitive groups (see results, section 3.3 for further details). Controls were also included in this analysis against which to compare the two patient groups.

Although patients received two different rTMS protocols, the clinical trial reporting these data showed no differences in treatment response between the protocols (Blumberger et al., 2018a), and preliminary comparisons found no significant differences in baseline performance, nor changes in cognitive performance, between patients receiving iTBS and those receiving HFL (Table 2.4.2). rTMS protocol (i.e. iTBS or HFL) was therefore not included in any of the models.

Table 2.4.2 Baseline cognitive scores and difference in pre/post cognitive scores separated by rTMS treatment type.

	Baseline Cognitive Performance			**Difference at follow-up**[a]		
	iTBS (n = 25)	**HFL (n =22)**		**iTBS (n = 25)**	**HFL (n =22)**	
Cognitive Test	M (SD)	M (SD)	t-test	M (SD)	M (SD)	t-test
SJS (NAS)	-0.10 (0.99)	-0.04 (1.00)	-0.24	0.02 (0.81)	-0.19 (0.99)	0.82
RAVLT 15 (iIQAS)	-0.96 (1.25)	-1.10 (1.14)	0.44	0.30 (0.84)	0.50 (1.01)	-0.74
RAVLT 7 (iIQAS)	-0.85 (0.98)	-0.94 (1.00)	-0.01	0.35 (0.57)	0.42 (1.05)	-0.39
TMT A (iIQAS)	-1.27 (1.19)	-1.14 (1.21)	-0.44	0.42 (1.05)	0.42 (1.18)	0.02
TMT B (iIQAS)	-1.16 (1.06)	-1.25 (1.01)	0.34	0.46 (0.80)	0.28 (0.89)	1.12
COWA (iIQAS)	-0.80 (1.08)	-0.99 (1.22)	0.63	0.44 (0.82)	0.28 (0.89)	0.67
Stroop C/W (iIQAS)	-1.01 (1.06)	-0.79 (1.04)	-0.82	0.49 (0.82)	0.19 (0.79)	1.26

[a] Absolute difference in pre/post scores were used (3-month follow up z score – baseline z score).

Abbreviations: iTBS: Intermittent theta burst stimulation; HFL: High frequency left; SJS: Size Judgment Span; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trails Making Test; COWA FAS: Controlled Auditory Word Association, version FAS; NAS: Normative-adjusted score; iIQAS: Individualized IQ-adjusted score.

Relationship Between Cognitive Improvement and Treatment Response

As verbal learning and memory (RAVLT 1-5) showed significant improvement over time in the GI cognitive cluster, but not in the SE cluster, further analyses were performed to determine whether this improvement had any association with antidepressant response to rTMS. Specifically, did the gains in verbal learning and memory seen in the GI group vary between responders and non-responders? To answer this question, two-way ANOVA was performed to compare the effect of cognitive cluster (GI/SE), treatment response (responder/non-responder), and the interaction between these two variables on change in verbal learning and memory. Absolute change in RAVLT 1-5 score was calculated (3-month post-treatment score – baseline score). The variables of cognitive cluster and treatment response showed no direct association ($\chi^2 = 1.15$, $p = 0.28$; see table 2.4.3).

Table 2.4.3 Contingency table of response and k-means derived neurocognitive cluster.

	Global impairment	**Selective executive dysfunction**	**Total**
Response	16	16	32
Non-response	10	5	15
Total	26	21	47

Relationship Between Cognitive Improvement and Predictors of Cluster Belonging

To further discern the contributing factors to improvement on verbal learning and memory at the 3-month follow-up, we investigated the degree to which baseline predictors of GI cluster belonging were associated with gains on the RAVLT 1-5 task. Only age showed significant correlations and was thus further explored. Post-hoc path analysis (PROCESS macro for SPSS, version 3.4; Hayes, 2012) was performed to explore whether there was a moderating effect of cluster membership on the relationship between age and task improvement

CHAPTER 3: RESULTS

3.1 Baseline analysis: Demographic Characteristics

Demographic characteristics for TRD and HV were similar in every measure except for highest level of education, wherein HV was significantly more educated than TRD ($p = 0.03$). For a full summary of results, see Table 3.1.1

Table 3.1.1 Summary of demographic variables of treatment-resistant depression patients (TRD) and healthy volunteers (HV) and clinical characteristics of the TRD sample.

	TRD (n = 60)		HV (n = 40)				
	M or %	SD	M or %	SD	*t* or χ^2	*p*	*95% CI*
Age (years)	43.07	12.22	42.28	12.60	0.31	0.76	-0.33, 0.46
Education (years)	**15.12**	**2.37**	**16.13**	**1.91**	**-2.24**	**0.03**	**-0.86, -0.05**
Estimated premorbid IQ	114.48	5.35	112.75	8.07	1.40	0.17	-0.14, 0.66
Sex (% female)	57.00		60.00		0.11	0.74	-16.36, 21.56
Anxiety comorbidity (% yes)	33.33						
Lifetime PTSD diagnosis (% yes)	31.70						
Disease duration (years)	17.58	11.80					
Current episode length (months)	24[a]	12-24[a]					
ATHF score	7.63	3.72					
HRSD score	22.22	3.98					
SDS score	22.80	13.90					
PDQ score	43.65	13.90					
BSI-A score	14.39	5.60					
Escitalopram equivalent dose (mg)	19.92	18.02					
Taking antidepressants (% yes)	71.67						
Lorazepam equivalent dose (mg)	0.43	1.19					
Taking benzodiazepines (% yes)	23.33						

[a] Median, first and third interquartile range reported rather than mean and standard deviation
Abbreviations: TRD: Treatment-resistant depression; HV: healthy volunteers; PTSD: Post-traumatic stress disorder; ATHF: Antidepressant Treatment History Form; HRSD: Hamilton Rating Scale for Depression; SDS: Sheehan Disability Scale; PDQ: Perceived Deficits Questionnaire; BSI-A: Brief Symptom Inventory, anxiety subscale.

3.2 Baseline Analysis – Normative versus Individualized Neuropsychological Performance

Normative Versus Relative Cognitive Scores

Sample mean scores for both NAS and iIQAS definitions of cognitive performance are summarized in Table 3.2.1.

Table 3.2.1 Mean neuropsychological performance by group with iIQASs as compared to standard normative scores.

	Normative adjusted score		**Individualized IQ-adjusted score**	
	TRD (n = 60)	**HV (n = 40)**	**TRD (n = 60)**	**HV (n = 40)**
Cognitive Domain	M (SD)	M (SD)	M (SD)	M (SD)
Working Memory	-0.07 (0.99)	0.00 (1.00)	-	-
Verbal Fluency	-0.07 (1.25)	0.43 (0.92)	-0.90 (1.15))	-0.68 (1.01)
Verbal Learning & Memory	-0.20 (1.20)	0.30 (1.10)	-1.03 (1.19)	-0.42 (1.00)
Inhibitory Control	-0.20 (1.00)	0.60 (1.50)	-0.90 (1.05)	-0.36 (0.92)
Speeded Attention	0.07 (1.21)	0.17 (1.21)	-1.21 (1.19)	-0.54 (1.06)
Task Switching	0.10 (1.00)	0.50 (1.00)	-1.21 (1.03)	-0.26 (1.30

Independent samples t-tests comparing percent change in cognitive scores in TRD and HV with normative versus relative adjustments were performed. All t-tests were significant (p<0.05 after FDR correction), with the IQ adjustment resulting in greater decreases in cognitive scores in MDD compared to HV. Mean percent change and statistics are summarized in Table 3.2.2.

Table 3.2.2 Independent samples t-test comparisons of mean percent change in cognitive scores with IQ adjustment relative to standard normative scoring in TRD versus HV.

	TRD (n=60)	**HV (n=40)**	t-test	95% CI
Verbal learning & memory	-20.45 (9.34)	-15.94 (10.40)	**-2.26***	-8.47, -0.55
Verbal Fluency	-19.65 (7.94)	-15.67 (11.22)	**-2.07***	-7.77, -0.16
Inhibitory control	-19.73 (8.38)	-15.14 (10.03)	**-2.48***	-8.26, -0.92
Speeded Attention	-21.55 (10.75)	-15.94 (11.31)	**-2.50***	-10.05, -1.16
Task shifting	-21.30 (10.13)	-15.21 (11.07)	**-2.84***	-10.35, -1.83

Abbreviations: TRD: treatment-resistant depression; HV: healthy volunteers

MANOVA: TRD versus HV

Two MANOVAs were performed, one using normative scores as the dependent variables, and the other using iIQASs (for all except the SJS) as the dependent variables. In both cases, a significant multivariate effect of group was found, indicating a difference in performance between TRD and HV at baseline. Similarly, univariate tests in both cases found that TRD were significantly worse compared to HV in domains of set shifting (TMT B), speeded attention (TMT A), verbal learning and memory (RAVLT 1-5), and inhibitory control (Stroop Colour/Word); whereas there were no significant group differences in verbal fluency (COWA FAS) or in working memory (SJS).

However, partial η^2 values, as well as observed power, for both multivariate and univariate effects were found to be greater when iIQASs were used as the dependent variables, as opposed to NAS. Results of both MANOVA analyses are summarized in Table 3.2.3.

Because iIQASs showed greater effect sizes for differences in TRD and HV compared to NAS in the MANOVAs, these scores were used in all further analyses. Neuropsychological profiles of the iIQASs are shown in Figure 3.2.1.

Table 3.2.3 MANOVA comparing TRD and HV cognitive performance, using both normative scoring and relative scoring.

	Normative adjusted score			**Individualized IQ-adjusted score**		
	F-test	Partial η^2	Observed power	F-test	Partial η^2	Observed power
Multivariate effect	3.01	0.16	0.89	4.12	0.21	0.97
Univariate effects						
Working memory	0.12	0.00	0.06	0.12	0.00	0.06
Verbal learning & memory	4.75*	0.05	0.58	7.35**	0.07	0.77
Verbal Fluency	0.17	0.00	0.07	0.93	0.01	0.16
Inhibitory control	4.17*	0.04	0.52	7.13**	0.07	0.75
Speeded Attention	5.34*	0.05	0.63	8.06**	0.08	0.80
Set shifting	11.26***	0.10	0.91	16.33***	0.14	0.98

p values indicated as follows: * <.05, ** <.01, *** <.001

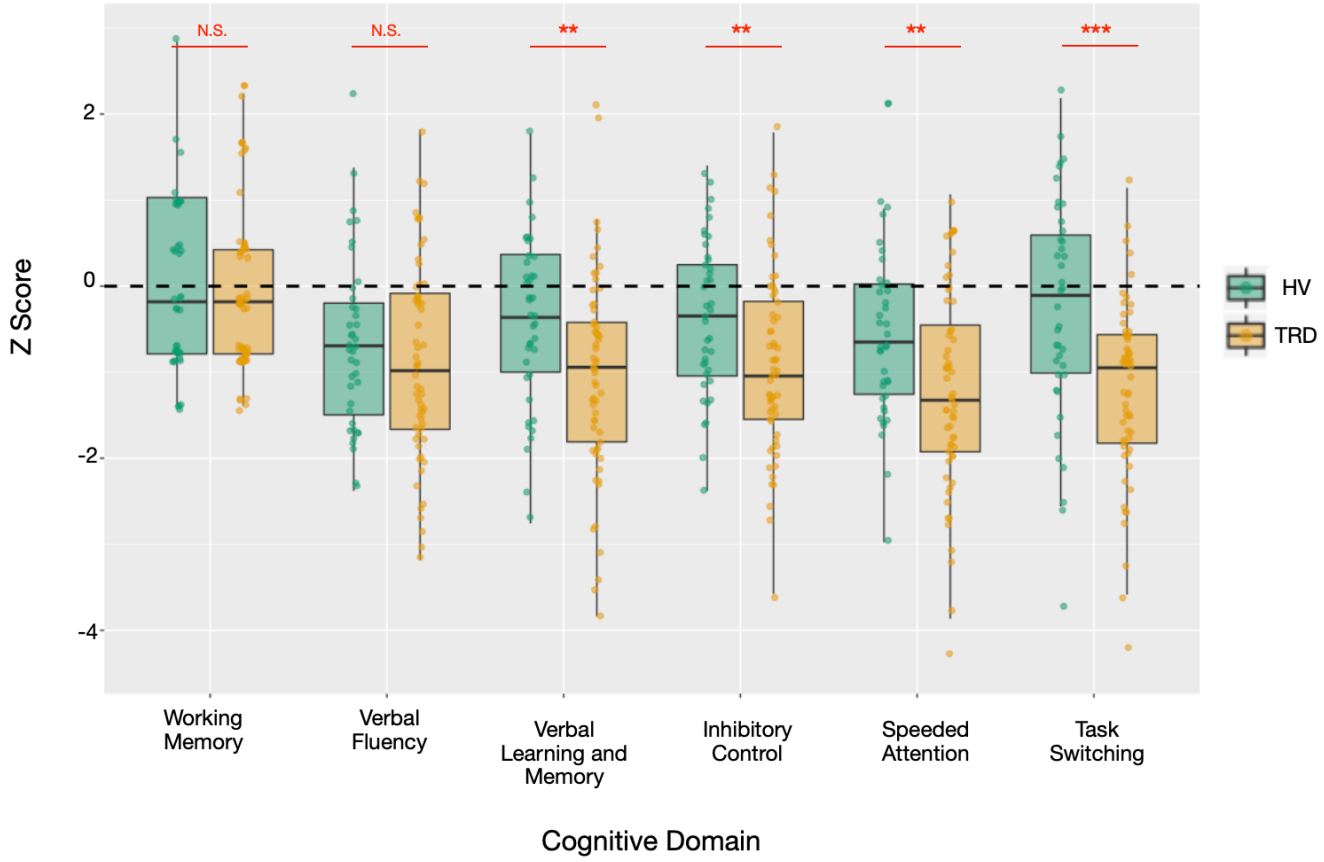

Figure 3.2.1 Neuropsychological profiles of patients with treatment-resistant depression (TRD) and the control group of healthy volunteers (HV). iIQASs are depicted.

3.3 Baseline Cognitive Clusters

The cluster analysis output yielded two subgroups of TRD based on cognitive functioning: A globally impaired group (GI) (n=34) and a selective executive dysfunction group (SE) (n = 26). The GI group showed lower scores compared to the CU SE group in working memory (SJS: F(1, 58) = 53.01, p<0.001, partial η 2 = 0.48), verbal learning and memory (RAVLT 1-5; F(1, 58)= 48.81, p<0.001, partial η 2 = 0.46), verbal fluency (COWA FAS; F(1, 58)=35.47, p<0.001, partial η 2 = 0.38), and inhibitory control (Stroop colour/word; F(1, 58) =15.18, p<0.001, partial η 2 = 0.21).

In contrast, the groups were not different in two domains of executive function: Speeded attention (TMT A; F(1, 58) = 3.26, p = 0.08, partial η^2 = 0.05) and task switching (TMT B; F(1, 58) = 2.10, p = 0.15, partial η^2 = 0.04). Cluster profiles are depicted in **Figure 3.3.1**, and cluster means are indicated in **Table 3.3.1**.

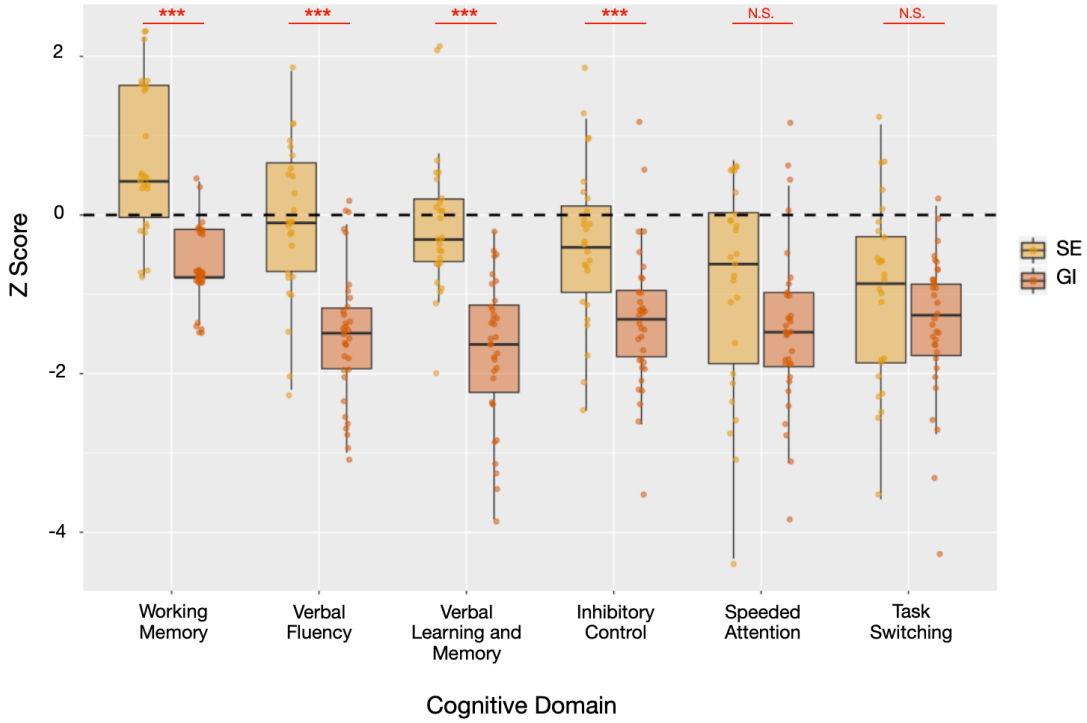

Figure 3.3.1 Patient cognitive clusters based on individualized neurocognitive test scores.

Table 3.3.1 Mean neurocognitive scores of derived clusters.

	GI (n = 34)	**SE (n = 26)**	**MANOVA**	
Cognitive Domain	M (SD)	M (SD)	*p*	*95% CI*
Working Memory	**-0.66 (0.47)**	**0.70 (0.96)**	**<0.001**	**-1.74, -0.99**
Verbal Fluency	**-1.51 (0.85)**	**-0.09 (0.98)**	**<0.001**	**-1.89, -0.94**
Verbal Learning & Memory	**-1.73 (0.90)**	**-0.12 (0.87)**	**<0.001**	**-2.07, -1.15**
Inhibitory Control	**-1.38 (0.90)**	**-0.36 (1.00)**	**<0.001**	**-1.45, -0.47**
Speeded Attention	-1.44 (1.00)	-0.89 (1.35)	0.15	-1.16, 0.06
Task Switching	-1.37 (0.91)	-0.99 (1.15)	0.08	-0.92, 0.15

Abbreviations: GI: Global impairment; SE: Selective executive dysfunction.

Differential Characteristics of GI and SE Subgroups

Demographic information for both subgroups used in the binomial logistic regression is shown in **Table 3.3.2**. Four patients had incomplete data in one or more covariate domains, leaving n=56 for this analysis; n=32 for GI, n=24 for SE. An omnibus test using a likelihood ratio of the full model found that there were significant differences between the fitted model and intercept-only model (χ^2=20.59, p<0.001), with Nagelkerke's pseudo r^2=0.413. Classification of GI was 62.5% correct, and classification of SE was 84.4% correct, with an overall percentage correct of 75.0%. Two steps were taken to load all contributing factors to the analysis. Significant predictors that contributed to the model were age (B(1) = 0.09, *p* = 0.003, S.E. = 0.03, wald value = 8.79, odds ratio = 1.09) and benzodiazepine use (B(1) = 2.56, *p* = 0.02, S.E. = 1.14, wald value = 5.08, odds ratio = 1.92).

The odds ratios indicate that for each increased year in age risk of global CD increased by 9%. Taking benzodiazepines increased the risk of global CD by 93%.

Table 3.3.2 Demographic and clinical characteristics of the cluster-derived neurocognitive subgroups.

	GI (n = 34)		SE (n = 26)				
	M	SD	M	SD	*t* or χ^2	*p*	*95% CI*
Age (years)	**47.74**	**9.75**	**36.96**	**12.59**	**43.74**	**<0.001**	**0.43, 1.51**
Education (years)	15.06	2.31	15.19	2.50	-0.21	0.83	-0.57, 0.46
Estimated premorbid IQ[a]	114.10	5.46	114.96	5.28	-0.61	0.54	-0.67, 0.35
Sex (% female)	53%		62%		0.44	0.51	-15.61, 31.73
Anxiety comorbidity (% yes)	29%		38%		0.54	0.46	-14.11, 31.76
Lifetime PTSD diagnosis (% yes)	31%		32%		0.02	0.90	-21.24, 24.16
Disease duration (years)	**20.44**	**10.39**	**13.54**	**12.46**	**2.29**	**0.03**	**0.07, 1.14**
Current episode length (months)	40.34	48.38	24.79	18.76	1.49	0.14	-0.13, -0.94
ATHF score	8.00	3.76	7.15	3.68	0.87	0.39	-0.29, 0.74
HRSD score	22.5	3.44	21.85	4.64	0.63	0.53	-0.35, 0.67
SDS score	23.50	4.67	21.88	5.18	1.27	0.21	-0.19, 0.84
PDQ score	44.32	14.76	42.77	12.92	0.43	0.67	-0.40, 0.62
BSI-A score	14.88	5.19	13.72	6.16	0.79	0.44	-0.31, 0.72
Escitalopram equivalent dose (mg)	19.91	18.59	19.94	17.57	-0.01	1.00	-0.53, 0.53
Taking antidepressants (% yes)	59%		69%		0.69	0.41	-14.25, 31.94
Lorazepam equivalent dose (mg)	**1.07**	**1.73**	**0.23**	**0.86**	**2.27**	**0.03**	**0.07, 1.10**
Taking benzodiazepines (% yes)	**35%**		**8%**		**6.28**	**0.01**	**5.49 – 44.75**

Abbreviations: TRD: Treatment-resistant depression; HV: healthy volunteers; PTSD: Post-traumatic stress disorder; ATHF: Antidepressant Treatment History Form; HRSD: Hamilton Rating Scale for Depression; SDS: Sheehan Disability Scale; PDQ: Perceived Deficits Questionnaire; BSI-A: Brief Symptom Inventory, anxiety subscale.

Mediation Analysis

Illness duration was found to be significantly different between GI and SE, with GI showing a longer illness duration, although this variable did not load into the regression model when the effects of age and benzodiazepine use were accounted for. Illness duration and age showed a

significant Pearson correlation (r = 0.46, p<.001), whereas illness duration was not related to benzodiazepine use (r = 0.13, p = 0.33).

The relationship between illness duration and age was thus further explored to determine whether age could explain the significant differences in illness duration between the GI and SE clusters. Using PROCESS macro for SPSS 26 (Hayes, 2012), path analysis indicated that the direct relationship between illness duration and neurocognitive cluster belonging (path c, β = 0.29) was no longer significant when controlling for the effects of age (path c', b = 0.03), which was significantly associated with both illness duration (path a, β = 0.48) and neurocognitive cluster (path b, β = 0.08). Instead, there was an indirect relationship between the two variables, which was shown to be mediated by the effect of age (path a x path b, β = 0.04). Paths are summarized in Figure 3.3.2.

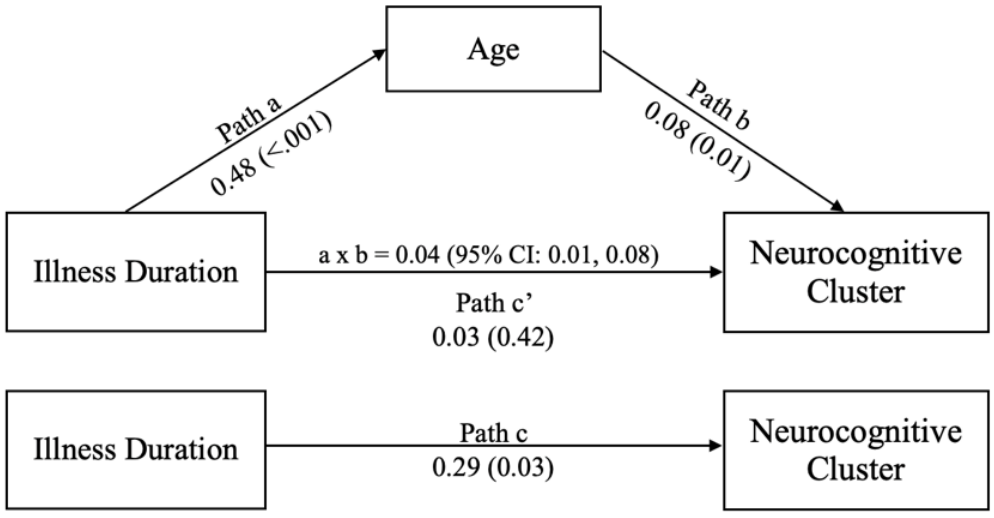

Figure 3.3.2 Path analysis demonstrating the mediating effect of age on the relationship between illness duration and neurocognitive cluster.

3.4 Cognitive Changes Associated with rTMS

Neurocognitive Changes: TRD versus HV

There was a significant multivariate effect of group ($F(7, 61) = 4.04$, p=.001, $\eta^2 = 0.32$) as well as a significant multivariate effect of time ($F(7, 61) = 7.58$, $p < 0.001$, $\eta^2 = 0.47$). The group by time interaction was not significant ($F(7, 61) = 1.06$, $p = 0.40$, $\eta^2 = 0.11$).

TRD were worse than HV in measures of working memory ($F(1, 130) = 4.624$ $p = 0.03$, $\eta^2 = 0.04$), verbal learning and memory ($F(1, 130) = 11.14$, $p = 0.001$, $\eta^2 = 0.08$), speed and attention ($F(1, 130) = 17.96$, p<.001, $\eta^2 = 0.12$), task switching ($F(1, 130) = 33.81$, p<0.001, $\eta^2 = 0.21$), verbal fluency ($F(1, 130) = 7.21$, $p = 0.01$, $\eta^2 = 0.05$), and inhibitory control ($F(1, 130) = 19.00$, p<0.001, $\eta^2 = 0.13$). There were no significant differences between TRD and HV in the measure of delayed verbal memory ($F(1, 130) = 2.79$, $p = 0.10$, $\eta^2 = 0.02$).

Significant improvement from baseline to follow-up was seen across most measures: verbal learning and memory $F(1, 67) = 11.62$, $p = 0.001$, $\eta^2 = 0.15$), delayed verbal memory ($F(1, 67) = 17.83$, p<0.001, $\eta^2 = 0.21$), speeded attention ($F(1, 67) = 19.13$, p<.001, $\eta^2 = 0.22$), task switching ($F(1, 67) = 5.06$, $p = 0.03$, $\eta^2 = 0.07$), verbal fluency ($F(1, 67) = 14.59$, p<.001, $\eta^2 = 0.18$), and inhibitory control ($F(1, 67) = 5.09$, $p = 0.03$, $\eta^2 = 0.07$). The only measure that did not show significant improvements over time was working memory ($F(1, 67) = 0.15$, $p = 0.70$, $\eta^2 = 0.00$).

Mean scores of TRD and HV are summarized in Table 3.4.1. Effects of diagnostic status and time are summarized in Figure 3.4.1.

Table 3.4.1 Mean neurocognitive performance by diagnostic status at baseline and at follow-up.

	Baseline		**Follow-Up**	
	TRD (n = 47)	HV (n = 22)	TRD (47)	HV (22)
Cognitive Domain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Working Memory	0.01 (1.02)	0.09 (1.01)	-0.07 (1.03)	0.26 (1.18)
Verbal Learning & Memory	-1.02 (1.18)	-.44 (0.97)	0.00 (0.93)	-0.62 (0.97)
Delayed Verbal Memory	-0.94 (1.01)	-0.69 (0.73)	-0.55 (0.92)	-0.32 (0.86)
Task Switching	-0.96 (0.89)	0.18 (0.97)	-0.63 (0.98)	0.29 (0.74)
Speeded Attention	-1.25 (1.25)	-0.50 (0.97)	-0.83 (1.19)	0.27 (0.83)
Verbal Fluency	-0.94 (1.11)	-0.35 (1.04)	-0.22 (1.03)	-0.59 (1.12)
Inhibitory Control	-0.87 (1.23)	-0.43 (1.07)	-0.47 (1.27)	0.01 (0.98)

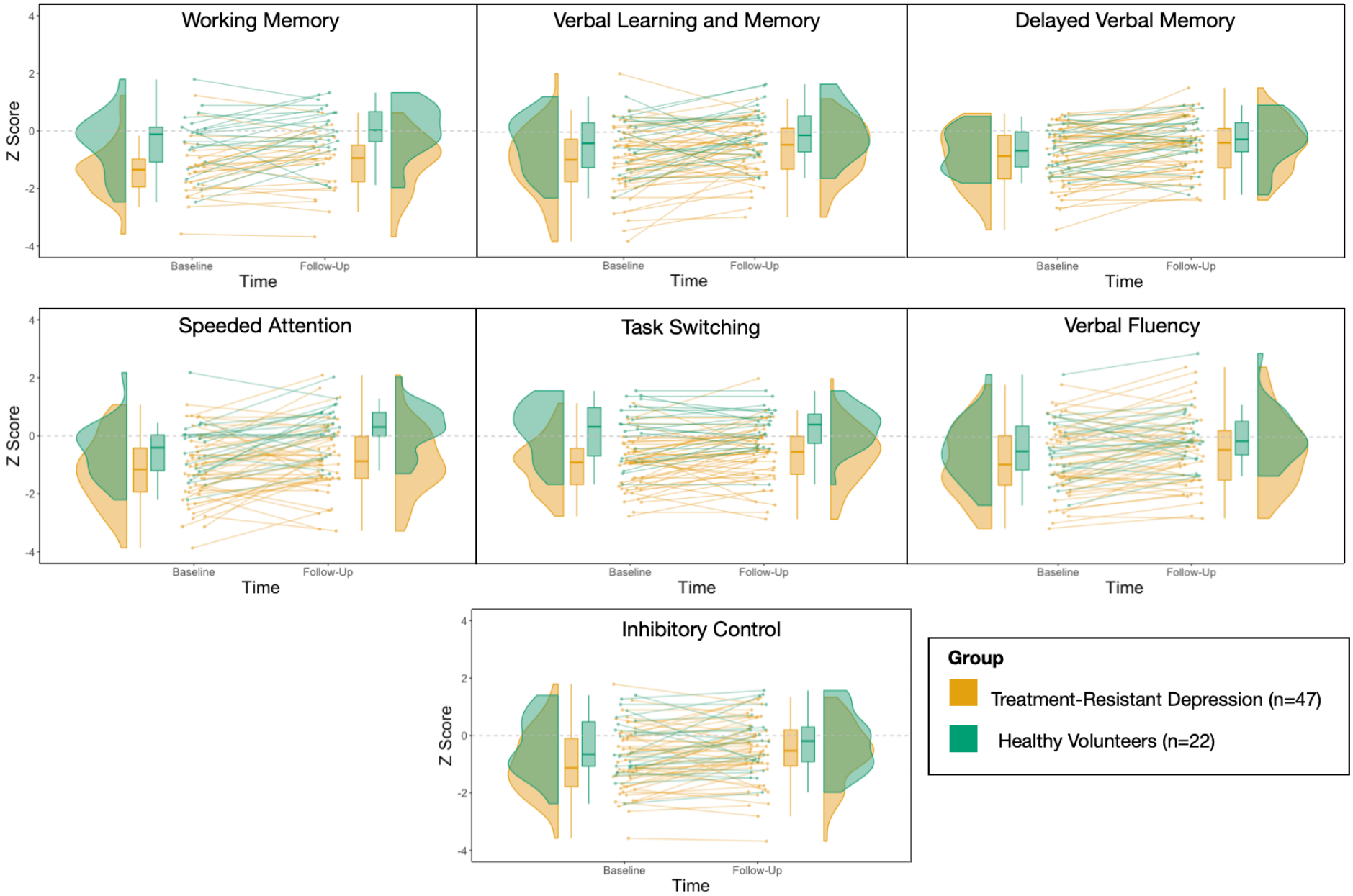

Figure 3.4.1 Changes in cognitive performance from baseline to follow-up in treatment-resistant depression and healthy volunteers.

Neurocognitive Changes: Relationship with Baseline Cognitive Status

The between-subjects effect of baseline cognitive status ($F(14, 122) = 6.23$, $p < .001$ $\eta^2 = 0.42$) was significant, as well as the within-subjects effect of time ($F(7, 60) = 8.39$, $p < .001$, $\eta^2 = 0.50$). Finally, the baseline cognitive status by time interaction ($F(14, 122) = 1.80$, $p = 0.04$, $\eta^2 = 0.17$) showed a significant effect.

The effects of group were significant for all measures; working memory (SJS; $F(2, 66) = 18.80$, $p < .001$, $\eta^2 = 0.36$), verbal learning and memory (RAVLT 1-5; $F(2, 66) = 17.40$, $p < .001$, $\eta^2 = 0.35$), delayed verbal memory (RAVLT 7; $F(2, 66) = 10.95$, $p < .001$, $\eta^2 = 0.25$), speeded attention (TMT A; $F(2, 66) = 8.32$, $p = 0.001$, $\eta^2 = 0.20$), task switching (TMT B; $F(2, 66) = 13.66$, $p < .001$, $\eta^2 = 0.29$) verbal fluency (COWA: $F(2, 66) = 13.74$, $p < .001$, $\eta^2 = 0.29$), and inhibitory control (Stroop Colour/Word; $F(2, 66) = 9.28$, $p < .001$, $\eta^2 = 0.22$).

SE performed worse than HV in only in the measure of task switching ($p = 0.01$), while GI showed worse performance compared to HV on all measures ($p < 0.01$ for all comparisons).

Domains of neuropsychological testing affected by time were verbal learning and memory (RAVLT 1-5; $F(1, 66) = 12.44$, $p = 0.001$, $\eta^2 = 0.16$), delayed verbal memory (RAVLT 7; $F(2, 66) = 19.96$, $p < .001$, $\eta^2 = 0.23$), speeded attention (TMT A; $F(2, 66) = 18.99$, $p < .001$, $\eta^2 = 0.22$), task switching (TMT B; $F(2, 66) = 7.48$, $p = 0.008$, $\eta^2 = 0.10$), verbal fluency (COWA; $F(2, 66) = 15.02$, $p < .001$, $\eta^2 = 0.19$), and inhibitory control (Stroop Colour/Word; $F(2, 66) = 7.96$, $p = 0.01$, $\eta^2 = 0.11$). Working memory did not improve with time ($F(2, 66) = 0.01$, $p = 0.95$, $\eta^2 = 0.00$).

Investigation of the significant group by time interaction showed that the neurocognitive groups differed in changes in verbal learning and memory across the two timepoints ($F(2, 66) = 1.97, 4.82$, $p = 0.01$, $\eta^2 = 0.13$). Further post-hoc analyses using Tukey's HSD corrections revealed that the GI subgroup showed a significantly greater change across the two timepoints compared to the SE subgroup and HV, wherein at baseline GI were significantly worse than both SE ($t = -5.65$, $p < .001$) and controls ($t = -4.63$, $p = 0.003$), but did not differ significantly from either groups at the follow-up timepoint; SE ($t = -2.73$, $p = 0.77$), HV ($t = -3.49$, $p = 0.20$). Furthermore, the GI subgroup showed significant improvements from baseline to follow up ($t = 4.62$, $p = 0.004$), whereas neither SE ($t = 0.30$, $p = 1.00$) nor HV ($t = 2.49$, $p = 0.91$) showed any changes across the timepoints.

Mean scores at each timepoint for SE and GI are summarized in Table 3.4.2. Effects of baseline cognitive status in the patient sample are summarized in Figure 3.4.2.

Table 3.4.2 Mean performance of the two neurocognitive clusters identified at baseline.

	Baseline		**Follow-up**	
	SE (n=21)	GI (n=26)	SE (n=21)	GI (n=26)
Cognitive Domain	M (SD)	M (SD)	M (SD)	M (SD)
Working Memory	0.86 (0.90)	-0.67 (0.42)	0.63 (0.80)	-0.62 (0.83)
Verbal Learning & Memory	-0.14 (0.81)	-1.73 (0.93)	-0.20 (0.99)	-0.96 (0.97)
Delayed Verbal Memory	-0.31 (0.72)	-1.44 (0.93)	-0.07 (0.78)	-0.93 (0.86)
Task Switching	-0.65 (1.05)	-1.21 (0.65)	-0.45 (1.09)	-0.78 (0.87)
Speeded Attention	-1.07 (1.39)	-1.39 (1.14)	-0.42 (1.31)	-1.16 (0.98)
Verbal Fluency	0.04 (1.01)	-1.54 (0.91)	0.19 (1.09)	-1.00 (1.16)
Inhibitory Control	-0.41 (1.04)	-1.36 (0.99)	0.02 (0.93)	-1.08 (1.02)

Abbreviations: SE: selective executive dysfunction; GI: global impairment

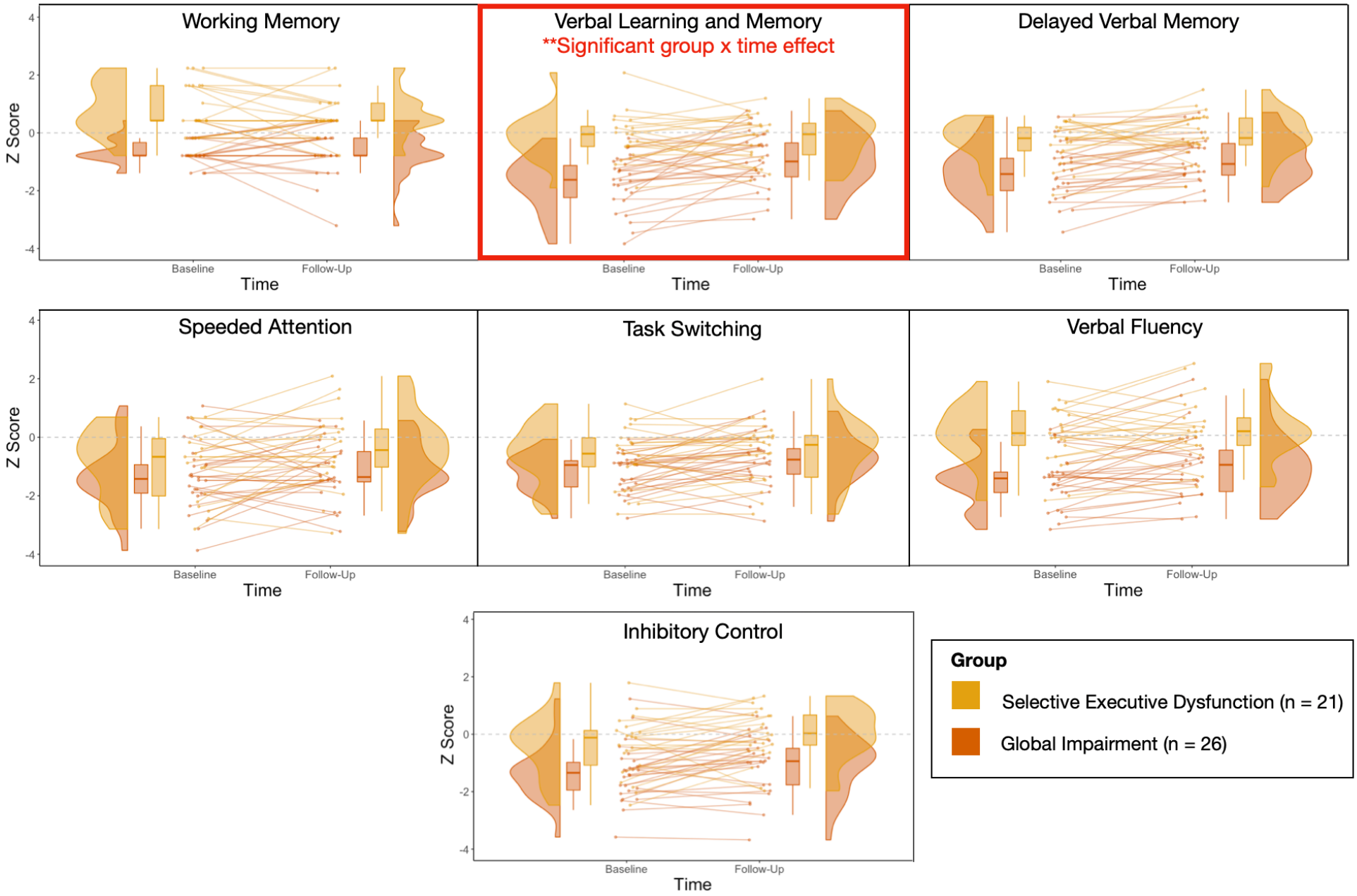

Figure 3.4.2 Changes in cognitive performance from baseline to follow-up in treatment-resistant depression neurocognitive subgroup

Relationship with Cognitive Improvement and Treatment Response

To determine whether the improvement in verbal learning and memory (RAVLT 1-5) performance identified in the GI cluster were associated with treatment response, a two-way ANOVA was performed with absolute change in RAVLT 1-5 score set as the dependent variable, with neurocognitive cluster (SE versus GI) and treatment response (responder/non-responder) set as the between-subjects factors.

This returned a model which found the main effect of neurocognitive cluster to be significant ($F(1, 43) = 5.56$, $p = 0.02$, $\eta^2 = 0.11$), while the main effect of response was not ($F(1, 43) = 0.94$, $p = 0.34$, $\eta^2 = 0.02$). However, the neurocognitive cluster by response interaction was significant ($F(1, 43) = 5.17$, $p = 0.004$, $\eta^2 = 0.18$).

Further inspection of the interaction found in responders, the GI cluster showed significantly more change in RAVLT 1-5 scores compared to the SE cluster ($t = 4.96$, $p<.001$). In contrast, in non-responders, there was no difference in the degree to which RAVLT 1-5 scores changed between GI and SE ($t = 0.40$, $p=0.98$).

The interaction effect on changes in RAVLT 1-5 scores is summarized in Figure 3.4.3.

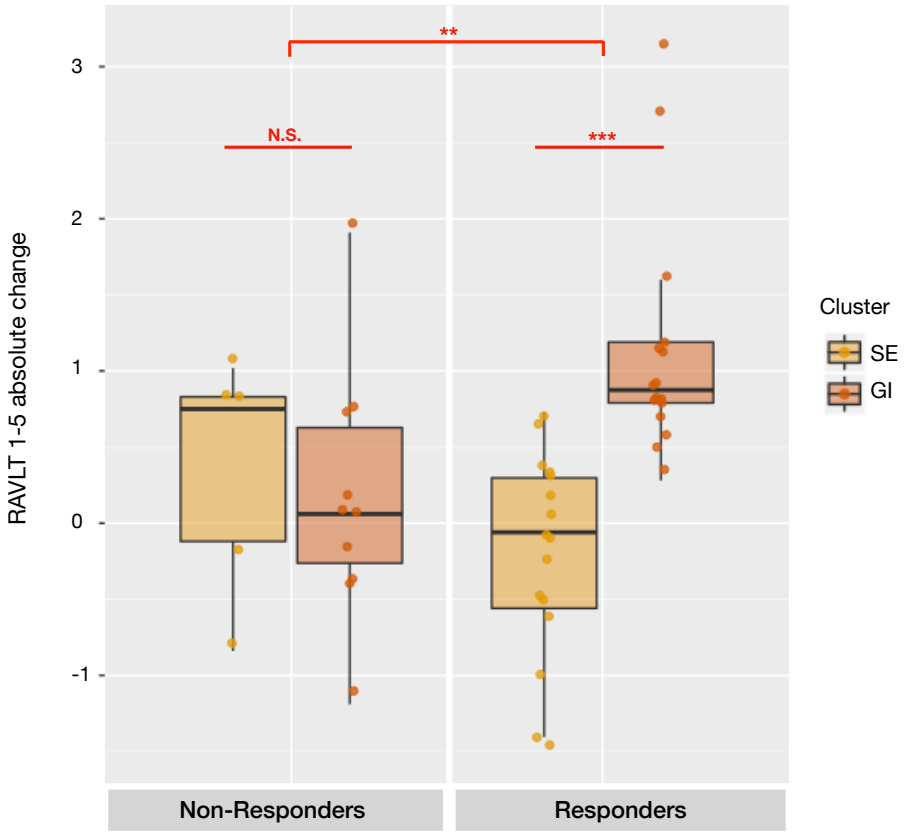

Figure 3.4.3 Interaction effect between neurocognitive cluster and treatment response on improvement in verbal learning and memory.

Relationship with Cognitive Improvement and Baseline Predictors of CD

Correlations were performed between the two predictors of GI cluster belonging, age and benzodiazepine use, and change in RAVLT 1-5 performance. Age showed a moderate positive correlation with RAVLT 1-5 change (r = 0.38, p = 0.001), whereas benzodiazepine dose showed a small, non-significant positive correlation (r = 0.15, p = 0.20).

There was a moderate positive relationship between age and RAVLT 1-5 improvement within the CI cluster (r = 0.60, p=0.001), whereas there was not a significant relationship between these variables within the CU cluster (r = 0.25, p = 0.26). Therefore, path analysis was used to

determine whether cluster membership acted as a moderator on the relationship between age and verbal learning and memory improvement, with percent change in HRSD included as a covariate in the model, using PROCESS macro for SPSS 26 (Hayes, 2012). There was indeed a significant moderating effect of cluster membership on age ($F(1,42) = 3.98$, $p = 0.05$). For the SE cluster, there was no relationship between age and change in RAVLT 1-5 score ($\beta = 0.00$, $p = 0.97$), whereas for the GI cluster, for each year in age, there was an added 0.05 point improvement in RAVLT 1-5 score at follow-up ($\beta = 0.05$, $p = 0.007$).

The relationship between age, neurocognitive cluster, and memory performance is plotted in figure 3.4.4.

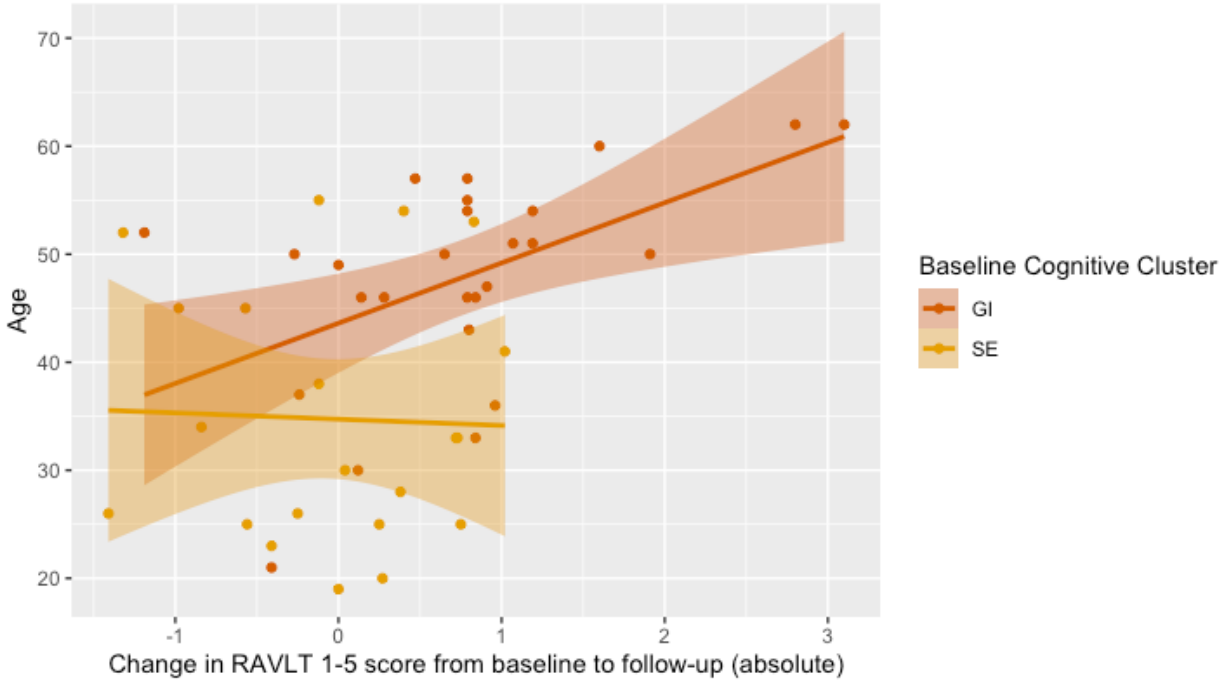

Figure 3.4.4 Baseline neurocognitive clusters showed a moderating effect on the relationship between age and absolute change in RAVLT 1-5 scores.

CHAPTER 4: DISCUSSION

4.1 Overview: Objectives and Findings

This thesis had two objectives:

1. To characterize CD in patients with treatment-resistant depression during an acute depressive episode.

2. To assess the cognitive benefits of an adequate course of high frequency repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex.

To accomplish these objectives, I conducted analyses on data obtained from the THREE-D study, a clinical trial investigating the non-inferiority of two repetitive transcranial magnetic stimulation protocols in patients with TRD (Blumberger et al., 2018a).

The key findings from the objectives are as follows:

1. Patients with TRD show worse performance in select cognitive domains when compared to a matched cohort of healthy volunteers; however, their scores are considered 'normal' with respect to normative databases. Controlling for an individual's premorbid functioning, on the other hand, allowed for better detection of cognitive deficits, and provided more clear insight into disorder-specific effects on cognition. However, cognitive function in TRD was found to be heterogeneous. Two cognitive subgroups emerged in the TRD sample, indicating about half of patients show global deficits in cognition, whereas the remaining half showed only selective deficits in executive functions. Older age and benzodiazepine use were identified as variables

contributing to heterogeneity, specifically with these variables predicting belonging to the global deficit subgroup.

2. rTMS is not associated with significant cognitive improvement in our sample. However, those who have worse cognitive deficits at baseline showed significant improvements over the course of treatment in the domain of verbal memory. Furthermore, improvements in verbal memory appeared to be associated to improvements in affective symptoms. Therefore, our data suggest that rTMS targeting of the left DLPFC affects large-scale networks involving both affect and cognition.

This final chapter will discuss the findings from these analyses, identify strengths and limitations, as well as explore the implications for future research and treatment of patients with TRD.

4.2 Adjusting for Premorbid Cognition Improves the Detection of Deficits in Treatment-Resistant Depression

TRD showed worse cognitive functioning compared to HV in several cognitive domains, namely verbal learning and memory, speeded attention, set shifting, and inhibitory control. However, due to the sample being highly educated and demonstrating high IQ according to the NAART task, sample means of the TRD group are considered to be within the normal range of normative scores. Recent studies have suggested adjusting for estimated premorbid IQ in patients can lead to more accurate depictions of the true CD experienced by patients with TRD (Douglas et al., 2018; Tran, Milanovic, Holshausen, & Bowie, 2021).

Using these same techniques in the current study, adjusting for premorbid IQ led to greater differences in cognitive performance between TRD and HV, while the domains that were impaired remained consistent. While adjusting for IQ, referred to as iIQAS, decreased the mean scores of both TRD and HV, this adjustment led to greater decreased in TRD scores. It must be noted that estimated premorbid functioning was used to adjust cognitive scores, whereas ideally longitudinal information on cognitive function prior to, and over time, is an ideal way to measure changes in cognitive ability due from a disorder (Douglas et al., 2020). However, the current findings assert that verbal reading tests, such as the NAART, are a useful surrogate measure when longitudinal data are not available, as is often the case in both clinical and research applications.

Furthermore, the method of premorbid adjustments may also bridge the gap between subjective reporting of CD and objective measures, which have been consistently reported as dissociated from one another (McDermott & Ebmeier, 2009; Petersen et al., 2019; Rock et al., 2014). This is evidenced by a recent study by Tran and colleagues (2021), which found an association between subjective dysfunction and individualized, but not normative, cognitive performance. This suggests that individualized cognitive scores may be more clinically relevant, as they seem to be more closely associated with a patient's perceived loss of cognitive and functional abilities.

Analyses on the entire TRD sample compared to matched HV using both normative and individualized cognitive scores were consistent with prior research suggesting that CD in TRD may be more circumscribed to a few cognitive domains rather than characterized by more severe generalized impairments such as those found in patients with schizophrenia (Heinrichs & Zakzanis, 1998; Vila-Rodriguez et al., 2017). Deficits in verbal learning/memory are frequently reported in MDD patients (den Hartog et al., 2003; Fossati et al., 2002, 2004; Philip Gorwood et

al., 2008), and the length of current depressive episode tends to correlate with greater verbal memory deficits (consistent with studies in first-episode depression failing to report verbal memory deficits, e.g. Basso and Bornstein, 1999), suggesting that this deficit is more pronounced in TRD (Fossati et al., 2004). In addition, the finding of deficits in executive function aligns with previous studies reporting deficits in attention and inhibitory components of executive function in TRD (Hammar et al., 2011; Tsaltas et al., 2011). The lack of a deficit in working memory in the TRD sample is intriguing, as deficits in this domain are consistently reported (Galecki et al., 2013; Gruber, Zilles, Kennel, Gruber, & Falkai, 2011; Stordal et al., 2004). This negative finding may be attributed to the use of the SJS test as a measure of working memory, which was designed in the southern United States and for geriatric subjects (Cherry et al., 2007). Differences in regional dialects may have importantly affected performance in our participants, whom were located in Vancouver, Canada (Boberg, 2005). A further explanation for the lack of finding may be associated with clinical heterogeneity in working memory presentation within the TRD group.

4.3 Cognitive Dysfunction is Heterogeneous in Treatment-Resistant Depression

The strategy to cluster our sample driven by neuropsychological data was an avenue to explore the presence of potential subgroups. I chose to conduct this cluster analysis using the individualized scores (iIQAS) as this method showed a larger gap in cognitive performance between TRD and HV, suggesting it is more sensitive to the impacts of depression on cognition. Cluster analysis yielded two groups based on cognitive performance: a selective executive dysfunction group (SE) and a globally impaired group (GI). The GI subgroup demonstrated

widespread impairment, whereas the SE subgroup performed significantly better than GI in all cognitive domains except speeded attention and task switching, reflected in TMT parts A and B performance. Furthermore, GI comprised a substantial portion of the TRD sample, with 34 of the 60 patients belonging to this subgroup, whereas 26 belonged to the SE subgroup.

Previous studies also report discrete neuropsychological subgroups in MDD samples (Douglas et al., 2018; Hermens et al., 2011; Martin et al., 2020; Pu et al., 2018; Vicent-Gil et al., 2020). The globally impaired subtype reported has some consistency with previous findings in the literature (Martin et al., 2020; Pu et al., 2018; Vicent-Gil et al., 2020). On the other hand, other studies have typically reported 3 subtypes: a subtype with mild or no deficits and a subtype with selective memory deficits, in addition to the globally impaired subtype (Martin et al., 2020; Pu et al., 2018; Vicent-Gil et al., 2020). Furthermore, Vicent-Gil et al. (2020) found that treatment resistance was a strong predictor of belonging to the selectively, or globally, impaired clusters. In this study, only TRD patients were invested, finding a globally impaired and a selective executive dysfunction cluster. Given the established associations between executive dysfunction and treatment-resistance, the data replicate this finding. It is unclear whether the 2-cluster solution reflects the true cognitive variation in TRD patients, or whether this was instead due to the relatively small sample size of 60 patients (Siddiqui, 2013), particularly as larger clustering studies have returned 3 cluster solutions in similar populations (*e.g.* Martin et al., 2020; S Pu et al., 2018; Muriel Vicent-Gil et al., 2020). However, the results suggest that most TRD patients present with some degree of CD, however the domains affected are heterogeneous across this subtype. While these findings should be expanded upon in larger scale studies, the clustering strategy shows promise for identifying depressive subgroups. This may improve characterization of patients with depression, and may prove particularly helpful if neuropsychological

subgrouping maps onto biomarkers such as brain imaging abnormalities (Rasetti & Weinberger, 2011).

The binomial logistic regression model elucidated sources of variation in the current sample, namely age and benzodiazepine use. Benzodiazepine dose loaded as the greatest predictor of CD in our sample. This finding may be of utmost clinical significance as the prescription of benzodiazepines is widespread for MDD patients (Liu, Ye, Watson, & Tepper, 2010). The findings converge with a significant body of literature pointing to the detrimental effects of benzodiazepines on cognition, with impairment encompassing many cognitive domains beyond memory and psychomotor processing speed (Crowe and Stranks, 2018). Specifically, a recent meta-analysis by Crowe and colleagues demonstrated negative effects on working memory, processing speed, divided attention, visuoconstruction, recent memory, and expressive language with Hedges' g effects sizes that range between -0.78 to -0.12. Although there were some improvements in cognitive performance in those who had discontinued benzodiazepine use, significant deficits persisted in recent memory, processing speed, visuo-construction, divided attention, working memory, and sustained attention, with Hedges' g effect sizes ranging between -1.4 to -0.7 (Crowe & Stranks, 2018). Further, benzodiazepine use has been linked to increased risk of dementia in elderly patients (Gallacher et al., 2012). The results of the current study suggest that this negative side effect may occur even at low dosage of medication, which was also found in a recent systematic review (Uzun, Kozumplik, Jakovljević, & Sedić, 2010). Stewart (2005) reported that cessation of benzodiazepines improved cognition in patients treated long-term with the medication; however, patients did not return to levels of functioning that matched the control group. Whether this is due to side effects of long-term use, or because the patients were cognitively impaired prior to benzodiazepine use, is unclear. The presence of psychiatric

comorbidities, in particular anxiety disorders, has been suggested as a potential confounder as they tend to be associated with increased rates of CD (Basso et al., 2007; Baune, Mcafoose, Leach, Quirk, & Mitchell, 2009; Nelson & Gregg, 2012). In the current sample, however, GI and SE had negligible differences in prevalence of anxiety comorbidities (GI = 29%, SE = 38%) and the clusters also showed no differences in levels of anxiety symptoms (BSI-A score, p=0.44). Despite benzodiazepines being primarily indicated to treat anxiety symptoms, they are used in a wide range of contexts, including insomnia (Riemann & Perlis, 2009), and even as a monotherapy for approximately 1 in 10 patients for the treatment of depression in the United States (Soric et al., 2019). Although the indication for benzodiazepine prescription is unclear in the current sample, it did not appear to be limited to patients with anxiety disorders. The findings regarding the detrimental effect of benzodiazepine is of particular relevance considering the small dose these patients were on, as the usual therapeutic dose ranges 2-8 mg of lorazepam equivalent dose (Johns Hopkins Psychiatry Guide, 2016). Our group also recently reported that this small dose of benzodiazepine use is associated with decreased effectiveness of repetitive transcranial magnetic stimulation (Kaster et al., 2019).

Other psychiatric medications did not show significant relationships with cluster belonging. Antidepressants and benzodiazepines were included in the logistic regression as other psychiatric medication classes (*e.g.* antipsychotics, stimulants) were taken by too few patients to provide meaningful signal. In contrast, a clustering study by Pu *et al*. (2018) found that antidepressants associated with better, and that antipsychotics were associated with worse, cognitive performance. However, their sample comprised of MDD, rather than TRD, and included a larger range of depression severity, briefer disease duration, and less stringent exclusion criteria related to psychotic and manic symptoms. Finally, while current medication does not provide

information on other aspects of pharmacological intervention, such as the duration of, or past medication use, we also assessed treatment history, through the use of the ATHF form, and did not find any significant contributing effect.

The relationship between age and CD in depression is converging with previous research; nearly 40% of geriatric MDD patients exhibit cognitive symptoms (Morimoto, Kanellopoulos, & Alexopoulos, 2014). In TRD, the relationship of CD and aging may be further pronounced, as the number and length of depressive episodes appears to increase a patient's risk for developing dementia, specifically Alzheimer's disease (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). As patients with TRD get older, they may become at higher risk for CD. In the current sample, normal changes of cognition across the lifespan alone cannot account for this effect as participants' scores were calculated from age-corrected normative data, except in the case of the SJS. Aging is associated with an increased risk for non-psychiatric medical conditions (e.g. diabetes mellitus, cardiovascular disease) which are known to affect cognition (Angermann & Ertl, 2018; Zheng, Yan, Yang, Zhong, & Xie, 2018). Patients with major unstable concomitant medical illnesses were excluded from the current study; however, we cannot rule out the effects of chronic medical conditions in our sample.

Interestingly, while no affective symptoms and disease characteristics loaded into the logistic regression model, GI had a significantly greater disease duration compared to SE (GI M = 20.44 years versus SE M = 13.46 years). Although this relationship was found to be mediated by age, it aligns with previous findings that depression may have a cumulative effect on cognition over time, evidenced by lesser dysfunction in patients with first-episode depression (Basso & Bornstein, 1999), as well as worse cognition associated with a greater number of depressive episodes (Dotson et al., 2008; Gorwood et al., 2014). However, as a longer history of depression

is by nature associated with older age, disentangling these factors remains a challenge. Future investigation of age-related decline in TRD is warranted. Regardless of the directionality of the relationship between age and disease duration, the findings suggest that it is imperative to identify and treat TRD patients before the emergence of cognitive decline that becomes increasingly likely over time.

Although other clinical characteristics did not load into the model, factors such as depression severity and treatment-resistance have been previously reported as risk factors for CD (Philip Gorwood et al., 2008; McDermott & Ebmeier, 2009; Muriel Vicent-Gil et al., 2020). In light of this, it is important to consider the homogeneity of the current sample, which included moderate to severely depressed patients who all showed at least some degree of treatment resistance. The ability to detect effects of severity and treatment resistance are affected when using a restricted range; thus, larger, heterogenous samples of MDD patients may provide better insight into the contributions of these factors.

4.4 Overlap of Improvements in Memory and Mood symptoms after rTMS in Patients with Baseline Dysfunction

rTMS did not show discernable longitudinal improvements in cognition in the entire sample, however patients belonging to the GI cognitive subgroup at baseline showed significant improvements in verbal memory at the follow-up assessment, whereas the SE subgroup and HV showed no significant changes in verbal memory across the two timepoints. It is important to note that GI showed significantly worse verbal memory performance at baseline compared to SE and HV, whereas at the follow-up GI performance was no different than the other groups.

Previous research has found that when cognitive interventions are not circumscribed to patients presenting with CD, a ceiling effect present in cognitively intact patients impacts a study's ability to identify the true benefits of the intervention (Douglas, Milanovic, Porter, & Bowie, 2020; Miskowiak, Ott, Petersen, & Kessing, 2016; Ott et al., 2016). Furthermore, patients with more severe cognitive symptoms tend to benefit more greatly from cognitive interventions (Miskowiak, Carvalho, Vieta, & Kessing, 2016). As cognition was not a primary outcome in the clinical trial from which these data were collected (Blumberger et al., 2018b), there was considerable variation in the cognitive presentation of the sample. Instead, change in cognition across the baseline-identified cognitive clusters was investigated, which allowed for the detection of improvement only in the subset of patients who had the greatest degree of CD at baseline. These findings therefore solidify the notion that cognitive interventions for TRD should be investigated specifically in samples who present with CD in an effort to reduce noise from cognitive variability and detect true effects.

Baseline analyses indicated that GI belonging was predicted by older age and benzodiazepine use. I therefore investigated the relationship between these variables and changes in cognitive symptoms in an attempt to discern potential mediation. Age showed a moderate positive correlation with improvement in verbal memory within the entire sample. In the path analysis, there was a moderating effect of age, where a positive relationship between age and memory improvement was found in patients with impaired memory performance at baseline.

Age has been previously reported a positive predictor of response to rTMS in patients with treatment-resistant depression. Specifically, Kaster *et al*. (2019) analyzed trajectories of antidepressant response on the complete THREE-D sample, finding that older age predicted belonging to a rapid response trajectory. Intervention for older TRD patients experiencing

cognitive function is extremely important, as chronic depression is a risk factor for dementia (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Furthermore, deficits in verbal memory are in particular associated with later-life depression (Thomas et al., 2009). An intervention that specifically targets this cognitive domain, such as rTMS, could be very promising in improving patients' quality of life by simulatenously treating their cognitive and affective symptoms (Bortolato et al., 2016).

Specificity of Improvement of Cognitive Domains

Verbal learning and memory showed improvement at the 3-month follow-up, whereas no other cognitive domains showed improvements associated with rTMS. A handful of previous studies have similarly reported improvement in memory following rTMS treatment, although it is important to note that these studies either did not employ a comparator group to control for practice effects from repeated neuropsychological testing (Fitzgerald, Hoy, D, & Kulkarni, 2009; Hoy et al., 2013; Martis et al., 2003), or had small sample sizes (between 6 – 14 subjects per condition depending on the study), reducing the ability to discriminate between true signal and noise (Hausmann et al., 2004; P. E. Holtzheimer et al., 2004; Kedzior, Rajput, Price, Lee, & Martin-Iverson, 2012; Padberg et al., 1999).

In contrast, studies in both healthy controls and clinical populations have found that high frequency stimulation of the left DLPFC is associated with gains in working memory functions (Brunoni & Vanderhasselt, 2014). Given the role of the left DLPFC in the central executive network, and its known implications in executive functioning, one would expect to see improvements in cognitive domains such as working memory, set shifting, and inhibitory control

(Miyake et al., 2000). Meta-analyses do indeed report improvements in executive functions, in addition to psychomotor speed and attention, using similar rTMS protocols (Martin et al., 2016; Serafini et al., 2015). However, these improvements may be transient, rather than persistent, effects of rTMS. Concerto *et al*. (2015) conducted sham-controlled rTMS to the left DLPFC in TRD patients and assessed executive function in patients over the course of treatment. They found that while subjects demonstrated improvements in inhibitory control (measured using the Stroop task) when tested immediately following treatment completion, these improvements did not last at the 3 or 6 month follow-up timepoints (Concerto et al., 2015). Changes in cognition were not assessed immediately following rTMS treatment, so whether transient cognitive benefits occurred is unknown. Future research is therefore needed to characterize the timelines of cognitive change due to rTMS across cognitive domains.

Biological Mechanisms of Cognitive Improvement

The relationship between treatment response and improvement in cognitive symptoms suggests that the mechanism of response to rTMS is similar for these symptom domains. A vast body of evidence points towards the subgenual anterior cingulate cortex (sgACC) a key node of the salience network, being critical in the antidepressant response to rTMS (Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Ge, Downar, Blumberger, Daskalakis, & Vila-Rodriguez, 2020; Weigand et al., 2018). On the other hand, cognitive functions are typically associated with activity of the central executive network (Seeley et al., 2007). Despite vastly different brain regions having relevance for these two symptom domains, there was nonetheless a relationship between antidepressant response and cognitive improvement. While the physiological basis of

the therapeutic effect of rTMS is not fully elucidated, evidence suggests that rTMS works by perturbing brain networks, causing changes in how different brain regions work together (Anderson et al., 2016). The DLPFC, targeted in the current study, is directly implicated in cognitive processes, and also has anatomical connectivity with regions implicated in both affective (*e.g.* the sgACC) and cognitive (*e.g.* posterior parietal cortex, orbitofrontal cortex) functions (Anderson et al., 2016). Recent work by our group examined physiological response to acute rTMS using a concurrent TMS-fMRI protocol, finding that TRD patients who showed greater transient alterations in functional connectivity during the concurrent TMS-fMRI stimulation, interpreted as an index of macro-scale neuroplasticity, showed better subsequent response to rTMS treatment (Ge et al. 2021, in preparation). This evidence suggests that patients with a greater index of neuroplasticity are more amenable to trans-network changes induced by rTMS, resulting in improvements across a number of symptom domains.

The DLPFC has well-established anatomical and functional connections with the hippocampus (Anderson et al., 2016). In a recent analysis on this same sample by our group, we found that functional connections of bilateral hippocampal subregions and the right dorsolateral prefrontal cortex were negatively correlated with delayed recall (RAVLT 7 performance) in TRD but not HV (Ge, et al., 2019). This suggests a depression-specific pattern of functional connectivity between the hippocampus and the DLPFC that is implicated in impaired memory functions. As the hippocampus and the DLPFC are important nodes of the default mode network (DMN) and the central executive network (CEN), respectively, the increased functional connectivity between these regions may represent a disruption in the typical anticorrelation patterns seen between these networks (Menon, 2011). A study by Liston et al. (2014) investigating changes in functional connectivity related to rTMS treatment in TRD found significant increases

anticorrelated connectivity between CEN and DMN nodes, such as between the left DLPFC and parahippocampal cortices. Furthermore, studies investigating structural changes in the brain following rTMS have found increased cell proliferation and brain-derived neurotrophic factor in the hippocampus in rat models of depression (Peng et al., 2018), as well as increases in hippocampal gray matter volume found in TRD patients (Hayasaka et al., 2017; Noda, Zomorrodi, Daskalakis, Blumberger, & Nakamura, 2018).

Together with the results of the current study, this suggests that rTMS may induce improvements in memory functions through connections between the DLPFC and limbic regions, altering not only the functional activity between key resting-state brain networks but perhaps also inducing structural changes in the hippocampus.

4.5 Limitations and Future Considerations

The current study was comprised of a modest sample size in a homogeneous sample of TRD and HV. Demographic and disease factors were not available for all TRD, further reducing the sample size for the logistic regression analysis. Furthermore, loss to follow-up contributed to further reductions in the sample size for the repeated-measures analysis, reducing the study's power to detect cognitive effects of rTMS. The limited sample size should thus be considered when interpreting the results of this study.

Characterizing Cognition in TRD at Baseline

Although the effects of benzodiazepine use in this sample are striking and converging with mounting evidence on the detrimental effect of chronic benzodiazepine use, a definite causal

relationship with CD cannot be inferred in the current data due to the cross- sectional nature of this study. Future research should work to characterize the timeline of benzodiazepine use and cognitive symptoms in TRD. The homogeneity of the sample, being a treatment-resistant, severely depressed cohort, indicates that findings cannot be generalized to the broader MDD population. Affective and patient-reported symptoms (e.g. depression severity, functional impairment) and disease characteristics (e.g. disease duration, length of current episode) are within a restricted range and by no means encompass the full scope of variation in MDD. Rather, this study characterizes the most important factors relating to CD in adults with severe, chronic, treatment- resistant depression. Future research comparing TRD to MDD may give a better understanding of what factors are specific to CD with TRD patients, and whether there are different predictors of dysfunction in the general MDD population.

Furthermore, while older age was also found to be a significant predictor of belonging to the GI cluster, it is important to note that the age of the sample ranged from 19-63 years. Caution is warranted when extrapolating these findings to geriatric samples, although a similar pattern is expected given previous findings in the literature (Thomas et al., 2009).

The sample in the current study was highly educated and intelligent with high socioeconomic status; these results may thus only apply to a narrow population and may not be generalized to the entire TRD population. Nonetheless, despite being a highly educated, intelligent cohort, a large portion of TRD displayed CD, both when defining dysfunction through normative, and relative, cognitive scores. The HV group was slightly (but significantly) more educated than the TRD group, which may indicate a greater degree of cognitive reserve in HV; however, this should not have biased the results of the study, as scores were converted to z scores using normative data.

Cognitive Effects of rTMS

An important limitation of the longitudinal analyses is the lack of a patient comparator group who did not receive rTMS intervention. While a demographically matched cohort of HV was included a comparator gorup, patients with TRD may show differences in practice effects from non-clinical populations, as has been reported in patients with schizophrenia (Beglinger et al., 2003).

Next, patients were not pre-screened for CD as cognition was not a primary outcome of the clinical trial for which these patients were recruited. This may have reduced the ability to detect meaningful improvements as a significant portion of our sample performed normally at baseline. Cognitive improvements were detected in patients who presented with baseline deficits in verbal learning and memory, however this resulted in a significant reduction in power to detect change as group sample sizes were further reduced by splitting the patients into cognitive subgroups (GI = 26, SE = 21, HV = 22).

Finally, cognitive function were assessed at two timepoints, namely at baseline and 3 months post-treatment. While this allowed the detection of longitudinal effects of rTMS on cognitive performance, it remains unclear whether transient effects on other cognitive domains also occurred.

Future studies seeking to assess the cognitive benefits of rTMS should (1) include clinically similar comparator groups, (2) pre-screen patients for CD, and (3) assess changes in cognition at multiple timepoints following the end of rTMS to provide more insight into the timelines of cognitive changes.

rTMS Protocol and Treatment Target

While this study employed a protocol of 30 daily treatments of high frequency stimulation to the left DLPFC, it must be noted that there is a vast number of options when it comes to parameters including treatment schedule, stimulation intensity, and frequency. As rTMS is still in the early days of development, further knowledge of the contribution of these parameters to efficacy is needed in order to exert maximal benefits (Cash, Cocchi, Lv, Fitzgerald, & Zalesky, 2020). Finally, the left DLPFC may not be the optimal site to target when treating CD. A study targeting both the left and right DLPFC noted greater cognitive gains in patients who received right sided stimulation (Nadeau et al., 2014). Furthermore, research suggests that the right DLPFC may be more relevant to cognitive functions such as attention, whereas the left DLPFC may be more involved in emotional processing (Grimm et al., 2008). Additional treatment targets, including parietal regions functionally linked to the hippocampus (Mielacher et al., 2020), or the dorsomedial prefrontal cortex (Downar, 2019), have also shown promise in targeting cognitive symptoms. Targeting alternative brain regions with rTMS may prove to be more efficacious and could be stimulated in addition to the left DLPFC, in TRD who experience cognitive symptoms.

4.6 Conclusions

This study found that TRD is associated with a heterogeneous presentation of CD, with global CD in roughly half of patients, and selective executive dysfunction in remaining patients. Global deficits were associated with older age and use of benzodiazepines. These findings have particularly important clinical implications in screening patients who may be at-risk for cognitive

dysfunction, as well as informing clinicians on the cognitive effects that even low doses of benzodiazepines can exert.

Secondly, rTMS was found to selectively improve verbal memory in patients who showed deficits in this domain at baseline. This impresses upon the need to screen for CD in studies investigating cognitive effects in order to detect actual cognitive benefits of treatment. Rather than attributing memory improvements as an epiphenomenon of improvement in symptoms, I hypothesize that patients who improved in these symptom domains had a greater index of neuroplasticity and were thus more amenable to rTMS-induced changes in both affective and cognitive neural pathway; however, future research into the neural mechanisms of cognitive improvement following rTMS is warranted.

Bibliography

Aita, S. L., Beach, J. D., Taylor, S. E., Borgogna, N. C., Harrell, M. N., & Hill, B. D. (2018). Executive, language, or both? An examination of the construct validity of verbal fluency measures. https://doi.org/10.1080/23279095.2018.1439830

Allott, K., Fisher, C. A., Amminger, G. P., Goodall, J., & Hetrick, S. (2016). Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain and Behavior*, *6*(10), e00527. https://doi.org/10.1002/brb3.527

Anderson, R. J., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2016). Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections, *127*, 3394–3405. https://doi.org/10.1016/j.clinph.2016.08.015

Angermann, C. E., & Ertl, G. (2018, December 1). Depression, Anxiety, and Cognitive Impairment: Comorbid Mental Health Disorders in Heart Failure. *Current Heart Failure Reports*. Current Science Inc. https://doi.org/10.1007/s11897-018-0414-8

Avery, D. H., Holtzheimer, P. E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D. L., … Roy-Byrne, P. (2006). A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biological Psychiatry*, *59*(2), 187–194. https://doi.org/10.1016/j.biopsych.2005.07.003

Bagherzadeh, Y., Khorrami, A., Zarrindast, M. R., Shariat, S. V., & Pantazis, D. (2016). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex enhances working memory. *Experimental Brain Research*, *234*(7), 1807–1818. https://doi.org/10.1007/s00221-016-4580-1

Balestri, M., Calati, R., Souery, D., Kautzky, A., Kasper, S., Montgomery, S., … Serretti, A. (2016). Socio-demographic and clinical predictors of treatment resistant depression: A prospective European multicenter study. *Journal of Affective Disorders*, *189*, 224–232. https://doi.org/10.1016/j.jad.2015.09.033

Basso, M. R., & Bornstein, R. A. (1999). Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology*, *13*(4), 557–563. https://doi.org/10.1037/0894-4105.13.4.557

Basso, M. R., Lowery, N., Ghormley, C., Combs, D., Purdie, R., Neel, J., … Bornstein, R. (2007). Comorbid anxiety corresponds with neuropsychological dysfunction in unipolar depression. *Cognitive Neuropsychiatry*, *12*(5), 437–456.

https://doi.org/10.1080/13546800701446517

Baune, B. T., Mcafoose, J., Leach, G., Quirk, F., & Mitchell, D. (2009). Impact of psychiatric and medical comorbidity on cognitive function in depression. *Psychiatry and Clinical Neurosciences*, *63*(3), 392–400. https://doi.org/10.1111/j.1440-1819.2009.01971.x

Beglinger, L. J., Ahmed, S., Tangphao-Daniels, O., Derby, M. A., Siemers, E., & Kareken, D. A. (2003). Serial testing for clinical trials: Practice effects and reliability in patients with schizophrenia and healthy volunteers. *Schizophrenia Research*, *60*(1), 123. https://doi.org/10.1016/s0920-9964(03)80892-7

Belleau, E. L., Treadway, M. T., & Pizzagalli, D. A. (2019). The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology. *Biological Psychiatry*, *85*, 443–453. https://doi.org/10.1016/j.biopsych.2018.09.031

Benzodiazepines | Johns Hopkins Psychiatry Guide. (n.d.). Retrieved February 25, 2021, from https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Psychiatry_Guide/787140/all/Benzodiazepines

Bergfeld, I. O., Mantione, M., Figee, M., Schuurman, P. R., Lok, A., & Denys, D. (2018, August 1). Treatment-resistant depression and suicidality. *Journal of Affective Disorders*. Elsevier B.V. https://doi.org/10.1016/j.jad.2018.04.016

Blair, J. R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the national adult reading test. *Clinical Neuropsychologist*, *3*(2), 129–136. https://doi.org/10.1080/13854048908403285

Blumberger, D. M., Mulsant, B. H., Fitzgerald, P. B., Rajji, T. K., Ravindran, A. V., Young, L. T., … Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World Journal of Biological Psychiatry*, *13*(6), 423–435. https://doi.org/10.3109/15622975.2011.579163

Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., … Downar, J. (2018a). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Www.Thelancet.Com*, *391*, 1683. Retrieved from www.thelancet.com

Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., … Downar, J. (2018b). Effectiveness of theta burst versus high-frequency repetitive

transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *The Lancet*, *391*(10131), 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2

Boberg, C. (2005). The North American regional vocabulary survey: New variables and methods in the study of North American English. *American Speech*, *80*(1), 22–60. https://doi.org/10.1215/00031283-80-1-22

Bortolato, B., Miskowiak, K. W., Köhler, C. A., Maes, M., Fernandes, B. S., Berk, M., & Carvalho, A. F. (2016). Cognitive remission: a novel objective for the treatment of major depression? *BMC Medicine*, *14*(1), 9. https://doi.org/10.1186/s12916-016-0560-3

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.04.004

Brommelhoff, J. A., Gatz, M., Johansson, B., McArdle, J. J., Fratiglioni, L., & Pedersen, N. L. (2009). Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of Swedish twins. *Psychology and Aging*, *24*(2), 373–384. https://doi.org/10.1037/a0015713

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition*, *86*(1), 1–9. https://doi.org/10.1016/j.bandc.2014.01.008

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics*, *85*(5), 270–288. https://doi.org/10.1159/000447034

Cash, R. F. H., Cocchi, L., Lv, J., Fitzgerald, P. B., & Zalesky, A. (2020). Functional Magnetic Resonance Imaging–Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. *JAMA Psychiatry*, 1–3. https://doi.org/10.1001/jamapsychiatry.2020.3794

Cherry, K. E., Elliott, E. M., & Reese, C. M. (2007). Age and individual differences in working memory: The size judgment span task. *Journal of General Psychology*, *134*(1), 43–65. https://doi.org/10.3200/GENP.134.1.43-65

Colvard, M. D. (2014). Key differences between Venlafaxine XR and Desvenlafaxine: An

analysis of pharmacokinetic and clinical data. *Mental Health Clinician*, *4*(1), 35–39. https://doi.org/10.9740/mhc.n186977

Concerto, C., Lanza, G., Cantone, M., Ferri, R., Pennisi, G., Bella, R., & Aguglia, E. (2015). Repetitive transcranial magnetic stimulation in patients with drug-resistant major depression: A six-month clinical follow-up study. *International Journal of Psychiatry in Clinical Practice*, *19*(4), 252–258. https://doi.org/10.3109/13651501.2015.1084329

Conradi, H. J., Ormel, J., & De Jonge, P. (2011). Presence of individual (residual) symptoms during depressive episodes and periods of remission: A 3-year prospective study. *Psychological Medicine*. https://doi.org/10.1017/S0033291710001911

Crawford, J. R., Deary, I. J., Starr, J., & Whalley, L. J. (2001). The NART as an index of prior intellectual functioning: A retrospective validity study covering a 66-year interval. *Psychological Medicine*, *31*(3), 451–458. https://doi.org/10.1017/s0033291701003634

Crowe, S. F., & Stranks, E. K. (2018). The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. *Archives of Clinical Neuropsychology*, *33*(7), 901–911. https://doi.org/10.1093/arclin/acx120

de Kwaasteniet, B. P., Rive, M. M., Ruhé, H. G., Schene, A. H., Veltman, D. J., Fellinger, L., … Denys, D. (2015). Decreased Resting-State Connectivity between Neurocognitive Networks in Treatment Resistant Depression . *Frontiers in Psychiatry* . Retrieved from https://www.frontiersin.org/article/10.3389/fpsyt.2015.00028

den Hartog, H. M., Derix, M. M. A., Van Bemmel, A. L., Kremer, B., & Jolles, J. (2003). Cognitive functioning in young and middle-aged unmedicated out-patients with major depression: Testing the effort and cognitive speed hypotheses. *Psychological Medicine*, *33*(8), 1443–1451. https://doi.org/10.1017/S003329170300833X

Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory: an introductory report. *Psychological Medicine*, *13*(3), 595–605. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6622612

Dotson, V. M., Resnick, S. M., & Zonderman, A. B. (2008). Differential association of concurrent, baseline, and average depressive symptoms with cognitive decline in older adults. *American Journal of Geriatric Psychiatry*, *16*(4), 318–330. https://doi.org/10.1097/JGP.0b013e3181662a9c

Douglas, K. M., Gallagher, P., Robinson, L. J., Carter, J. D., McIntosh, V. V. W., Frampton, C.

M. A., … Porter, R. J. (2018). Prevalence of cognitive impairment in major depression and bipolar disorder. *Bipolar Disorders*, *20*(3), 260–274. https://doi.org/10.1111/bdi.12602

Douglas, K. M., Milanovic, M., Porter, R. J., & Bowie, C. R. (2020). Clinical and methodological considerations for psychological treatment of cognitive impairment in major depressive disorder. https://doi.org/10.1192/bjo.2020.53

Douglas, K. M., & Porter, R. J. (2009). Longitudinal Assessment of Neuropsychological Function in Major Depression. *Australian & New Zealand Journal of Psychiatry*, *43*(12), 1105–1117. https://doi.org/10.3109/00048670903279887

Downar, J. (2019). Towards a personalized approach to rTMS target selection in depression. *Brain Stimulation*, *12*(2), 552. https://doi.org/10.1016/j.brs.2018.12.825

DSM 5. (2013). *DSM 5*. *American Journal of Psychiatry*. https://doi.org/10.1176/appi.books.9780890425596.744053

Elgamal, S., Denburg, S., Marriott, M., & MacQueen, G. (2010). Clinical factors that predict cognitive function in patients with major depression. *Canadian Journal of Psychiatry*. https://doi.org/10.1177/070674371005501004

Evans, V. C., Chan, S. S., Iverson, G. L., Bond, D. J., Yatham, L. N., & Lam, R. W. (2013). Systematic review of neurocognition and occupational functioning in major depressive disorder. *Neuropsychiatry*. https://doi.org/10.2217/npy.13.3

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., … Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*. https://doi.org/10.1371/journal.pmed.1001547

Fitzgerald, P. B., Hoy, K., D, & Kulkarni, J. (2009). A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depression and Anxiety*, *26*(3), 229–234. https://doi.org/10.1002/da.20454

Fossati, P., Coyette, F., Ergis, A. M., & Allilaire, J. F. (2002). Influence of age and executive functioning on verbal memory of inpatients with depression. *Journal of Affective Disorders*, *68*(2–3), 261–271. https://doi.org/10.1016/S0165-0327(00)00362-1

Fossati, P., Guillaume, L. B., Ergis, A. M., & Allilaire, J. F. (2003). Qualitative analysis of verbal fluency in depression. *Psychiatry Research*. https://doi.org/10.1016/S0165-1781(02)00300-1

Fossati, P., Harvey, P.-O., Le Bastard, G., Ergis, A.-M., Jouvent, R., & Allilaire, J.-F. (2004). Verbal memory performance of patients with a first depressive episode and patients with unipolar and bipolar recurrent depression. *Journal of Psychiatric Research*, *38*(2), 137–144. https://doi.org/10.1016/j.jpsychires.2003.08.002

Fox, M. D., Buckner, R. L., White, M. P., Greicius, M. D., & Pascual-Leone, A. (2012). Efficacy of TMS targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. https://doi.org/10.1016/j.biopsych.2012.04.028

Galecki, P., Talarowska, M., Moczulski, D., Bobinska, K., Opuchlik, K., Galecka, E., … Lewinski, A. (2013). Working memory impairment as a common component in recurrent depressive disorder and certain somatic diseases. *Neuro Endocrinology Letters*, *34*(5), 436–445. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23922050

Gallacher, J., Elwood, P., Pickering, J., Bayer, A., Fish, M., & Ben-Shlomo, Y. (2012). Benzodiazepine use and risk of dementia: Evidence from the Caerphilly Prospective Study (caps). *Journal of Epidemiology and Community Health*. https://doi.org/10.1136/jech-2011-200314

Galletly, C., Gill, S., Rigby, A., Carnell, B. L., & Clarke, P. (2016). Assessing the effects of repetitive transcranial magnetic stimulation on cognition in major depressive disorder using computerized cognitive testing. *Journal of ECT*, *32*(3), 169–173. https://doi.org/10.1097/YCT.0000000000000308

Ge, R., Downar, J., Blumberger, D. M., Daskalakis, Z. J., Lam, R. W., & Vila-Rodriguez, F. (2019). Structural network integrity of the central executive network is associated with the therapeutic effect of rTMS in treatment resistant depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 217–225. https://doi.org/10.1016/j.pnpbp.2019.01.012

Ge, R., Downar, J., Blumberger, D. M., Daskalakis, Z. J., & Vila-Rodriguez, F. (2020). Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2019.10.012

Ge, R., Torres, I., Brown, J. J., Gregory, E., McLellan, E., Downar, J. H., … Vila-Rodriguez, F. (2019). Functional disconnectivity of the hippocampal network and neural correlates of memory impairment in treatment-resistant depression. *Journal of Affective Disorders*, *253*,

248–256. https://doi.org/10.1016/j.jad.2019.04.096

Golden, C. (1978). A Manual for the Clinical and Experimental Use of the Stroop Color and Word Test. *Faculty Books and Book Chapters*. Retrieved from https://nsuworks.nova.edu/cps_facbooks/47

Goodall, J., Fisher, C., Hetrick, S., Phillips, L., Parrish, E. M., & Allott, K. (2018, June 1). Neurocognitive Functioning in Depressed Young People: A Systematic Review and Meta-Analysis. *Neuropsychology Review*. Springer New York LLC. https://doi.org/10.1007/s11065-018-9373-9

Gorwood, P., Richard-Devantoy, S., Baylé, F., & Cléry-Melun, M. L. (2014). Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests. *European Neuropsychopharmacology*, *24*(10), 1630–1640. https://doi.org/10.1016/J.EURONEURO.2014.07.013

Gorwood, Philip, Corruble, E., Falissard, B., & Goodwin, G. M. (2008). Toxic effects of depression on brain function: Impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *American Journal of Psychiatry*, *165*(6), 731–739. https://doi.org/10.1176/appi.ajp.2008.07040574

Gregory, E., Torres, I. J., Ge, R., Blumberger, D. M., Downar, J. H., Daskalakis, Z. J., … Vila-Rodriguez, F. (2020). Predictors of cognitive impairment in treatment-resistant depression. *Journal of Affective Disorders*, *274*, 593–601. https://doi.org/10.1016/j.jad.2020.05.101

Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., … Northoff, G. (2008). Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. *Biological Psychiatry*, *63*(4), 369–376. https://doi.org/10.1016/j.biopsych.2007.05.033

Groves, S. J., Douglas, K. M., & Porter, R. J. (2018). A Systematic Review of Cognitive Predictors of Treatment Outcome in Major Depression. *Frontiers in Psychiatry*, *9*, 382. https://doi.org/10.3389/fpsyt.2018.00382

Gruber, O., Zilles, D., Kennel, J., Gruber, E., & Falkai, P. (2011). A systematic experimental neuropsychological investigation of the functional integrity of working memory circuits in major depression. *European Archives of Psychiatry and Clinical Neuroscience*, *261*(3), 179–184. https://doi.org/10.1007/s00406-010-0165-3

Gupta, M., Holshausen, K., Best, M. W., Jokic, R., Milev, R., Bernard, T., … Bowie, C. R. (2013). Relationships among neurocognition, symptoms, and functioning in treatment-resistant depression. *Archives of Clinical Neuropsychology*, *28*(3), 272–281. https://doi.org/10.1093/arclin/act002

Halahakoon, D. C., Lewis, G., Roiser, J. P., & Psychiatry, J. (2019). Cognitive Impairment and Depression — Cause , Consequence , or Coincidence ?, *76*(3), 2018–2019. https://doi.org/10.1111/jcpp.12483

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*, 56–62. https://doi.org/10.1136/jnnp.23.1.56

Hammar, Å., Strand, M., Årdal, G., Schmid, M., Lund, A., & Elliott, R. (2011). Testing the cognitive effort hypothesis of cognitive impairment in major depression. *Nordic Journal of Psychiatry*, *65*(1), 74–80. https://doi.org/10.3109/08039488.2010.494311

Hausmann, A., Kemmler, G., Walpoth, M., Mechtcheriakov, S., Kramer-Reinstadler, K., Lechner, T., … Conca, A. (2004). No benefit derived from repetitive transcranial magnetic stimulation in depression: A prospective, single centre, randomised, double blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*(2), 320–322. https://doi.org/10.1136/jnnp.2002.009209

Hayasaka, S., Nakamura, M., Noda, Y., Izuno, T., Saeki, T., Iwanari, H., & Hirayasu, Y. (2017). Lateralized hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. *Psychiatry and Clinical Neurosciences*, *71*(11), 747–758. https://doi.org/10.1111/pcn.12547

Hayasaka, Y., Purgato, M., Magni, L. R., Ogawa, Y., Takeshima, N., Cipriani, A., … Furukawa, T. A. (2015). Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *Journal of Affective Disorders*, *180*, 179–184. https://doi.org/10.1016/j.jad.2015.03.021

Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling [White paper]. Retrieved from http://www.afhayes.com/public/process2012.pdf. *Unpublished Manuscript*.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*, *12*(3), 426–445. https://doi.org/10.1037/0894-4105.12.3.426

Helgadóttir, B., Hallgren, M., Kullberg, C. L. E., & Forsell, Y. (2018). Sticking with it? Factors associated with exercise adherence in people with mild to moderate depression. *Psychology of Sport and Exercise*, *35*, 104–110. https://doi.org/https://doi.org/10.1016/j.psychsport.2017.11.011

Hermens, D. F., Redoblado Hodge, M. A., Naismith, S. L., Kaur, M., Scott, E., & Hickie, I. B. (2011). Neuropsychological clustering highlights cognitive differences in young people presenting with depressive symptoms. *Journal of the International Neuropsychological Society*, *17*(2), 267–276. https://doi.org/10.1017/S1355617710001566

Holtzheimer, P. E., Russo, J., Claypoole, K. H., Roy-Byrne, P., & Avery, D. H. (2004). Brief Report SHORTER DURATION OF DEPRESSIVE EPISODE MAY PREDICT RESPONSE TO REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION. *Depression and Anxiety*, *19*, 24–30. https://doi.org/10.1002/da.10147

Holtzheimer, P., Mcdonald, W., Mufti, M., Kelley, M., Quinn, S., Corso, G., & Epstein, C. M. (2010). Accelerated repetitive transcranial magnetic stimulation (aTMS) for treatment-resistant depression. *Depress Anxiety*. https://doi.org/10.1002/da.20731.Accelerated

Hoy, K. E., Thomson, R. H., Cherk, M., Yap, K. S. K., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Effect of magnetic seizure therapy on regional brain glucose metabolism in major depression. *Psychiatry Research - Neuroimaging*. https://doi.org/10.1016/j.pscychresns.2012.08.003

Huang, M. L., Luo, B. Y., Hu, J. B., Wang, S. S., Zhou, W. H., Wei, N., … Xu, Y. (2012). Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: A double-blind, randomized, sham-controlled trial. *Australian and New Zealand Journal of Psychiatry*, *46*(3), 257–264. https://doi.org/10.1177/0004867411433216

Inada, T., & Inagaki, A. (2015). Psychotropic dose equivalence in Japan. *Psychiatry and Clinical Neurosciences*, *69*(8), 440–447. https://doi.org/10.1111/pcn.12275

Ionescu, D. F., Rosenbaum, J. F., & Alpert, J. E. (2015). Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues in Clinical Neuroscience*, *17*(2), 111–126. https://doi.org/10.1007/978-3-642-40308-8_2

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state

functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kaster, T. S., Downar, J., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., … Blumberger, D. M. (2019). Trajectories of response to dorsolateral prefrontal rTMS in major depression: A three-D study. *American Journal of Psychiatry*, *176*(5), 367–375. https://doi.org/10.1176/appi.ajp.2018.18091096

Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G. S., Souery, D., … Kasper, S. (2019). Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatrica Scandinavica*, *139*(1), 78–88. https://doi.org/10.1111/acps.12959

Kedzior, K. K., Rajput, V., Price, G., Lee, J., & Martin-Iverson, M. (2012). Cognitive correlates of repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant depression- a pilot study. *BMC Psychiatry*, *12*. https://doi.org/10.1186/1471-244X-12-163

Kelliny, M., Croarkin, P. E., Moore, K. M., & Bobo, W. V. (2015). Profile of vortioxetine in the treatment of major depressive disorder: an overview of the primary and secondary literature. *Therapeutics and Clinical Risk Management*, *11*, 1193–1212. https://doi.org/10.2147/TCRM.S55313

Kobrosly, R. W., van Wijngaarden, E., Seplaki, C. L., Cory-Slechta, D. A., & Moynihan, J. (2014). Depressive symptoms are associated with allostatic load among community-dwelling older adults. *Physiology and Behavior*, *123*, 223–230. https://doi.org/10.1016/j.physbeh.2013.10.014

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, *201*, 239–243. https://doi.org/10.1016/j.bbr.2009.03.004

Kornstein, S. G., & Schneider, R. K. (2001). Clinical Features of Treatment-Resistant Depression. *The Journal of Clinical Psychiatry*, *62*(suppl 16), 18–25.

Lam, R. W., Kennedy, S. H., McIntyre, R. S., & Khullar, A. (2014). Cognitive dysfunction in major depressive disorder: Effects on psychosocial functioning and implications for treatment. *Canadian Journal of Psychiatry*. https://doi.org/10.1177/070674371405901206

Lee, R. S. C., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of*

Affective Disorders, *140*(2), 113–124. https://doi.org/10.1016/J.JAD.2011.10.023

Leggett, L. E., Soril, L. J. J., Coward, S., Lorenzetti, D. L., Mackean, G., & Clement, F. M. (2015). Repetitive transcranial magnetic stimulation for treatment-resistant depression in adult and youth populations: A systematic literature review and meta-analysis. *Primary Care Companion to the Journal of Clinical Psychiatry*, *17*(6), 379–388. https://doi.org/10.4088/PCC.15r01807

LeMoult, J., & Gotlib, I. H. (2019). Depression: A cognitive perspective. *Clinical Psychology Review*, *69*(June 2018), 51–66. https://doi.org/10.1016/j.cpr.2018.06.008

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, J. H., & Fischer, J. S. (2004). Neuropsychological Assessment. Oxford University Press. *New York*.

Lin, K., Xu, G., Lu, W., Ouyang, H., Dang, Y., Lorenzo-Seva, U., … Lee, T. M. C. (2014). Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: a prospective longitudinal study. *Journal of Affective Disorders*, *168*, 184–191. https://doi.org/10.1016/J.JAD.2014.06.032

Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., … Dubin, M. J. (2014a). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*, *76*(7), 517–526. https://doi.org/10.1016/j.biopsych.2014.01.023

Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., … Dubin, M. J. (2014b). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*, *76*(7), 517–526. https://doi.org/10.1016/j.biopsych.2014.01.023

Listunova, L., Roth, C., Bartolovic, M., Kienzle, J., Bach, C., Weisbrod, M., & Roesch-Ely, D. (2018). Cognitive impairment along the course of depression: Non-pharmacological treatment options. *Psychopathology*, *51*(5), 295–305. https://doi.org/10.1159/000492620

Liu, X., Ye, W., Watson, P., & Tepper, P. (2010). Use of benzodiazepines, hypnotics, and anxiolytics in major depressive disorder: Association with chronic pain diseases. *Journal of Nervous and Mental Disease*, *198*(8), 544–550. https://doi.org/10.1097/NMD.0b013e3181e9daf7

Loo, C. K., Mitchell, P. B., Croker, V. M., Malhi, G. S., Wen, W., Gandevia, S. C., & Sachdev, P. S. (2003). Double-blind controlled investigation of bilateral prefrontal transcranial

magnetic stimulation for the treatment of resistant major depression. *Psychological Medicine*, *33*(1), 33–40. https://doi.org/10.1017/S0033291702006839

Loo, C., Sachdev, P., Elsayed, H., McDarmont, B., Mitchell, P., Wilkinson, M., … Gandevia, S. (2001). Effects of a 2- to 4-week course of repetitive Transcranial Magnetic Stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biological Psychiatry*, *49*(7), 615–623. https://doi.org/10.1016/S0006-3223(00)00996-3

Luber, B., & Lisanby, S. H. (2014, January 15). Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *NeuroImage*. Academic Press Inc. https://doi.org/10.1016/j.neuroimage.2013.06.007

MacQueen, G. M., Galway, T. M., Hay, J., Young, L. T., & Joffe, R. T. (2002). Recollection memory deficits in patients with major depressive disorder predicted by past depressions but not current mood state or treatment status. *Psychological Medicine*. https://doi.org/10.1017/S0033291701004834

Maeshima, H., Baba, H., Satomura, E., Shimano, T., Inoue, M., Ishijima, S., … Arai, H. (2016). Residual memory impairment in remitted depression may be a predictive factor for recurrence. *Journal of Clinical Psychiatry*. https://doi.org/10.4088/JCP.14m09694

Martin, D. M., McClintock, S. M., Forster, J., & Loo, C. K. (2016). Does Therapeutic Repetitive Transcranial Magnetic Stimulation Cause Cognitive Enhancing Effects in Patients with Neuropsychiatric Conditions? A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Neuropsychology Review*, *26*(3), 295–309. https://doi.org/10.1007/s11065-016-9325-1

Martin, D. M., Wollny-Huttarsch, D., Nikolin, S., McClintock, S. M., Alonzo, A., Lisanby, S. H., & Loo, C. K. (2020). Neurocognitive Subgroups in Major Depressive Disorder. *Neuropsychology*. https://doi.org/10.1037/neu0000626

Martis, B., Alam, D., Dowd, S. M., Hill, S. K., Sharma, R. P., Rosen, C., … Janicak, P. G. (2003). Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clinical Neurophysiology*. https://doi.org/10.1016/S1388-2457(03)00046-4

McClintock, S. M., Cullum, C. M., Husain, M. M., Rush, A. J., Knapp, R. G., Mueller, M., … Kellner, C. H. (2010). Evaluation of the effects of severe depression on global cognitive

function and memory. *CNS Spectrums*, *15*(5), 304–313. https://doi.org/10.1017/S109285290002753X

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2009.04.022

McDonald, W. M., Easley, K., Byrd, E. H., Holtzheimer, P., Tuohy, S., Woodard, J. L., … Epstein, C. M. (2006). Combination rapid transcranial magnetic stimulation in treatment refractory depression. *Neuropsychiatric Disease and Treatment*, *2*(1), 85–94. Retrieved from /pmc/articles/PMC2671728/

Mcewen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., & Nasca, C. (n.d.). Mechanisms of stress in the brain. https://doi.org/10.1038/nn.4086

McIntyre, R. S., Cha, D. S., Soczynska, J. K., Woldeyohannes, H. O., Gallaugher, L. A., Kudlow, P., … Baskaran, A. (2013). Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety*. https://doi.org/10.1002/da.22063

McLoughlin, D. M., Mogg, A., Eranti, S., Pluck, G., Purvis, R., Edwards, D., … Knapp, M. (2007). The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: A multicentre pragmatic randomised controlled trial and economic analysis. *Health Technology Assessment*, *11*(24). https://doi.org/10.3310/hta11240

Meijsen, J. J., Campbell, A., Hayward, C., Porteous, D. J., Deary, I. J., Marioni, R. E., & Nicodemus, K. K. (2018). Phenotypic and genetic analysis of cognitive performance in Major Depressive Disorder in the Generation Scotland: Scottish Family Health Study. *Translational Psychiatry*, *8*(1), 1–9. https://doi.org/10.1038/s41398-018-0111-0

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2011.08.003

Mielacher, C., Schultz, J., Kiebs, M., Dellert, T., Metzner, A., Graute, L., … Hurlemann, R. (2020). Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder. *Personalized Medicine in Psychiatry*, *23–24*, 100066. https://doi.org/10.1016/j.pmip.2020.100066

Milev, R. V, Giacobbe, P., Kennedy, S. H., Blumberger, D. M., Daskalakis, Z. J., Downar, J., … Ravindran, A. V. (2016). Canadian Network for Mood and Anxiety Treatments

(CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. *The Canadian Journal of Psychiatry*, 1–15. https://doi.org/10.1177/0706743716660033

Miller, E. K., & Cohen, J. D. (2001). An Integrative Theory of Prefrontal Cortex Function. *Annual Review of Neuroscience*, *24*(1), 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Mishkin, M. (1997). Hierarchical organization of cognitive memory. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.1997.0132

Miskowiak, K.W., Ott, C. V., Petersen, J. Z., & Kessing, L. V. (2016). Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. *European Neuropsychopharmacology*, *26*(12), 1845–1867. https://doi.org/10.1016/j.euroneuro.2016.09.641

Miskowiak, Kamilla W., Carvalho, A. F., Vieta, E., & Kessing, L. V. (2016, October 1). Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations. *European Neuropsychopharmacology*. Elsevier B.V. https://doi.org/10.1016/j.euroneuro.2016.08.011

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Morimoto, S. S., Kanellopoulos, T., & Alexopoulos, G. S. (2014). Cognitive Impairment in Depressed Older Adults: Implications for Prognosis and Treatment. *Psychiatric Annals*. https://doi.org/10.3928/00485713-20140306-05

Morimoto, S. S., Manning, K. J., Kim, J. U., & Cote, S. E. (2018). Non-Pharmacological Cognitive Remediation Strategies for Treatment of Depression and Cognitive Impairment. *Current Behavioral Neuroscience Reports*, *5*(3), 198–209. https://doi.org/10.1007/s40473-018-0158-5

Mosimann, U. P., Schmitt, W., Greenberg, B. D., Kosel, M., Müri, R. M., Berkhoff, M., … Schlaepfer, T. E. (2004). Repetitive transcranial magnetic stimulation: A putative add-on treatment for major depression in elderly patients. *Psychiatry Research*, *126*(2), 123–133.

https://doi.org/10.1016/j.psychres.2003.10.006

Mukaka, M., White, S. A., Terlouw, D. J., Mwapasa, V., Kalilani-Phiri, L., & Faragher, E. B. (2016). Is using multiple imputation better than complete case analysis for estimating a prevalence (risk) difference in randomized controlled trials when binary outcome observations are missing? *Trials*, *17*, 341. https://doi.org/10.1186/s13063-016-1473-3

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015, September 1). Resting-state functional connectivity in major depressive disorder: A review. *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2015.07.014

Murphy, J. A., Sarris, J., & Byrne, G. J. (2017). A Review of the Conceptualisation and Risk Factors Associated with Treatment-Resistant Depression. https://doi.org/10.1155/2017/4176825

Murrough, J. W., Iacoviello, B., Neumeister, A., Charney, D. S., & Iosifescu, D. V. (2011). Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2011.06.006

Nadeau, S. E., Bowers, D., Jones, T. L., Wu, S. S., Triggs, W. J., & Heilman, K. M. (2014). Cognitive effects of treatment of depression with repetitive transcranial magnetic stimulation. *Cognitive and Behavioral Neurology*, *27*(2), 77–87. https://doi.org/10.1097/WNN.0000000000000031

Nelson, J. M., & Gregg, N. (2012). Depression and anxiety among transitioning adolescents and college students with ADHD, dyslexia, or comorbid ADHD/dyslexia. *Journal of Attention Disorders*, *16*(3), 244–254. https://doi.org/10.1177/1087054710385783

Noda, Y., Zomorrodi, R., Daskalakis, Z. J., Blumberger, D. M., & Nakamura, M. (2018). Enhanced theta-gamma coupling associated with hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. *International Journal of Psychophysiology*, *133*, 169–174. https://doi.org/10.1016/j.ijpsycho.2018.07.004

Oquendo, M. A., Baca-Garcia, E., Kartachov, A., Khait, V., Campbell, C. E., Richards, M., … Mann, J. J. (2003). A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. *The Journal of Clinical Psychiatry*, *64*(7), 825–833. https://doi.org/10.4088/jcp.v64n0714

Ott, C. V., Bjertrup, A. J., Jensen, J. H., Ullum, H., Sjælland, R., Purdon, S. E., … Miskowiak, K. W. (2016). Screening for cognitive dysfunction in unipolar depression: Validation and evaluation of objective and subjective tools. *Journal of Affective Disorders*, *190*. https://doi.org/10.1016/j.jad.2015.10.059

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.63.5.530

Ozcan, S., Gica, S., & Gulec, H. (2020). Suicidal behavior in treatment resistant major depressive disorder patients treated with transmagnetic stimulation(TMS) and its relationship with cognitive functions. *Psychiatry Research*, *286*, 112873. https://doi.org/10.1016/j.psychres.2020.112873

Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., D. Greenberg, B., … Möller, H. J. (1999). Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: Comparative study of fast, slow and sham rTMS. *Psychiatry Research*, *88*(3), 163–171. https://doi.org/10.1016/S0165-1781(99)00092-X

Pallanti, S., Di Rollo, A., Antonini, S., Cauli, G., Hollander, E., & Quercioli, L. (2012). Low-frequency rTMS over right dorsolateral prefrontal cortex in the treatment of resistant depression: Cognitive improvement is independent from clinical response, resting motor threshold is related to clinical response. *Neuropsychobiology*. https://doi.org/10.1159/000336999

Peng, Z., Zhou, C., Xue, S., Bai, J., Yu, S., Li, X., … Tan, Q. (2018). Mechanism of Repetitive Transcranial Magnetic Stimulation for Depression •REVIEW•. *Shanghai Arch Psychiatry*, *30*(2), 84–92. https://doi.org/10.11919/j.issn.1002-0829.217047

Petersen, J. Z., Porter, R. J., & Miskowiak, K. W. (2019). Clinical characteristics associated with the discrepancy between subjective and objective cognitive impairment in depression. *Journal of Affective Disorders*, *246*(October 2018), 763–774. https://doi.org/10.1016/j.jad.2018.12.105

Pimontel, M. A., Rindskopf, D., Rutherford, B. R., Brown, P. J., Roose, S. P., & Sneed, J. R. (2016). A Meta-Analysis of Executive Dysfunction and Antidepressant Treatment Response in Late-Life Depression. *American Journal of Geriatric Psychiatry*, *24*(1), 31–41. https://doi.org/10.1016/j.jagp.2015.05.010

Preiss, M., Shatil, E., Cermakova, R., Cimermannova, D., & Flesher, I. (2013). Personalized Cognitive Training in Unipolar and Bipolar Disorder: A Study of Cognitive Functioning . *Frontiers in Human Neuroscience* . Retrieved from https://www.frontiersin.org/article/10.3389/fnhum.2013.00108

Price, C. J. (2000). The anatomy of language: contributions from functional neuroimaging. *Journal of Anatomy*. https://doi.org/10.1046/j.1469-7580.2000.19730335.x

Pu, S, Noda, T., Setoyama, S., & Nakagome, K. (2018). Empirical evidence for discrete neurocognitive subgroups in patients with non-psychotic major depressive disorder: clinical implications. *Psychological Medicine*, 1–13. https://doi.org/10.1017/s003329171800034x

Pu, Shenghong, Setoyama, S., & Noda, T. (2017). Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. *Scientific Reports*, *7*(1), 1–6. https://doi.org/10.1038/s41598-017-12142-8

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.05.028

Radvansky, G. A., & Tamplin, A. K. (2012). Memory. In *Encyclopedia of Human Behavior: Second Edition*. https://doi.org/10.1016/B978-0-12-375000-6.00229-9

Rao, D., Xu, G., Lu, Z., Liang, H., Lin, K., & Tang, M. (2019). Comparative study of cognitive function between treatment-resistant depressive patients and first-episode depressive patients. *Neuropsychiatric Disease and Treatment*, *15*, 3411–3417. https://doi.org/10.2147/NDT.S226405

Rasetti, R., & Weinberger, D. R. (2011). Intermediate phenotypes in psychiatric disorders. *Current Opinion in Genetics and Development*. https://doi.org/10.1016/j.gde.2011.02.003

Reppermund, S., Ising, M., Lucae, S., & Zihl, J. (2009). Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. *Psychological Medicine*, *39*(4), 603–614. https://doi.org/10.1017/S003329170800411X

Riemann, D., & Perlis, M. L. (2009, June). The treatments of chronic insomnia: A review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Medicine Reviews*. Sleep Med Rev. https://doi.org/10.1016/j.smrv.2008.06.001

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–

2040. https://doi.org/10.1017/S0033291713002535

Rund, B. R., Sundet, K., Asbjørnsen, A., Egeland, J., Landrø, N. I., Lund, A., … Hugdahl, K. (2006). Neuropsychological test profiles in schizophrenia and non-psychotic depression. *Acta Psychiatrica Scandinavica*. https://doi.org/10.1111/j.1600-0447.2005.00626.x

Schulze-Rauschenbach, S. C., Harms, U., Schlaepfer, T. E., Maier, W., Falkai, P., & Wagner, M. (2005). Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *British Journal of Psychiatry*. https://doi.org/10.1192/bjp.186.5.410

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Serafini, G., Pompili, M., Belvederi Murri, M., Respino, M., Ghio, L., Girardi, P., … Amore, M. (2015). The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review. *Neuropsychobiology*, *71*(3), 125–139. https://doi.org/10.1159/000381351

Sheehan, D. V., Harnett-Sheehan, K., & Raj, B. A. (1996). The measurement of disability. In *International Clinical Psychopharmacology*. https://doi.org/10.1097/00004850-199606003-00015

Sheehan, David V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In *Journal of Clinical Psychiatry* (Vol. 59, pp. 22–33).

Siddiqui, K. (2013). Heuristics for Sample Size Determination in Multivariate Statistical Techniques. *World Applied Sciences Journal*, *27*(2), 285–287. https://doi.org/10.5829/idosi.wasj.2013.27.02.889

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased Amygdala and Decreased Dorsolateral Prefrontal BOLD Responses in Unipolar Depression: Related and Independent Features. *Biological Psychiatry*, *61*(2), 198–209. https://doi.org/10.1016/j.biopsych.2006.05.048

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on

neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*. https://doi.org/10.1037/a0028727

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: Bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology*, *6*(MAR). https://doi.org/10.3389/fpsyg.2015.00328

Soric, M. M., Paxos, C., Dugan, S. E., Fosnight, S. M., Turosky, J. Z., Sadana, P., … Safi, I. M. (2019). Prevalence and predictors of benzodiazepine monotherapy in patients with depression: A national cross-sectional study. *Journal of Clinical Psychiatry*, *80*(4). https://doi.org/10.4088/JCP.18m12588

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0800005105

Stewart, S. A. (2005). The effects of benzodiazepines on cognition. *Journal of Clinical Psychiatry*. https://doi.org/10.1176/ajp.138.4.aj1384536

Stopford, C. L., Thompson, J. C., Richardson, A. M. T., Neary, D., & Snowden, J. S. (2010). Working memory in Alzheimer's disease and frontotemporal dementia. *Behavioural Neurology*, *23*(4), 177–179. https://doi.org/10.3233/BEN-2010-0288

Stordal, K. I., Lundervold, A. J., Egeland, J., Mykletun, A., Asbjørnsen, A., Landrø, N. I., … Lund, A. (2004). Impairment across executive functions in recurrent major depression. *Nordic Journal of Psychiatry*, *58*(1), 41–47. https://doi.org/10.1080/08039480310000789

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: Lessons from studies of the frontal lobes. *Annual Review of Psychology*, *53*, 401–433. https://doi.org/10.1146/annurev.psych.53.100901.135220

Sullivan, M., Edgley, K., & Dehoux, E. (1990). A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use.

Thomas, A.J., Gallagher, P., LJ, R., RJ, P., AH, Y., IN, F., & JT, O. (2009). A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychological Medicine*, *39*(5), 725-733 9p. https://doi.org/10.1017/S0033291708004042

Tovar-Perdomo, S., McGirr, A., Van den Eynde, F., Rodrigues dos Santos, N., & Berlim, M. T. (2017). High frequency repetitive transcranial magnetic stimulation treatment for major depression: Dissociated effects on psychopathology and neurocognition. *Journal of Affective Disorders*, *217*, 112–117. https://doi.org/10.1016/j.jad.2017.03.075

Tran, T., Milanovic, M., Holshausen, K., & Bowie, C. R. (2021). What is normal cognition in depression? Prevalence and functional correlates of normative versus idiographic cognitive impairment. *Neuropsychology*, *35*(1), 33–41. https://doi.org/10.1037/neu0000717

Trevizol, A. P., & Blumberger, D. M. (2019). An Update on Repetitive Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder. *Clinical Pharmacology & Therapeutics*, cpt.1550. https://doi.org/10.1002/cpt.1550

Tsaltas, E., Kalogerakou, S., Papakosta, V.-M., Kontis, D., Theochari, E., Koutroumpi, M., … Oulis, P. (2011). Contrasting patterns of deficits in visuospatial memory and executive function in patients with major depression with and without ECT referral. *Psychological Medicine*, *41*(05), 983–995. https://doi.org/10.1017/S0033291710001443

Tulving, E. (1985). How many memory systems are there? *American Psychologist*. https://doi.org/10.1037/0003-066x.40.4.385

Uzun, S., Kozumplik, O., Jakovljević, M., & Sedić, B. (2010). Side effects of treatment with benzodiazepines. In *Psychiatria Danubina*. https://doi.org/10.1016/S0959-8049(02)81277-1

Vanderhasselt, M. A., & De Raedt, R. (2009). Impairments in cognitive control persist during remission from depression and are related to the number of past episodes: An event related potentials study. *Biological Psychology*, *81*(3), 169–176. https://doi.org/10.1016/J.BIOPSYCHO.2009.03.009

Vicent-Gil, M., Keymer-Gausset, A., Serra-Blasco, M., Carceller-Sindreu, M., de Diego-Adeliño, J., Trujols, J., … Portella, M. J. (2018). Cognitive predictors of illness course at 12 months after first-episode of depression. *European Neuropsychopharmacology*, *28*(4), 529–537. https://doi.org/10.1016/j.euroneuro.2018.02.001

Vicent-Gil, M., Portella, M. J., Serra-Blasco, M., Navarra-Ventura, G., Crivillés, S., Aguilar, E., … Cardoner, N. (2020). Dealing with heterogeneity of cognitive dysfunction in acute depression: A clustering approach. *Psychological Medicine*. https://doi.org/10.1017/S0033291720001567

Vieta, E., Popovic, D., Rosa, A. R., Solé, B., Grande, I., Frey, B. N., … Kapczinski, F. (2013,

January 1). The clinical implications of cognitive impairment and allostatic load in bipolar disorder. *European Psychiatry*. No longer published by Elsevier. https://doi.org/10.1016/j.eurpsy.2011.11.007

Vila-Rodriguez, F., Lang, D. J., Baitz, H., Gicas, K., Thorton, A. E., Ehmann, T. S., … Honer, W. G. (2017). Verbal memory improvement in first-episode psychosis APOE-ε4 carriers: A pleiotropic effect? *Neuropsychiatric Disease and Treatment*. https://doi.org/10.2147/NDT.S150488

Weigand, A., Horn, A., Caballero, R., Cooke, D., Stern, A. P., Taylor, S. F., … Fox, M. D. (2018). Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. *Biological Psychiatry*, *84*(1), 28–37. https://doi.org/10.1016/j.biopsych.2017.10.028

Weintraub, S., Bauer, P. J., Zelazo, P. D., Wallner-Allen, K., Dikmen, S. S., Heaton, R. K., … Gershon, R. C. (2013). I. NIH TOOLBOX COGNITION BATTERY (CB): INTRODUCTION AND PEDIATRIC DATA. *Monographs of the Society for Research in Child Development*, *78*(4), 1–15. https://doi.org/10.1111/mono.12031

Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult*, *23*(1), 29–34. https://doi.org/10.1080/23279095.2015.1004574

World Health Organization. (2017). Depression and other common mental disorders: global health estimates. *World Health Organization*, 1–24.

Zaninotto, L., Solmi, M., Veronese, N., Guglielmo, R., Ioime, L., Camardese, G., & Serretti, A. (2016, September 1). A meta-analysis of cognitive performance in melancholic versus non-melancholic unipolar depression. *Journal of Affective Disorders*. Elsevier B.V. https://doi.org/10.1016/j.jad.2016.04.039

Zaremba, D., Schulze Kalthoff, I., Förster, K., Redlich, R., Grotegerd, D., Leehr, E. J., … Dannlowski, U. (2019). The effects of processing speed on memory impairment in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 494–500. https://doi.org/10.1016/j.pnpbp.2019.02.015

Zheng, F., Yan, L., Yang, Z., Zhong, B., & Xie, W. (2018). HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. *Diabetologia*, *61*(4), 839–848. https://doi.org/10.1007/s00125-017-4541-7

APPENDIX A. Participant Inclusion and Exclusion Criteria

The inclusion and exclusion criteria listed here was originally documented in the THREE-D study protocol for the Non-Invasive Neurostimulation Therapy (NINET) Lab study site (University of British Columbia, Vancouver, Canada).

Patient Inclusion Criteria:
Patients were included if they:
(1) were outpatients
(2) were voluntary and competent to consent to treatment
(3) had a Mini-International Neuropsychiatric Interview (MINI) confirmed diagnosis of MDD, single or recurrent
(4) between the ages of 18 and 65 years
(5) failed to achieve a clinical response to an adequate dose of an antidepressant based on an Antidepressant Treatment History Form (ATHF) score of at least 3 in the current episode OR were unable to tolerate at least 2 separate trials of antidepressants of inadequate dose and duration (ATHF 1 or 2)
(6) had a score ≥ 18 on the HRSD-17 item
(7) were no increase or initiation of any psychotropic medication in the 4 weeks prior to screening
(8) were able to adhere to the treatment schedule
(9) passed the TMS adult safety screening (TASS) questionnaire

Patient Exclusion Criteria:
Patients were excluded if they:
(1) had a history of substance dependence or abuse within the last 3 months
(2) had a concomitant major unstable medical illness, cardiac pacemaker or implanted medication pump
(3) had active suicidal intent
(4) were pregnant
(5) had a lifetime Mini-International Neuropsychiatric Interview (MINI) diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms
(6) had a MINI diagnosis of obsessive compulsive disorder, post-traumatic stress disorder (current or within the last year), anxiety disorder (generalized anxiety disorder, social anxiety disorder, panic disorder), or dysthymia, assessed by a study investigator to be primary and causing greater impairment than MDD
(7) had a diagnosis of any personality disorder, and assessed by a study investigator to be primary and causing greater impairment than MDD

(8) had failed a course of ECT in the current episode or previous episode

Health Volunteer Inclusion Criteria:
Participants were be included if they:
(1) were voluntary and competent to consent to the study
(2) were between the ages of 18 and 65
(3) were fluent in English, sufficient to complete interviews and cognitive testing
(4) had no history of Axis I or Axis II disorders, as determined by the MINI

Health Volunteer Exclusion Criteria:
Participants will be excluded if they:
(1) had a lifetime Mini-International Neuropsychiatric Interview (MINI) diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms
(2) had a MINI diagnosis of obsessive compulsive disorder, post-traumatic stress disorder (current or within the last year), anxiety disorder (generalized anxiety disorder, social anxiety disorder, panic disorder), dysthymia or any personality disorder
(3) had history of mood disorders or psychosis in first degree relative (parents, siblings, offspring)
(4) were unable to provide family history of biological family (i.e., adopted persons are not eligible)
(5) had a history of substance dependence within the last 3 months
(6) had a concomitant major unstable medical illness
(7) had any significant neurological disorder or insult including, but not limited to: any condition likely to be associated with increased intracranial pressure, space occupying brain lesion, cerebral aneurysm, Parkinson's disease, Huntington's chorea, multiple sclerosis, significant head trauma with loss of consciousness for greater than or equal to 5 minutes
(8) had a non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview).
(9) had a personal or family history of seizures