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Neurobiological Correlates of Anxiety and Comorbid Social Phobia in Adolescents with Major Depressive Disorder: A Repetitive Transcranial Magnetic Stimulation Clinical Trial

by

Madelyn Reid Worth

A THESIS

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Abstract

This study examined repetitive transcranial magnetic stimulation (rTMS) as a treatment for adolescents with major depressive disorder. The study was exploratory, considering the potential influence of comorbid anxiety on treatment response and neurobiological correlates. Adolescents underwent a three-week rTMS clinical trial. Depression and anxiety symptoms were compared pre- and post-treatment to determine treatment response. As well fMRI scans were reviewed, identifying functional connectivity differences based upon comorbid anxiety. Findings indicated a significant relation between depressive symptom response and comorbid social phobia symptoms such that participants without social phobia symptoms were more likely to show a significant reduction in depressive symptoms. Neurobiological differences in terms of functional connectivity were found, based upon anxiety severity, comorbid social phobia symptoms, and anxiety symptom treatment response. These findings indicate that the presence of comorbid anxiety is associated with neurobiological differences that may in turn influence rTMS treatment response. Discussions of these findings are included in this document.

Keywords: repetitive transcranial magnetic stimulation, major depressive disorder, social phobia, anxiety severity, treatment response, functional connectivity

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List of Abbreviations

Abbreviation	Definition
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
ECT	Electroconvulsive Therapy
fMRI	Functional Magnetic Resonance Imaging
GAD	Generalized Anxiety Disorder
MDD	Major Depressive Disorder
MPFC	Medial Prefrontal Cortex
PCC	Posterior Cingulate Cortex
rTMS	Repetitive Transcranial Magnetic Stimulation
TRD	Treatment Resistant Depression

Chapter 1: Introduction

Major depressive disorder (MDD) is a common and often debilitating disorder (Lim et al., 2018). Unfortunately, for many of the individuals experiencing MDD, traditional treatment options of medication and psychotherapy, are not effective. One possible alternative treatment is repetitive transcranial magnetic stimulation (rTMS). It targets the underlying neurobiology of MDD, working to stimulate key brain regions that are highly associated with MDD. It is currently recognized as an adult treatment option but has yet to find common use amongst adolescent populations.

The present study seeks to add to the current rTMS-adolescent MDD literature. The focus of the study is to evaluate rTMS as an intervention for adolescents with treatment-resistant MDD, a uniqueness being an additional focus on its effectiveness for those adolescents with comorbid anxiety. The comorbidity rates between MDD and anxiety disorders are exceptionally high, with estimates reaching as high as 75% (Garber & Weersing, 2010). Thus, the present study considers the impacts of anxiety comorbidities and will attend to three main aspects of comorbid anxiety. First, the study examines how varying levels of anxiety severity influence treatment efficacy, as well as functional connectivity within brain regions highly associated with MDD and anxiety disorders. Secondly, consideration will be given to the influence of social phobia, which is a common comorbidity observed in individuals with MDD. Finally, the study will seek to find functional connectivity abnormalities that may explain or predict significant decreases in anxiety symptoms following the rTMS MDD treatment.

Chapter 2: Review of the Literature

Major Depressive Disorder (MDD)

MDD during adolescence is a key public health concern in Canada. It is characterized by a consistent, overwhelming feeling of sadness or hopeless that often makes a person feel as if life is not worth living and even suicidal. MDD is associated with a variety of other symptoms, such as significant changes in appetite, sleeping patterns, energy levels, and concentration (American Psychological Association, 2013). MDD's reach extends far beyond these symptoms; it impacts daily functioning, peer and family relationships as well as school success (Kovacs & Goldstone, 1991; Quiroga, Janosz, Bisset & Morin, 2013).

Adolescents with MDD demonstrate decreased social-interpersonal skills, along with general difficulties in social relationships (Fröjd et al., 2008; Kovacs & Goldstone, 1991). Compared to both typically developing peers, and those with non-clinical levels of neuroticism, adolescents with MDD tend to have decreased peer interactions, and fewer close friends, if any (Kovacs & Goldstone, 1991). In turn, adolescents with MDD tend to experience decreased, or lower, levels of both peer and family social support compared to adolescents without MDD (Lewinsohn, Rohdea, & Seeleya, 1998). Additionally, adolescent females with MDD are significantly more likely to have disengaged friendships, which manifest as friendships involving lower than typical levels of closeness and satisfaction compared to adolescents without MDD, as well as adolescent males in general (Selfhout, Branje, & Meeus, 2009). This may be related to the finding that adolescents with MDD partake in greater than average levels of co-rumination – regularly or repeatedly discussing problems with a focus on the negative – with both their parents and peers but engage in lower than average amounts of co-problem solving with their peers (Waller, Silk, Stone, & Dahl, 2014). These adolescents are bringing negativity and

dwelling into their relationships, without seeking support, which could in turn harm their relationships and decrease their overall likeability. Additionally, adolescents with MDD appear to be sensitized to social interactions (Steger & Kashdan, 2009). These adolescents report experiencing a greater number of negative social interactions than their peers, along with a greater perception of not belonging. As belonging is associated with well-being in MDD populations (Steger & Kashdan, 2009), an increase in negativity within relationships and a decrease in quality of relationships is observed in adolescent MDD populations.

Adolescent MDD is associated with a lower than average grade point average (GPA) and significant decrease in GPA (Fröjd et al., 2008; Hishinuma, Chang, McArdle, & Hamagami, 2012). Adolescents with MDD are also more likely than their peers to struggle with concentration, reading, writing, and independent schoolwork (Fröjd et al., 2008). As well, they are more likely to perceive their school-workload as overly high or demanding, and their own competence as lower than average or required to succeed (Fröjd et al., 2008; Quiroga et al., 2013). These risks are not only observed in clinical MDD populations; adolescents with subthreshold depressive symptoms are also observed as having school challenges (Humensky et al., 2010). These students report a cycle of negative thinking and procrastination, such that their negative thoughts and perceptions keep them doing their homework, which in turn increases their negative thoughts (Humensky et al., 2010). Additionally, MDD not only impacts an adolescent's perception of school and academic performance, but also affects the very basis of school success: attendance. Adolescents with higher symptoms of depression are 23% more likely than their peers to drop out of school (Quiroga et al., 2013).

MDD, and the hopelessness often associated with it, can also lead to substance abuse problems. Increased depressive symptoms are associated with frequent intoxication, as well as

earlier onset of alcohol consumption (Johannessen, Andersson, Bjorngaard, & Pape, 2017). Studies have shown that adolescents who have experienced a major depressive episode (MDE) are close to three-times as likely as their peers to have an alcohol use disorder (AUD; Schepis & Rao 2009). MDEs are periods of time, two weeks or more, where an individual experiences a number of depressive symptoms, whereas MDD is longer lasting and made up of numerous MDEs (APA, 2013). As well, when considering adolescents diagnosed with a depressive disorder prior to the age of fifteen, their diagnosis is predictive of frequent alcohol use and intoxication, regular illicit drug use, and daily smoking (Sihvola et al., 2008). In more severe cases of MDD, individuals' experiences of hopeless extend so far that they attempt suicide. In fact, MDD is believed to double an adolescent's likelihood of making a suicide attempt (Galaif, Sussman, Newcomb, & Locke, 2007). Additionally, estimates of how many adolescents who attempt suicide are diagnosed with MDD range upwards of 35% (Bridge, Goldstein, & Brent, 2006).

For many adolescents with MDD, accessing and experiencing improvement following treatment is sadly quite rare. In fact, studies have shown that only 12% of adolescents with MDD will actually seek professional help (Statistics Canada, 2012). As well, when considering informal help – such as discussing with a friend or searching the internet – the estimates remain low at only 27% (Statistics Canada, 2012). On top of this, of the limited few that actually seek help, it is estimated 10% - 60% will not respond to treatment (Fava, 2003; Al-Harbi, 2012). These individuals are classified as having treatment-resistant depression (TRD), meaning that the well-known treatments such as drug treatment (e.g., selective serotonin reuptake inhibitors) and talk therapy (e.g., cognitive behavioural therapy) are unable to significantly reduce their depressive symptoms.

There is evidence that MDD has a significant negative impact on the lives of adolescents; it harms their peer and family relationships, decreases their school success and sense of competence, and even puts their lives at risk. Of concern is the fact that adolescent MDD is on the rise; in the United States, prevalence ratings have grown from a prevalence rate of 8.7% in 2005 to a prevalence rate of 11.3% in 2014 (Mojtabai, Olfson, & Han, 2016). That is a 23% increase in less than ten years. It is not clear why MDD is on the rise in adolescent population, however, there are a number of risk factors to be aware of when contemplating the development of MDD. For example, individuals with a highly neurotic temperament are more likely than their peers to experience a depressive episode or even an MDD following a stressful life event (APA, 2013). Stressful life events in general also increase the risk of MDD (APA, 2013). Adverse childhood experiences (ACE; e.g., experiencing abuse, being neglected, or witnessing violence) are particularly salient risk factors; the risk further increases with a greater number of stressful life events and/or by way of a greater variety in the types of stressful experiences (APA, 2013). As well, family history of MDD increases an individual's risk (APA, 2013). In fact, an individual with an immediate family member diagnosed with MDD is anywhere from two to four times more likely to have MDD than the general population (Sullivan, Neale, & Kendler, 2000). Comorbidities also increase the risk of MDD (APA, 2013); anxiety disorder, substance use, and borderline personality disorder are some of the most commonly observed preceding comorbid disorders (APA, 2013).

Neurobiological Correlates of MDD. Although they are not considered to be risk factors, there are a variety of neurobiological correlates associated with MDD. The connection between MDD and the brain is an empirically validated relationship. A variety of significant neurobiological abnormalities have been observed within the brains of MDD populations. An

atypical imbalance has been observed between the left and right dorsolateral prefrontal cortex (DLPFC) in individuals with MDD, such that the left DLPFC is hypoactive and the right DLPFC is hyperactive (Grimm et al., 2008). This imbalance is believed to be associated with both affective and attentional negative biases, such that individuals with MDD are more inclined to perceive and attend to negativity, ultimately reinforcing their depressive symptoms (Salehinejad, Ghanavai, Rostami, & Nejati, 2017). Additionally, many abnormalities have been observed within the default mode network (DMN), a network involved in self-referential processing, affective cognition, and emotion regulation (Fang et al., 2016). The DMN is comprised of the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), posterior cingulate cortex (PCC) and precuneus, the lateral parietal cortex, and the hippocampus and parahippocampal cortex (Raichle, 2015). The vmPFC, which is involved in perception of self and others, often demonstrates reduced functionally connectivity in individuals with MDD, relative to the general population (Murrough et al., 2016). Similarly, the PCC, which is implicated in episodic memory retrieval, is also associated with reduced connectivity in MDD (Lou et al., 2004; Yang et al., 2016). The hippocampus, which is associated with memory recall, as well as emotion processing and regulation, has also been identified as performing abnormally in an MDD population (Krishnan, 1991).

Research specifically examining adolescent MDD populations, has identified decreased functional connectivity associated with the subgenual anterior cingulate cortex (sgACC) with the exception of the connections between the sgACC and the amygdala, and the sgACC and the insula (Connolly et al., 2013; Cullen et al., 2009). The elevated levels of functional connectivity observed with the amygdala and insula may be explained by the fact that both regions are involved in emotion; additionally, adult MDD studies have determined that both regions are

involved in rumination in depression (Connolly et al., 2013). Considering the breadth of neurobiological abnormalities associated with MDD, a trend can be identified in that the majority of the regions and networks are somehow involved in emotion and affect, which is an experience and part of life that is highly impacted by MDD.

MDD is a substantial disorder, with notable prevalence and detrimental outcomes. Furthering the knowledge and understanding of MDD is paramount, especially as researchers continue to consider new treatment opinions. However, it is crucial that one understands that to truly comprehend MDD, they must recognize it in a full, real-world context, which includes psychological comorbidities, comorbid anxiety disorders in particular.

Anxiety Disorders

Anxiety disorders, much like MDD, are a significant public health concern (Merikangas et al., 2010). Anxiety disorders are characterized by excessive fear or worry that significantly impacts an individual's behaviour and overall quality of life. Anxiety disorders are differentiated from developmentally normative states of anxiousness in that they are both excessive and persistent (APA, 2013). The excessive anxiety observed in anxiety disorders is often considered to be uncontrollable and typically results in avoidant behaviours, such that individuals with anxiety disorders avoid anxiety-inducing activities and experiences, even if it is things they desire or even need (APA, 2013). Additionally, this anxiety is not acute or short-term occurrence: for diagnosis, it is required to last six months or more (APA, 2013).

The details and experience of an anxiety disorder is dependent on the type of anxiety disorder. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) recognizes a variety of different anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, separation anxiety disorder, and specific phobia

(APA, 2013). Each of these disorders has its own prevalence ratings, risk factors, symptomology, and comorbidities. These differences are what make each disorder unique, along with being the factors that determine the potential outcomes or risks of each disorder.

The prevalence rates for anxiety disorders not only vary from one anxiety disorder to the next, but also within a single disorder, a fact that is in part based upon age ranges. For example, separation anxiety is most commonly observed in children, with a prevalence rate of approximately 4%, which is more than twice the prevalence rate found for adult populations (APA, 2013). Social anxiety disorder has a relatively synonymous prevalence rate between adult and child populations, and GAD has triple the prevalence estimate for adults that it does for adolescents (APA, 2013). Despite the variance from one anxiety disorder to another, however, there is a significant representation of anxiety disorders in general within adolescent populations. In fact, a study examining over 10,000 American adolescents determined that anxiety disorders were the most common mental health condition, with a prevalence rate of 32% (Merikangas et al., 2010). This may represent an overall increase in the prevalence rate of anxiety disorders, as previous studies with adolescent samples have cited more conservative prevalence estimates of 20% (Masi, Mucci, & Millepiedi, 2001). In any case, the prevalence rates of anxiety disorders in youth today is cause for great concern, both clinically and socially.

Anxiety disorders considered both individually and in general have a relatively well-known prognosis. First, anxiety disorders are known for leading an individual to miss out on opportunities in any number of settings (Mowrer, 1960; Salters-Pedneault, Tull, & Roemer, 2004). As explained above, anxiety disorders typically lead to avoidant behaviours that function to minimize anxiety by simply avoiding triggers or anxiety-inducing stimuli. This avoidance often results in the individual with an anxiety disorder missing out on opportunities such as class

presentations, performances, jobs, promotions at work, or even relationships, both platonic and romantic. Considering school success, adolescents with an anxiety disorder are at significant risk for school dropout (Van Ameringen, Mancini, & Farvolden, 2003). One study found that out of a sample of 200 individuals meeting diagnostic criteria for an anxiety disorder, nearly half reported having dropped out of school (e.g., secondary or post-secondary) and nearly a quarter of those individuals attributed it to their anxiety (Van Ameringen et al., 2003). Additionally, individuals with anxiety disorders are more likely to have difficulty finding employment and succeeding in their field once employment is found (Waghorn, Chant, White, & Whiteford, 2005). This is partially attributable to anxiety-induced school challenges, but it might also be explained by the finding that individuals with anxiety disorders tend to accomplish significantly fewer things than their fellow employees (Waghorn et al., 2005). Anxiety disorders also have a significant impact on mother-child attachment relationships, such that adolescents with an anxiety disorder are more likely to demonstrate a more disorganize or insecure attachment style and are more likely to demonstrate hostility towards their mothers (Brumariu, Obsuth, & Lyons-Ruth, 2013). Along with significantly impacting maternal relationships, anxiety disorders also appear to negatively impact both friendships and romantic relationships (Brumariu et al., 2013).

In addition to leading to missed opportunities, school dropout, and relationship challenges, anxiety disorders are also associated with increased risk of suicide and substance misuse or abuse (Sharifian, Lavasani, Ejei, Taremian, & Amrai, 2011; Low, Lee, Johnson, Williams, & Harris, 2008). Researchers have found a significant, positive correlation between the presence of an anxiety disorder and suicidal ideation in adolescent populations, such that adolescents with an anxiety disorder are at a significantly greater risk of being suicidal (Sharifian

et al., 2011). In fact, more than 70% of individuals who report a having made a suicide attempt also have an anxiety disorder (Nepon, Belik, Bolton, & Sareen, 2010).

For some individuals, alcohol consumption, smoking, and illicit drug use can become self-administered coping mechanisms. These substances are often used as a form of self-medication in order to manage the daily challenges faced by adults and adolescents alike. Research with adult populations has shown that this practice of substance misuse, or abuse, is more common in individuals with an anxiety disorder than the general public. Considering adolescent populations, the literature is less conclusive, though there are increasingly findings support the relationship between anxiety disorders and substance misuse. Low et al. (2008) found a strong association between anxiety disorders with alcohol consumption. Other studies have found similar results, though only for female adolescents (Johannessen et al., 2017; Wu et al., 2010). Researchers have also demonstrated that adolescents with anxiety disorders are more likely to be frequent cigarette smokers than their same-age peers (Wu et al., 2010). There does not, however, appear to be a significant positive correlation between adolescent anxiety disorders and illicit drug (Low et al., 2008; Wu et al., 2010).

For many adolescents diagnosed with an anxiety disorder, their diagnosis will be a lifetime diagnosis. Based upon the specific diagnosis, prognoses and remission rates do vary; however, the majority of anxiety disorders have a less than 50% full remission rate (APA, 2013). The DSM-5 reports that without proper treatment, full remission rates are very low for individuals with panic disorder, agoraphobia, and GAD, estimated at 10% (APA, 2013). Social anxiety disorder has remission rate estimates as high as 60%, though many of these individuals will experience symptoms for several years or longer (APA, 2013). Only 30% of individuals diagnosed with social anxiety disorder who do not receive adequate treatment are expected to

experience remission within one year (APA, 2013). Separation anxiety disorder is the only anxiety disorder that truly appears to have promising remission rates, with the majority of children diagnosed with the disorder being free of any anxiety diagnosis by adulthood (APA, 2013; Kessler et al., 2012). Ultimately, it is quite possible that a significant number of adolescents with an anxiety disorder will experience symptoms throughout their lifetime.

Comorbid Anxiety Disorders. Of concern is the fact that, much like MDD, anxiety disorders often exist and interact with comorbidities that ultimately worsen prognosis. Comorbidities can exasperate symptoms, increase likelihood of school and relational difficulties, and make treatment more challenging. One of the more commonly observed comorbidities for anxiety disorders in general is MDD, with comorbidity estimates ranging from 10-15% (Angold, Costello, & Erkanli, 1991; Axelson & Birmaher, 2001; Costello et al., 2003). There are mixed findings regarding how this comorbidity impacts the treatment of either anxiety or MDD, with some studies suggesting the comorbidity predicts worse outcomes, and others suggesting that anxiety treatments successfully target depressive symptoms and vis versa (Curry et al., 2006; Rhode, Clarke, Lewinsohn, Seeley, & Kaufman, 2001). It appears that in most cases, however, whether it impacts treatment success or not, the comorbidity does increase the required dosage of SSRIs an individual requires (Garber & Weering, 2010).

Adolescents with comorbid MDD and anxiety disorders tend to have more severe symptoms in terms of both anxious and depressive symptoms than adolescents with single-diagnosis MDD or anxiety disorders (O'Neil et.al., 2010). Social anxiety symptoms, fear, negative mood, ineffectiveness, and anhedonia are all observed at significantly higher levels in adolescents with comorbidity than those with a single disorder (O'Neil et al., 2010; Franco, Saavedra, & Silverman, 2007). Compared to adolescents who have a singular diagnosis of

anxiety, adolescents with comorbidity are also involved in significantly fewer extracurricular activities, have worse peer relationships, and poorer academic performance (Franco et al., 2007). In addition, adolescents with comorbid MDD and anxiety disorders also report significantly greater family dysfunction that adolescents with just one of the disorders (O'Neil et al., 2010). This MDD-anxiety comorbidity is also significantly correlated with increased suicide rates, and reports are that it may account for nearly 23% of suicidal youth (Foley, Goldstone, & Costello, 2006; Spruyt, 2016). The comorbidity more than doubles the suicide rates for MDD alone, raising prevalence rates from 8% to 20% (Spruyt, 2016). As well, the suicide rates quadruples for those with a singular diagnosis of panic disorder, resulting in almost 24% suicide risk, (compared to rates of 7% for those not diagnosed with a panic disorder; Spruyt, 2016). Considering these findings, the power of this comorbidity is very clear.

This comorbidity is particularly powerful as there are theories that anxiety disorders act as risk factors for MDD, actually increasing the likelihood of an MDD diagnosis later in life (Bittner et al., 2007). Childhood anxiety disorders in particular are believed to drastically increase the risk of MDD and anxiety disorder comorbidity in adolescence (Garber & Weering, 2010). This may be explained by the finding that anxiety-rooted avoidance of social situations can often lead to peer rejection, which over time produces depressive symptoms like lowered self-worth and sadness (Gazelle & Ladd, 2003). It is also important to note that the MDD-anxiety comorbidity is not symmetrical, as the rates of individuals with MDD who have a comorbid anxiety disorder are much higher than the rates of individuals with anxiety disorders that also have MDD, ranging from 15% to as high as 75% (Angold et al., 1999; Avenevoli, Stolar, Dieker, & Merikangas, 2001; Yorbik, Birmaher, Alexson, Williamson, & Ryan, 2004). The underlying cause of this asymmetry has yet to be identified.

Comorbid Social Phobia. Social anxiety disorder, also referred to as social phobia, is the most commonly observed comorbid anxiety disorder (Stein et al., 2001). In fact, 31% of adolescents with MDD will also be diagnosed with social phobia (Barbee, 2008). Adolescents with social phobia are at some of the highest risk for developing MDD, and even more concerning, the MDD experienced by these adolescents is associated with greater severity of MDD symptoms (Stein et al., 2001). Adolescents with this comorbidity demonstrate overall increases in their symptom count, as well as increased suicidal ideation and attempts (Stein et al., 2001). Social anxiety disorder also tends to have the lowest recovery rates of the anxiety disorders (Bruce et al., 2005). This prognosis is only worsened by the co-occurrence of MDD, and can in turn make MDD longer-lasting and more challenging to treat (Dalrymple & Zimmerman, 2007). Some researchers suggest that this comorbidity may be better treated by an alternative, targeted intervention focusing on the unique characterizes associated with the interacting disorder than the separate, traditional anxiety and MDD treatments (Stein et al., 2001).

Neurobiological Correlates of Anxiety Disorders. In addition to the social-emotional and behavioural symptoms, social phobia, and anxiety disorders in general, also has neurobiological symptoms and associated abnormalities. Individuals with anxiety disorders demonstrate increased activation in sensory processing regions, including the occipital cortex and thalamus, when faced with threatening stimuli (Duval, Javanbakht, & Liberzon, 2015). These regions are particularly responsive in adolescents with social phobia (Duval et al., 2015).

A variety of emotion processing regions are also implicated in anxiety disorders (Duval et al., 2015). Abnormalities have been identified in the ventral striatum for individuals with social phobia (Duval et al., 2015), and decreased levels of activation are observed when

anticipating events like giving a speech (Duval et al., 2015). Additionally, anxiety disorders are associated with amygdala abnormalities, including hyperactivation when facing threats (Duval et al., 2015). The amygdala abnormalities also include volume, though the forms of the abnormalities are inconsistent across varying anxiety disorders (Duval et al., 2015). For example, panic disorder is associated with decreased amygdala volume, but GAD is associated with increased amygdala volume (Kim, Dager, & Lyoo, 2012; Schienle, Ebner, & Schafer, 2011; Duval et al., 2015). Additionally, hyperactivity of the insula is also associated with a variety of anxiety disorder (Carre et al., 2014). In particular, hyperactivity of the insula has been observed in individuals with social phobia, when the individual feels threatened (Duval et al., 2015). Finally, the dorsal anterior cingulate cortex (dACC) has been observed to be hyperactive in response to threat in individuals with social phobia (Bruhl et al., 2011). In terms of dACC volume, social phobia and GAD are both associated with increased volume, but panic disorder is associated with decreased volume (Pannekoek, van der Werff, Stein, & van der Wee, 2013; Schienle et al., 2011; Bruhl et al., 2014). See Figure 1 for a neurocircuit of anxiety.

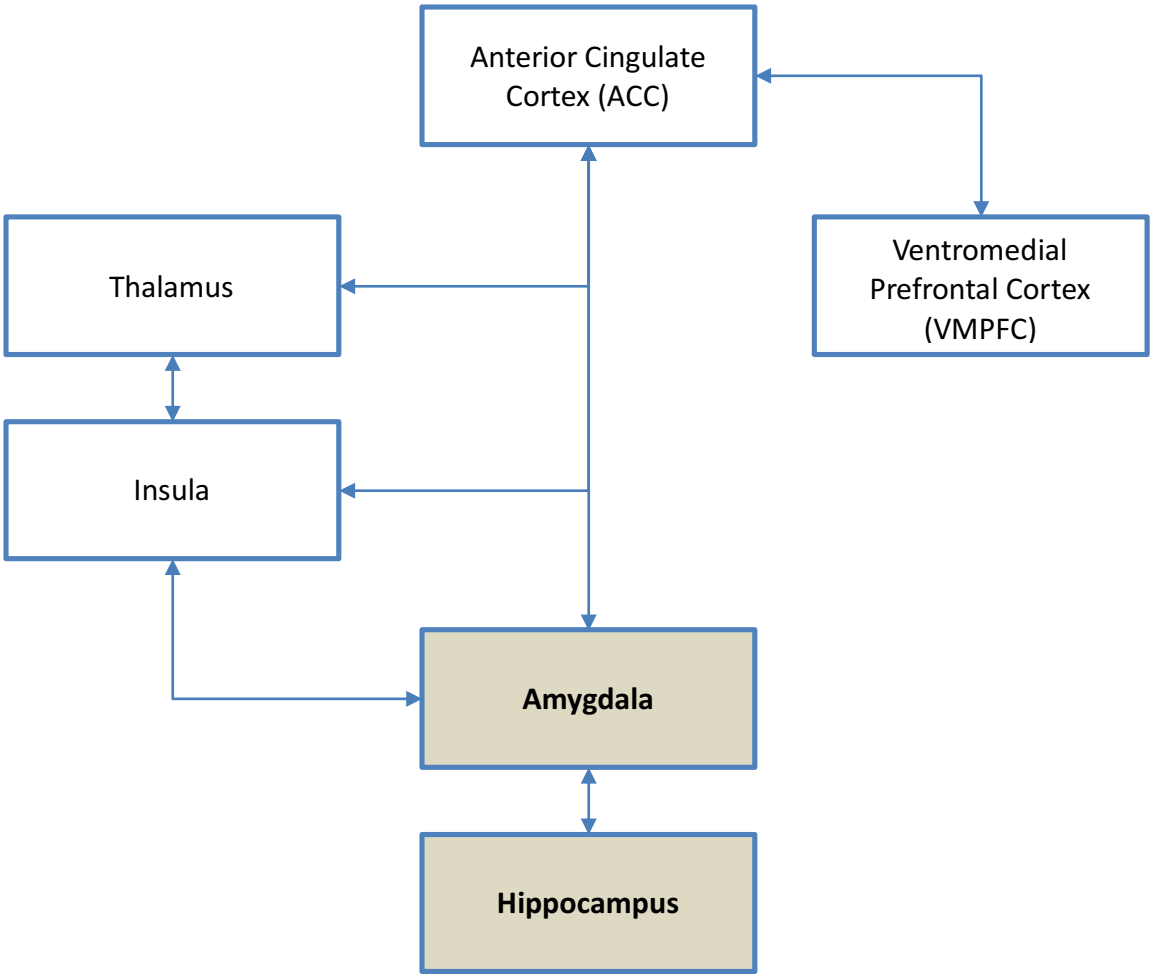

Figure 1. Basic neurocircuit schematic of anxiety.

Finally, anxiety disorders are also implicated in the emotion modulation regions. In individuals with social phobia, the medial prefrontal cortex (MPFC) shows increased volume and abnormal activation, findings that are indicative of both increased and decreased activation in response to threats (Blair et al., 2011; Liao et al., 2011; Sripada et al., 2009). However, the findings vary from one anxiety disorder to another. For example, GAD has been observed as having a normative MPFC volume, and decreased activation in response to threat (Cha et al., 2014; Blair et al., 2011). In terms of the hippocampus, the majority of anxiety disorders, including social phobia, panic disorder, and GAD, are associated with decreased volume (Duval

et al., 2015). As well, studies have shown increased activation in the hippocampus in individuals with anxiety disorders when faced with threats (Bruhl et al., 2011; Duval et al., 2015).

Having reviewed the impacts of anxiety disorders, as well as the comorbidity of anxiety disorders with MDD, the next step is to consider what can be done. As previously stated, the common treatment options, SSRIs and CBT, do not necessarily work for everyone. Thus, newer treatment options, such as repetitive transcranial magnetic stimulation, are becoming more well-known, and increasingly researched, as well as used.

Repetitive Transcranial Magnetic Stimulation

History of Repetitive Transcranial Magnetic Stimulation. Repetitive transcranial magnetic stimulation (rTMS) is a relatively new form of treatment. Over 30 years ago, Barker, Jalinous, and Freeston (1985) introduced and tested the proposition of a neural-stimulation technique that employed magnetic pulses. This method was offered as a replacement for electrical stimulation, and marketed as quick and easy to use, contact-free, and non-invasive (Barker et al., 1985). As time went on, this method became known as transcranial magnetic stimulation (TMS), and as the technology advanced, allowing for rapidly repeating pulses, it evolved into rTMS (Noohi & Amirsalari, 2016). rTMS today can be offered as either low- or high-frequency, which work to either inhibit or excite targeted regions of the brain (Gorsler, Baumer, Weiller, Munchau, & Liepert, 2003).

Initially, TMS was used primarily for evaluative purposes. Researchers and clinicians would utilize TMS in the examination of motor pathways, evaluating the effects of a spinal cord injury, or identifying the speech and memory areas of a seizure surgery patient prior to the surgery (Hayes, Allatt, Wolfe, & Brown, 1989; Davey, Kalaitzakis, & Epstein, 1988). In one of the first studies to demonstrate that TMS could have some sort of treatment effect, Pascual-

Leone, Gates, and Dhuna (1991) used rTMS to create speech errors. This research offered evidence that rTMS could produce effects lasting beyond the cessation of the rTMS pulses; it was also one of the first studies to use rTMS instead of single-pulse TMS (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011). Shortly thereafter, Hoflich, Kasper, Hufnagel, Ruhrmann, and Moller (1993) published a research paper examining the potential effectiveness of TMS as a depression treatment, though the study provided minimal significant findings. Since then, several studies have shown that rTMS can significantly reduce depressive symptoms (Kolbinger, Hoflich, Hufnagel, Moller, & Kasper, 1995; George et al., 1995; Pascual-Leone, Rubio, Pallardo, & Catala, 1996). Of note, rTMS showed early evidence in reducing depressive symptoms in individuals with Treatment Resistant Depression (TRD), in contrast to some studies that had found previous treatments ineffective (e.g., Pascual-Leone et al., 1996). In 2002, rTMS – and TMS alike – was approved as a medical treatment by the Canadian Association of Health, and six years later, in 2008, the US Food and Drug Administration followed suit (Noohi & Amirsalari, 2016).

rTMS is presently recognized as an effective treatment for adults with MDD, though it has yet to be officially approved as a treatment regime for adolescents (Wall et al., 2013). rTMS is considered to be a promising alternative for the traditional MDD treatments – such as SSRIs and CBT – and is primarily used for individuals with TRD (Wall et al., 2013). It is one of a select few treatments considered to be effective alternatives for individuals with TRD; one of the other primary alternatives is electroconvulsive therapy (ECT; Magnez, Aminov, Shmuel, Dreifuss, & Dannon, 2016). ECT predates rTMS and is often considered superior as the more established of the two treatments; however, this does not necessarily mean that it is the better

treatment option (Horvath et al., 2011; Furtado, Hoy, Maller, Savage, Daskalakis, & Fitzgerald, 2016).

Comparing rTMS and ECT. Comparing ECT with rTMS, there are several factors to consider, including treatment efficacy, side effects, and financial costs. First considering treatment efficacy, both ECT and rTMS have been proven as effective MDD treatments, even for those with TRD (Magnezi et al., 2016; Janicak et al., 2002). Throughout the literature, however, ECT does appear to be more effective in decreasing depressive symptoms, but whether or not it is significantly more effective varies from one study to the next (Magnezi et al., 2016; Janicak et al., 2002).

Considering side effects of the two treatments, there is consensus throughout the literature that ECT produces a greater number of longer-lasting and moderately severe side effects (Magnezi et al., 2016). Where 60% of participants receiving ECT reported side effects, only 30% of those receiving rTMS reported experiencing any side effects (Magnezi et al., 2016). In addition, the side effects reported were much more severe for those undergoing ECT. ECT commonly led to memory losses, whereas the most frequently observed rTMS side effects are headaches that resolved themselves following the conclusion of each treatment session (Magnezi et al., 2016). In addition, ECT has been associated with hospitalizations (Janicak et al., 2002). These side effects combined with public knowledge of outdated ECT techniques, which rarely involved aesthesia, leads to a great deal of negative stigma and fear surround ECT (Payne & Prudic, 2009).

Considering costs, American data suggests that many individuals seeking treatment choose ECT based upon the lower costs, despite interest in rTMS (Magnezi et al., 2016). Generally, research has demonstrated that ECT is the cheaper and more cost-effective option, in

terms of both total service costs and informal care costs (i.e., estimated costs that would be required for services instead provided free-of-charge by friends and family; Vallejo-Torres et al., 2015; Knapp et al., 2008). There is some evidence indicating that the actual treatment costs are not significantly different (Knapp et al., 2008); a single rTMS session is actually less expensive than one ECT session (Knapp et al., 2008). Moreover, research suggests that ECT is more profitable than rTMS, with ECT providing a hospital more than twice the final income earned via rTMS (Magnezi et al., 2016).

Ultimately, rTMS seems to be quite comparable to ECT. Though it may be costlier to patients and health care system, it is also associated with fewer and less severe side effects, as well as decreased stigma (Knapp et al., 2008; Magnezi et al., 2016; Janicak et al., 2002). Research has shown that patients actually tend to prefer rTMS, particularly because of the decreased risk, compared to ECT (Magnezi et al., 2016; Janicak et al., 2002). This preference is, of course, of utmost value, since there can be no treatment without patient desire and cooperation.

Current Study

Given the paucity of literature examining rTMS as an MDD treatment in adolescent populations, this study aims to contribute to the current body of literature. It intends to do so by gaining a better understanding via a sample of adolescents participating in this rTMS treatment, both neurobiologically and in terms of self-reported response to treatment. Specifically, this study will consider some of the variables that may impact how adolescents interact with rTMS treatment and explore the nature of those impacts. In this way, the study will not only strengthen the literature, but also produce novel findings useful in furthering both research and treatment for youth with comorbid MDD and social anxiety disorder. As such, the present study will explore

both the measured effects of rTMS on treatment-resistant MDD and serve as an exploratory study considering the effects of this treatment for youth with comorbid anxiety.

Throughout this study, the following questions will be addressed: (1) Are there functional connectivity differences based upon anxiety severity (e.g., mild, moderate, and severe anxiety)?, (2) Does rTMS treatment response differ by the way of anxiety severity, and if so, in what ways?, (3) Are there functional connectivity differences between adolescents with MDD and those with MDD and comorbid social phobia symptoms?, (4) Do comorbid social phobia symptoms impact rTMS treatment response, and if so, in what ways?, and (5) Are there functional connectivity differences between those whose anxiety symptoms significantly decreased following treatment and those whose did not?

Chapter 3: Methodology

Participants

Participants (N = 37) were adolescents (M_{age} = 18.57, *SD* = 2.12) with TRD recruited through advertisements and by clinicians in Calgary and the surrounding area. The participants ranged from 12 to 22 years of age, with 22 males and 15 females. All participants met diagnostic criteria for MDD based upon the Lifetime version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL). The K-SADS-PL was administered by lead researchers from the project who had training with the measure. All participants completed the screening interview portion of the K-SADS-PL and the supplemental mood disorder measure; none of the remaining supplemental measures were administered. In addition, all participants had previously failed to respond to a minimum of at least one SSRI eight-week treatment, thus classifying them a treatment resistant.

Individuals were excluded if they had a history of seizures, epilepsy, hypertension, or a diagnosis of bipolar disorder, psychosis, pervasive developmental disorder, eating disorder, or post-traumatic stress disorders. Left-handed individuals were also excluded. As well, individuals who were pregnant were excluded, since pregnancy disallows scanning via the 3T MRI.

Of the potential 37 participants, five were excluded. Three participants were excluded due to excessive head motion during the scan, and two others were excluded as statistically significant outliers in terms of overall neurobiological functional connectivity, leaving a final *N* = 32 (see Figure 1). These participants were further separated into groups for the analyses. For the anxiety analyses, they were separated into three severity groups: Mild (*n* = 7), moderate (*n* = 11), and severe (*n* = 10). For the comorbid social phobia symptom analyses, participants were separated into two groups; those with MDD and comorbid social phobia symptoms (*n* = 12) and

those with MDD but no social phobia symptoms (n = 20). Finally, for the anxiety symptom responder analyses, participants were separated into two groups: anxiety symptom responders (n = 16) and anxiety symptoms non-responders (n = 12).

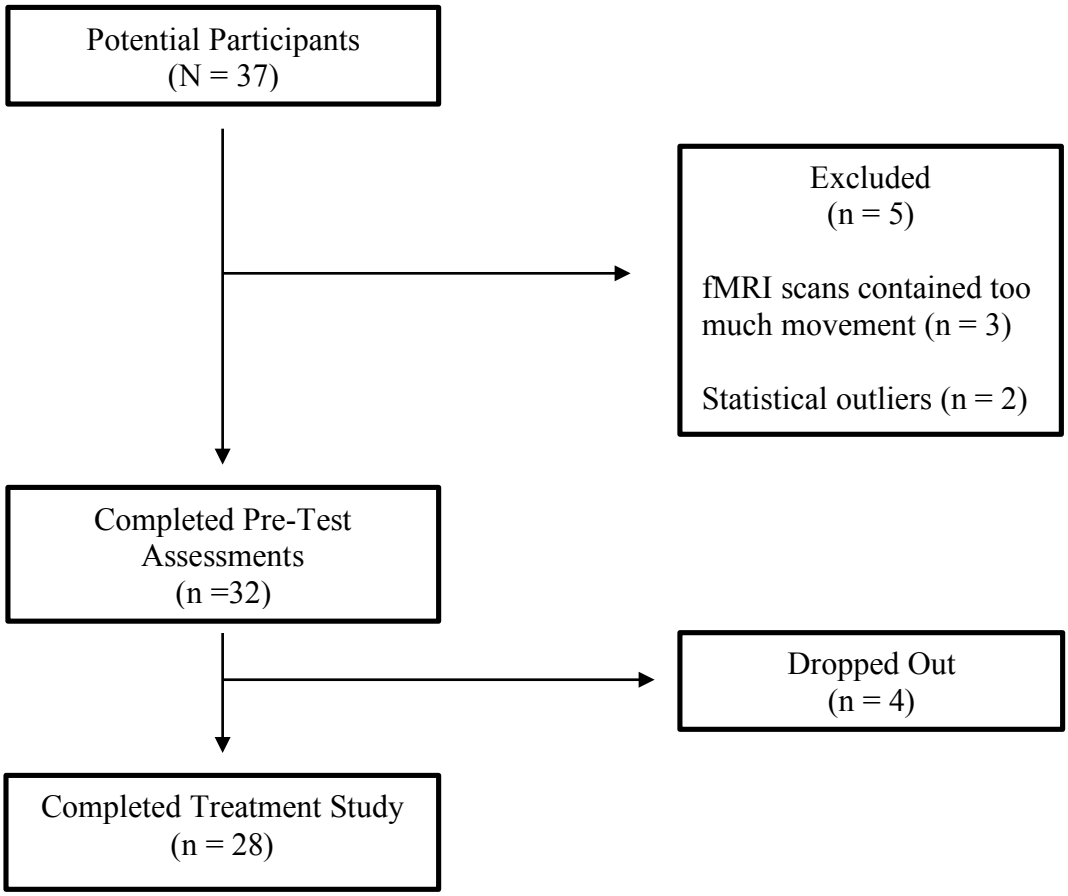

Figure 2. Consort diagram for inclusion within this study.

Measures

A variety of measures were utilized throughout the study. The Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967), and the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) were employed throughout the study to monitor depressive symptoms. Both measures were conducted at baseline, following the first and second weeks of treatment,

and once more at the end of the treatment for a total of four times for each participant. However, for the present study, the HAM-D was the primary outcome measure, as the HAM-D scores were used to determined treatment response. Participants with a greater than 50% reduction in HAM-D score from baseline to post-treatment were considered a treatment responder.

The HAM-D was chosen as the primary outcome measure in part due to its substantial utility and longevity in the field. Reviewing rTMS literature, a number of studies utilized the HAM-D as a treatment response measure (Kedzior, Rajput, Price, Lee, & Martin-Iverson, 2012; Pallanti et al., 2014). This supports the use of the HAM-D as replication of methods throughout the literature is a highly recommended practice. Additionally, research has found the HAM-D to be a reliable measure of depressive symptoms (Iannuzzo, Jaeger, Goldberg, Kafantaris, & Sublette, 2006). It is also shown to have adequate validity (Bagby, Ryder, Schuller, & Marshall, 2004).

Similar to the HAM-D, the BDI-II is an outcome measure used by rTMS researchers, which is substantiated by its use in previous clinical trials (Kedzior et al., 2012; Dunlop et al., 2015). The BDI-II in particular was included in this study because of its user-friendly, self-report style (Beck, Steer, & Brown, 1996). Additionally, psychometric evaluation indicates acceptable reliability and validity levels for the measure (Titov et al., 2011).

A number of other assessments were administered only before and after the four-week treatment in order to compare baseline symptoms with those observed post-treatment. The measures provided an estimate of a variety of mental disorder symptoms, both externalizing and internalizing symptoms, along with intellectual functioning. Each of the measures are described below.

The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL; Kaufman et al., 1997) was used a screener for the presence of disorders. It has a strong history as a semi-structured clinical interview, demonstrating strong reliability and validity for clinical use (Kaufman et al., 1997). It has also been used in previous research studies and clinical trials, in turn supporting it use as a research tool (Keller et al., 2001). Additionally, it is user-friendly, and easy to interpret both during administration and review. For this study, the K-SADS-PL screener was used to identify those demonstrating social phobia symptoms, who in turn were classified as the social phobia symptom group.

The Children's Depression Rating Scale-Revised (CDRS-R; Poznanski, Mokros, Grossman, & Freeman, 1985) was used as an additional depression measure. Researchers have found it to be a reliable and valid measure for adolescent population. (Mayes, Bernstein, Haley, Kennard, & Emslie, 2010).

The Patient Health Questionnaire for Adolescences (PHQ-A; Spitzer, Kroenke, & Williams, 1999) was also employed as a depressive symptom measure. Like the previous depression measures, the PHQ-9 has a history of use in rTMS studies (Cohen, Gorden, Ozbek, & Dubin, 2014). It is also considered to be reliable and valid (Kroenke, Spitzzer, & Williams, 2001), and since the PHQ-A is nearly identical to the PHQ-9, with only a few words changed to be more age appropriate, it too is believed to be a valuable tool.

The Hamilton Anxiety Rating Scale (Ham-A; Hamilton, 1959) was used to record anxiety symptoms, and determine anxiety treatment response. Anxiety treatment response was defined as a greater than 50% reduction in Ham-A score from baseline to post-treatment. As well, the anxiety severity classifications provided by the Ham-A were used as the severity indicators for the analyses (<17 indicates mild severity, 18-24 indicates moderate severity, and

25 plus indicates severe). The Ham-A was chosen as an anxiety measure due to its simplicity of use, as well as its strong reliability and validity for adolescent samples (Clark & Donovan, 1994).

Finally, the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011) was utilized as the cognitive ability measure throughout the study. It was chosen because it could be administered quickly, decreasing, or ideally avoiding, participant fatigue during the series of pre- and post-test assessments and measures. Additionally, it has been thoroughly validated as one of the Wechsler intelligence tests (Wechsler, 2011).

Imaging

All participants received magnetic resonance imaging (MRI) scans at both baseline and treatment completion. These scans were conducted at the Alberta Children's Hospital in Calgary, Canada on a general electric (GE) Healthcare Discovery MR750w 3.0T magnetic resonance scanner. Whole-brain fMRI data and T1-weighted anatomical images were collected during each scan.

The whole-brain fMRI data was used to analyze functional connectivity. The fMRI data gathered was resting-state data and was retrieved while participants were looking up at a dark cross on an otherwise blank screen and were instructed to "think of nothing in particular." The portion of the scan used to acquire whole-brain fMRI data was five minutes in duration and used a gradient echo EPI sequence. The acquisition parameters included: echo time (TE) = 30 milliseconds (msec), repetition time (TR) = 2000 msec, interleaved and bottom/up, flip angle = 90°, flip angle = 230 mm, and the data acquisition matrix was 64 x 64. As well the voxel size was 3.6 x 3.6 x 3.6 mm.

For the T1-weighted anatomical imaging acquisition parameters included: TE = 3.15 msec, TR = 8.27 msec, inversion time (TI) = 600, flip angle = 10°, slice thickness = 0.8 mm, 226

slices, and the data acquisition matrix was 300 x 300. The 0.8 mm slice thickness was within the Nyquist frequency limits, and therefore considered acceptable for mapping the topography of the brain cortex. The T1-wieghted anatomical images were used for anatomical referencing in the treatment study. Additionally, this data was used to transform participant's fMRI data for use in statistical analysis.

rTMS Intervention Protocol

All the rTMS treatment session were conducted at the Alberta Children's Hospital, specifically in the Pediatric TMS Laboratory. Each treatment session included two treatment administrators, both of whom had completed a multi-session training program that explained not only how to set up and administer the treatment, but also the underlying theories of how rTMS works. One treatment administrator would be responsible for the administration of the pulses, where the other was responsible for the placement the coil and monitoring of the participant. The sessions employed a Magstim SuperRapid2 air-cooled 90mm figure of eight coils (Magstim, Wales UK). As well, a neuro-navigation system was used to co-register the TMS coil to each participants' structural MRI (Brainsight2, Rogue research, Montreal). Prior to beginning treatment, each participant's resting motor threshold (RMT) had to be determined. This was done by placing surface electromyographic electrodes over the right first dorsal interosseous (FDI) muscle – used to record motor evoked potentials (MEP) – and applying single-pulse TMS over the left primary motor cortex. The RMT was found once a MEP of more than 0.5mV in five of ten consecutive trials was recorded (Kirton et al., 2010).

The rTMS intervention target for this study was the left DLPFC. The coil placement for targeting this region was found using the 5cm rule – move 5 cm from the RMT site, toward the nasion, and following the left superior oblique plane (George et al., 1995; George et al., 1996;

Herwig et al., 2001; Herwig et al., 2003). Once this location was identified, the coil was placed there, just above the scalp at 45-degree angle to midline. From here, the location was co-registered in three dimensions to confirm its placement within the left DLPFC.

The rTMS intervention itself consisted of 3000 suprathreshold (120% RMT) pulses per treatment session. Each session was broken down into 75 trains, which lasted 30 seconds each and consisted on 40 10 Hz pulses over four seconds followed by a 26 second pause where no pulses where given. The overall sessions typically lasted 37.5 minutes and were provided over fifteen consecutive weekdays. On day one, six, and eleven, participants were assessed for adverse responses to the treatment, using the Pediatric TMS Safety and Tolerability Measure.

Data Analysis

The fMRI resting-state and T1-weighted anatomical images were exported from OsiriX and converted into NifTI files. From here the images were preprocessed in MATLAB (MathWorks Inc., United Kingdom, 2016a) using SPM12 (www.fil.ion.ucl.ac.uk/spm/). The T1-weighted anatomical images were first normalized to the Montreal Neurological Institute (MNI) space and divided into gray matter, white matter, and cerebral spinal fluid (CSF). The fMRI images were then realigned to identify and acquire the central slice and were motion corrected, co-registered to the preprocessed T1-weightedantomical images and normalized to MNI space. Finally, the fMRI images were smoothed using a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel which minimizes noise in the images and potential effects of individual differences. Once the images were all preprocessed, the Artifact Detection Tools (ART) toolbox was opened and used to measure motion in the scans. Participants whose scans demonstrated head movement of greater than 0.5 mm in the x, y, or z planes were considered to be outliers and removed from the sample.

From here, functional connectivity analyses were conducted using MATLAB (MathWorks Inc., 2016a) and the CONN-fMRI functional connectivity toolbox (www.nitrc.org/projects/conn/; Whitfield-Gabrieli & Nieto-Castanon, 2012). The regions of interest (ROIs) identified were chosen *a priori* based upon the literature and known associations with MDD and social anxiety disorder (Connolley et al., 2013; Duval et al., 2015; Fang et al., 2016; Raichle, 2015; Salehinejad et al., 2017). The following ROIs were selected within the CONN-fMRI toolbox: Left DLPFC, medial prefrontal cortex (mPFC), PCC, left lateral parietal lobe (LLP), right lateral parietal lobe (RLP), left and right hippocampi, left and right posterior parahippocampal gyri (paHC), and the right and left amygdala. Each ROI was spherical and 10 mm in diameter and based upon MNI coordinates. See Figure 3 for the ROIs and their place in a neurocircuit of depression.

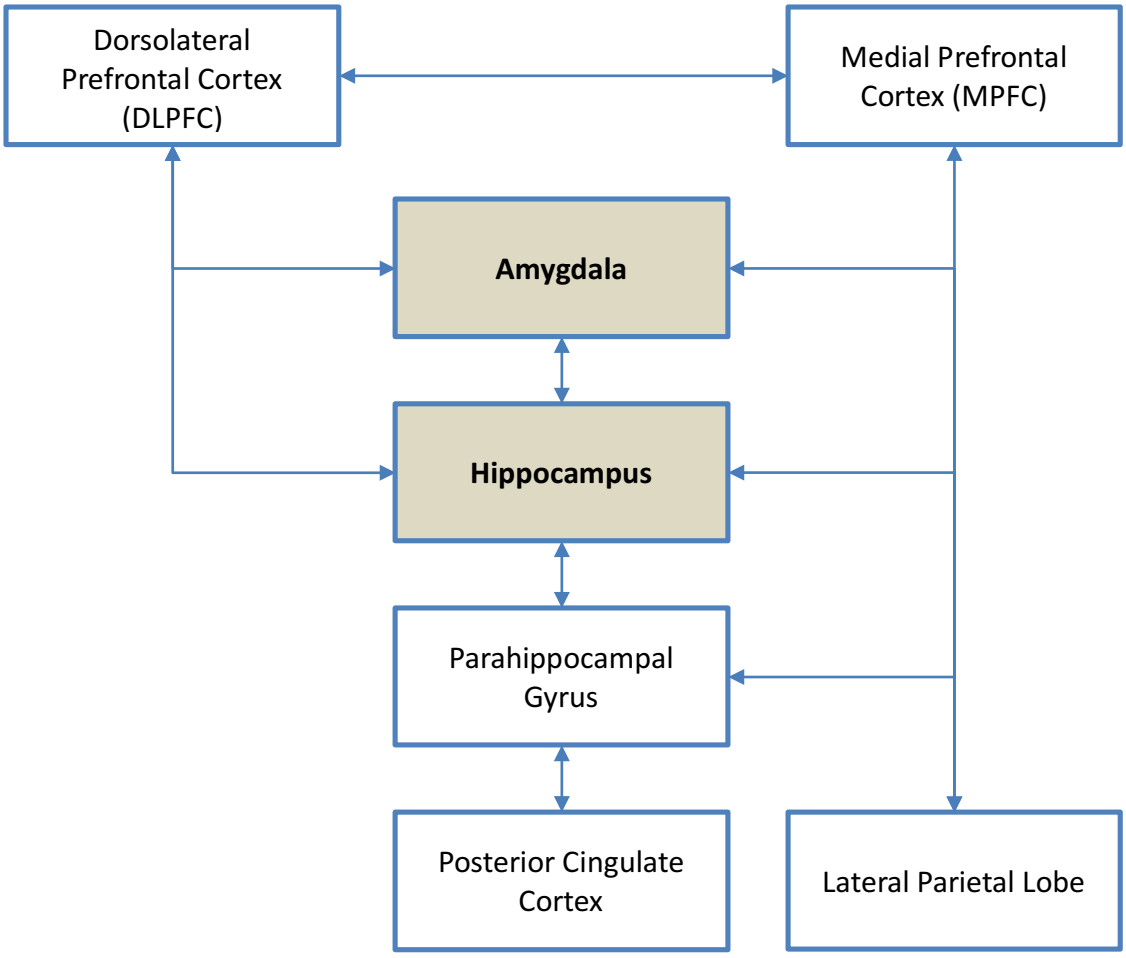

Figure 3. Basic neurocircuit schematic of depression.

Once the ROIs were selected, a denoising process was conducted. First, white matter, CSF, and motion were all identified as confounds. As well, the ROI time-series were band-pass filtered ($0.008 < f < 0.09$ Hz). The CONN-fMRI toolbox utilized built in software (nitrc.org/projects/artifact detect/) to identify motion outliers, along with a built-in Compcor method (i.e., anatomical component-based method for denoising) to estimate and remove white matter and CSF noise (Behzadi, Restom Liau, & Liu, 2007; Chai, Castanon, Ongur, & Whitfield-Gabrieli, 2012; Whitfield-Gabrieli & Nieto-Castanon, 2017).

Following denoising, correlational maps were made from the sources' residual BOLD time-course. From there Pearson's correlation coefficients were generated between a source's

time-course and each other voxel's time course. The correlation coefficients then underwent a Fisher's r-to-z transformation, converting them to normally distributed scores in preparation for General Linear Model (GLM) analyses.

Statistical Analysis

All data was exported from MATLAB 2016a and statistically analyzed in SPSS 21. Demographic and symptom data were analyzed. Chi-square tests of independence were conducted examining the relations between treatment response and anxiety severity as well as social phobia symptom comorbidity. Additionally, multivariate analyses of variance (MANOVAs) were conducted examining differences in neurobiological correlates based upon anxiety severity, social phobia symptom comorbidity, and anxiety treatment response. Wilks' Lambda was used as the critical statistic to identify any potential neurobiological differences. Follow-up independent sample t-tests were then conducted for the comorbidity and anxiety responder examinations, and post-hoc analyses using the Scheffé post hoc criterion were run for the anxiety severity analyses. Bonferroni corrections for multiple comparisons were also conducted for the follow-up examinations of neurobiological differences based upon anxiety severity, as the dependent variables were compared across the three anxiety severity groups. No other corrections for multiple comparisons were conducted as the hypotheses being examined were considered to be distinct, with differing independent variables.

Chapter 4: Results

Preliminary Analyses

Descriptive Statistics. Prior to running the statistical analyses, descriptive statistics were run for each of the dependent variables (see Table 1). Skewness and kurtosis values were reviewed to determine whether the variables were normally distributed. Based upon cutoff values of +/-2 for skewness and +/-4 for kurtosis, all of the variables were considered normally distributed (Field, 2009).

Table 1.

Descriptive Statistics on Functional Connectivity Variables

Variable	N	Mean	Std. Deviation	Skewness	Kurtosis
pPaHCR_pPaHCL	32	.740	.268	-.759	.392
pPaHCR_HippocampusR	32	.510	.261	-.007	-.601
pPaHCR_HippocampusL	32	.431	.233	.031	.883
pPaHCR_MPFC	32	.273	.212	.249	-.378
pPaHCR_LLP	32	.199	.256	-1.226	1.571
pPaHCR_RLP	32	.283	.198	-.495	-.269
pPaHCR_PCC	32	.264	.280	-.027	.161
pPaHCR_LDLPFC	32	-.015	.256	.350	-.530
pPaHCL_HippocampusR	32	.503	.269	.370	-.239
pPaHCL_HippocampusL	32	.617	.254	.199	-1.017
pPaHCL_MPFC	32	.301	.273	-.248	-.367
pPaHCL_LLP	32	.313	.317	-.463	-.575
pPaHCL_RLP	32	.285	.282	.150	.093
pPaHCL_PCC	32	.284	.272	-.164	.223
pPaHCL_LDLPFC	32	-.004	.268	.365	-.404
HippocampusR_HippocampusL	32	.816	.250	-.005	-.730
HippocampusR_MPFC	32	.268	.222	-.225	.435
HippocampusR_LLP	32	.207	.291	-.378	.351
HippocampusR_RLP	32	.213	.290	.085	-.530
HippocampusR_PCC	32	.105	.244	-.228	-.645
HippocampusR_LDLPFC	32	-.043	.286	-.597	.430
HippocampusL_MPFC	32	.270	.264	-.178	.746
HippocampusL_LLP	32	.231	.281	.097	-.289
HippocampusL_RLP	32	.203	.232	.020	.994
HippocampsL_PCC	32	.102	.197	-.569	-.389
HippocampusL_LDLPFC	32	-.033	.321	.257	.686
MPFC_LLP	32	.536	.381	-.456	-.786

MPFC_RLP	32	.506	.296	-.457	1.066
MPFC_PCC	32	.458	.282	.605	-.369
MPFC_LDLPFC	32	-.252	.198	-.015	-.715
LLP_RLP	32	.910	.315	-1.056	1.342
LLP_PCC	32	.548	.365	-.205	.376
LLP_DLPFC	32	-.084	.374	.007	-.737
RLP_PCC	32	.630	.325	.287	.494
RLP_LDLPFC	32	-.073	.346	.347	-.836
PCC_LDLPFC	32	.026	.290	-.486	3.098

Note. pPaHCR = right posterior parahippocampal gyrus. pPaHCL = left posterior parahippocampal gyrus. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

The functional connectivity variables were analyzed for outliers using boxplots. Sixteen functional connectivity variables were identified as having statistically significant outliers. The following functional connectivity variables had outliers: The right posterior parahippocampal gyrus to left posterior parahippocampal gyrus, left hippocampus, right lateral parietal lobe, left lateral parietal lobe, and posterior cingulate cortex; the left posterior parahippocampal gyrus to the posterior cingulate cortex; the right hippocampus to right lateral parietal lobe, left lateral parietal lobe, and left dorsolateral prefrontal cortex; the left hippocampus to right lateral parietal lobe, left lateral parietal lobe, and medial prefrontal cortex; the right lateral parietal lobe to left lateral parietal lobe, medial prefrontal cortex, and posterior cingulate cortex; and the posterior cingulate cortex to left dorsolateral prefrontal cortex. In this case none of these outliers appeared to impact the normality of the variables, and thus were not removed from the data set. However, it is still valuable to note that although the impacts were not statistically significant, these outliers did shift the variables' means.

Finally, consideration was given to the potential differences between the participants based upon ages. The participants were split into two groups, those under 18 years-of-age, and those 18 year-of-age and older. Between group t tests were run considering the various

neurobiological correlates as well as treatment response. The results indicated that treatment response did not differ based upon the age groups ($p > .05$), nor did the majority of the neurobiological areas. However, one notable variable that did demonstrate difference was the connection between the MPFC and left lateral parietal lobe, such that the younger participants showed significantly higher levels of functional connectivity than the older participants, $t = 2.417$, $p = .022$. This should be taken into consideration when the results of this study are reviewed.

Question 1: Are there functional connectivity differences based upon anxiety severity (e.g., mild, moderate, and severe anxiety)?

The literature provides vast and varied evidence for neurobiological abnormalities based upon the presence of an anxiety disorder, and this question explored the significance of potential impacts of varying levels of anxiety severity. Thus, it is worthwhile to examine potential functional connectivity differences between participants with mild, moderate, and severe and anxiety. This was done by employing a MANOVA, which analyzed the functional connectivity between all of the pre-identified regions of interest and measured the presence of significant differences among the three anxiety severity groups.

As a result of the MANOVA, one significant between-group difference was found for the functional connectivity between the left and right hippocampus, $F(2,32) = 3.326$, $p = .05$. A post-hoc analysis was then completed using Scheffé post hoc criterion, which did not reveal any significant differences between the anxiety severity groups ($p = .201$).

Question 2: Does rTMS treatment response differ by the way of anxiety severity, and if so, in what ways?

MDD and anxiety disorders have a long history of comorbidity, which can in turn make both increasingly difficult to treat and support. Based upon the premise that interacting anxiety can impact treatment response, this research question explores how baseline severity of anxiety may affect participants' response to rTMS. Depression and anxiety symptom response were both evaluated, with a 50% or greater reduction in symptoms classifying a treatment response.

A chi-square test of independence was conducted examining the relation between anxiety severity and depressive symptom treatment response (see Figure 2). The results of this analysis showed that there was no significant relation between these two variables ($\chi^2 = 2.491$, $p = .288$).

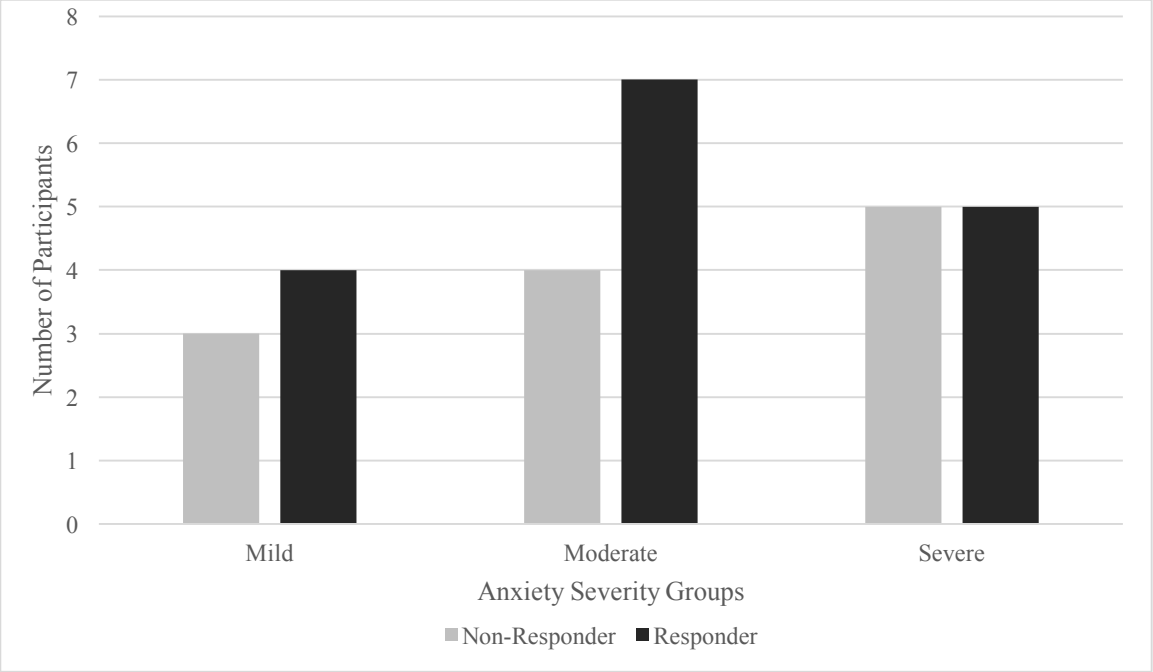

Figure 4. Bar chart demonstrating MDD treatment response rates for varying levels of anxiety severity.

A chi-square test of independence was also run, reviewing the relation between anxiety severity and anxiety symptom treatment response (see Figure 3). The findings demonstrated that there is no significant association between the two variables, (χ^2 =0.398, p = .820).

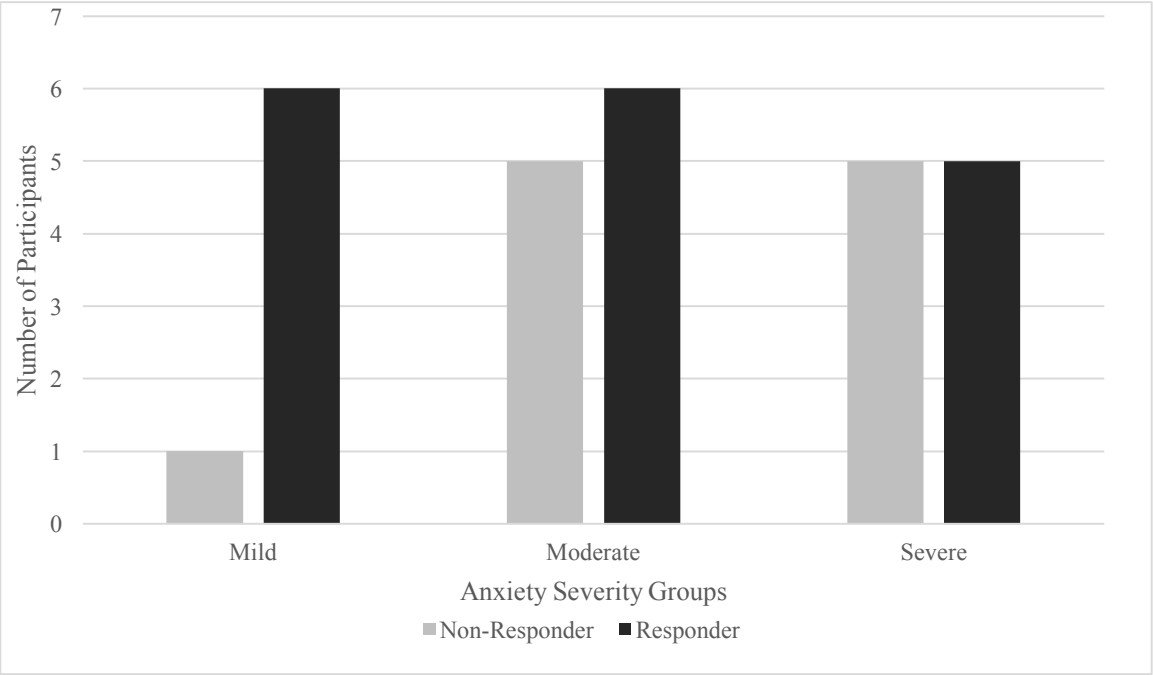

Figure 5. Bar chart demonstrating anxiety symptom treatment response rates for varying levels of anxiety severity.

Question 3: Are there functional connectivity differences between adolescents with MDD and those with MDD and comorbid social phobia symptoms?

Based on the fact that rTMS targets neurobiological abnormalities in individuals with major depressive disorder, this question examined whether or not there may be additional or contrasting neurobiological abnormalities in individuals who also have comorbid social phobia symptoms. The potential neurobiological differences were analyzed using pre-test fMRI scans. The analyses focused on differences between the MDD-only and comorbid social phobia symptom groups in terms of functional connectivity.

First considering functional connectivity, statistical analyses were conducted for the DMN ROIs as well as the left DLPFC. Due to potential interdependence among the functional connectivity connections associated with each ROI, multivariate analyses of variance (MANOVAs) were utilized. A separate MANOVA was examined for each of the ROIs.

Beginning with the right posterior parahippocampal gyrus, a MANOVA was performed on the ten right posterior parahippocampal gyrus connectivity variables (see Table 2). MANOVA results showed that there is a statistically significant difference between the MDD-only and MDD-social phobia symptom groups, with Wilks' Lambda $\lambda = .470$, $F(10,21) = 2.365$, $p = .046$, partial $\eta^2 = .530$. This suggests that individuals with MDD on its own will show greater right posterior parahippocampal gyrus functional connectivity than individuals with MDD and social phobia symptoms. Additionally, when follow-up independent-samples t tests were analyzed a statistically significant difference was identified for the right posterior parahippocampal gyrus-right lateral parietal lobe connection, $t = 2.064$, $p = .048$, Cohen's d = 0.738 (see Table 3). This indicates greater functional connectivity between these two regions in participants with MDD on its own.

Table 2.
Right posterior parahippocampal gyrus functional connectivity variables

Variable	N	Mean	Std. Deviation
pPaHCR and pPaHCL	32	0.740	0.268
pPaHCR and right hippocampus	32	0.510	0.261
pPaHCR and left hippocampus	32	0.431	0.233
pPaHCR and MPFC	32	0.273	0.212
pPaHCR and LLP	32	0.199	0.256
pPaHCR and RLP	32	0.283	0.198
pPaHCR and PCC	32	0.264	0.281
pPaHCR and LDLPFC	32	-0.015	0.256

pPaHCR and right amygdala	32	0.415	0.277
pPaHCR and left amygdala	32	0.305	0.239

Note. pPaHCR = right posterior parahippocampal gyrus. pPaHCL = left posterior parahippocampal gyrus. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

Table 3.
Significant independent samples t-test results comparing MDD-only and social phobia symptom comorbidity on right posterior parahippocampal gyrus functional

Variable	Group	n	Mean	St. Deviation	*t*	df	*p*
pPaHCR and RLP	MDD-only	20	0.336	0.179	2.064	30	.048
	social phobia symptom comorbidity	12	0.194	0.205			

Note. pPaHCR = right posterior parahippocampal gyrus. RLP = right lateral parietal lobe. MDD = major depressive disorder.

To explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was performed using the nine left posterior parahippocampal gyrus connectivity variables (see Table 4). The results demonstrated there is no statistically significant difference between the MDD-only and MDD-social phobia symptom groups, with Wilks' Lambda $\lambda = .655$, $F(9,22) = 1.288$, $p = .298$.

Table 4.

Left posterior parahippocampal gyrus functional connectivity variables

Variable	N	Mean	Std. Deviation
pPaHCL and right hippocampus	32	0.503	0.270
pPaHCL and left hippocampus	32	0.617	0.254
pPaHCL and MPFC	32	0.301	0.273
pPaHCL and LLP	32	0.313	0.317
pPaHCL and RLP	32	0.285	0.282
pPaHCL and PCC	32	0.284	0.272
pPaHCL and LDLPFC	32	-0.004	0.268
pPaHCL and right amygdala	32	0.338	0.276
pPaHCL and left amygdala	32	0.396	0.289

Note. pPaHCL = left posterior parahippocampal gyrus. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

To explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was performed on the eight right hippocampus connectivity variables (see Table 5), as well as the seven left hippocampus connectivity variables (see Table 6). The results showed that there was no statistically significant difference between the MDD-only and comorbid social phobia symptom groups in terms of right hippocampus functional connectivity (Wilks' Lambda $\lambda = .776$, $F(8,23) = 0.832$, $p = .584$) or left hippocampus functional connectivity (Wilks' Lambda $\lambda = .378$, $F(7,24) = 1.294$, $p = .295$).

Table 5.

Right hippocampus functional connectivity variables

Variable	N	Mean	Std. Deviation
right hippocampus and left hppocampus	32	0.817	0.250
right hippocampus and MPFC	32	0.268	0.222
right hippocampus and LLP	32	0.207	0.291
right hippocampus and RLP	32	0.213	0.290
right hippocampus and PCC	32	0.105	0.244
right hippocampus and left DLPFC	32	-0.043	0.286
right hippocampus and right amygdala	32	0.668	0.291
right hippocampus and left amygdala	32	0.517	0.249

Note. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

Table 6.

Left hippocampus functional connectivity variables

Variable	N	Mean	Std. Deviation
left hippocampus and MPFC	32	0.270	0.264
left hippocampus and LLP	32	0.231	0.281
left hippocampus and RLP	32	0.203	0.232
left hippocampus and PCC	32	0.102	0.197

left hippocampus and left DLPFC	32	-0.033	0.321
left hippocampus and right amygdala	32	0.504	0.283
left hippocampus and left amygdala	32	0.656	0.271

Note. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

To explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was conducted examining the MPFC and its six connectivity variables (see Table 7). The analysis demonstrated a statistically significant difference in MPFC functional connectivity between MDD-only participants and those with comorbid social phobia symptoms, with Wilks' Lambda $\lambda = .495$, $F(6,25) = 4.243$, $p = .004$, partial $\eta^2 = .505$. Follow-up independent samples t tests indicated that a number of MPFC connections were significantly different; MDD-only and comorbid social phobia symptom groups. The MPFC and left lateral parietal lobe connection was significantly different between the groups, $t = 2.597$, $p = .014$, Cohen's d = 0.932; participants with MDD on its own showed greater functional connectivity levels than did those with comorbid social phobia symptoms. MPFC and left DLPFC connection was significantly different between the groups, $t = -2.177$, $p = .038$, Cohen's d = 0.816; participants in the comorbid social phobia symptom group demonstrated greater functional connectivity levels than those with MDD only. As well, the MPFC and left amygdala connection was significantly different between the groups, $t = -2.133$, $p = .041$, Cohen's d = 0.669, with the comorbid social phobia symptom group again demonstrating greater levels of functional connectivity. See Table 8 for descriptive and significance statistics for each of the significant independent samples t test.

Table 7.

Medial prefrontal cortex functional connectivity variables

Variable	N	Mean	Std. Deviation
MPFC and LLP	32	0.536	0.381
MPFC and RLP	32	0.506	0.296
MPFC and PCC	32	0.458	0.282
MPFC and LDLPFC	32	-0.252	0.198
MPFC and right amygdala	32	0.105	0.224
MPFC and left amygdala	32	0.136	0.289

Note. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

Table 8.

Significant independent samples t-test results comparing MDD-only and social phobia symptom comorbidity on medial prefrontal cortex functional connectivity

Variable	Group	n	Mean	St. Deviation	*t*	df	*p*
MPFC and LLP	MDD-only	20	0.661	0.331	2.597	30	.014
	social phobia symptom comorbidity	12	0.329	0.380			
MPFC and LDLPFC	MDD-only	20	-0.308	0.198	-2.177	30	.038
	social phobia symptom comorbidity	12	-0.159	0.166			
	MDD-only	20	0.057	0.251	-2.133	30	.041

MPFC and left amygdala	social phobia symptom comorbidity	12	0.270	0.309

Note. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. LDLPFC = left dorsolateral prefrontal cortex. MDD = major depressive disorder.

To explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was conducted examining the left lateral parietal lobe and its five connectivity variables (see Table 9). Similarly, a multivariate analysis was run examining the right lateral parietal lobe and its four connectivity variables (see Table 10). The MANOVA results revealed that no statistically significant difference existed between the MDD-only and comorbid social phobia symptom groups for left lateral parietal lobe functional connectivity (Wilks' Lambda $\lambda = .963$, $F(5,26) = 0.202$, $p = .959$), nor for right lateral parietal lobe functional connectivity (Wilks' Lambda $\lambda = .926$, $F(4,27) = 0.540$, $p = .708$).

Table 9.

Left lateral parietal lobe cortex functional connectivity variables

Variable	N	Mean	Std. Deviation
LLP and RLP	32	0.910	0.315
LLP and PCC	32	0.548	0.364
LLP and LDLPFC	32	-0.084	0.374
LLP and right amygdala	32	0.083	0.264
LLP and left amygdala	32	0.144	0.211

Note. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

Table 10.

Right lateral parietal lobe cortex functional connectivity variables

Variable	N	Mean	Std. Deviation
RLP and PCC	32	0.630	0.325
RLP and LDLPFC	32	-0.073	0.346

RLP and right amygdala	32	0.126	0.237
RLP and left amygdala	32	0.106	0.214

Note. RLP = right lateral parietal lobe. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

To explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was conducted that considered the PCC and its three connectivity variables (see Table 11). The results showed that there's no statistically significant difference between the MDD-only and comorbid social phobia symptom groups, with Wilks' Lambda $\lambda = .827$, $F(3,28) = 1.953$, $p = .144$.

Table 11.

Posterior cingulate cortex functional connectivity variables

Variable	N	Mean	Std. Deviation
PCC and LDLPFC	32	0.026	0.290
PCC and right amygdala	32	0.062	0.340
PCC and left amygdala	32	0.019	0.267

Note. PCC = posterior cingulate cortex. LDLPFC = left dorsolateral prefrontal cortex.

Following this, to explore significant differences between the MDD-only group and the MDD-social phobia symptom group, a MANOVA was run examining the left DLPFC and its two connectivity variables (see Table 12). The analysis demonstrated that there is no statistically significant difference between the MDD-only and comorbid social phobia symptom groups, with Wilks' Lambda $\lambda = .937$, $F(2,29) = 0.969$, $p = .391$.

Table 12.

Left DLPFC functional connectivity variables

Variable	N	Mean	Std. Deviation

LDLPFC and right amygdala	32	0.079	0.268
LDLPFC and left amygdala	32	0.092	0.366

Note. LDLPFC = left dorsolateral prefrontal cortex.

Finally, the potential group difference using the left and right amygdalae's functional connectivity was examined using an independent samples t test. The results were non-significant, t = -0.069, p = .946, such that there is no notable difference between the MDD-only and comorbid social phobia symptom groups.

Question 4: Do comorbid social phobia symptoms impact rTMS treatment response, and if so, in what ways?

Given the relative lack of evidence regarding rTMS as a depression treatment, there is limited support for regarding the impact of comorbidities. This question gives new insights into the potential impact of one of the more frequent and impairing comorbidities: social phobia. A comparison of pre- and post-test HAMD scores allowed the researcher to estimate how many participants demonstrated a positive treatment response (50% or greater reduction in symptom count) in both the comorbid and non-comorbid groups (see Figure 4).

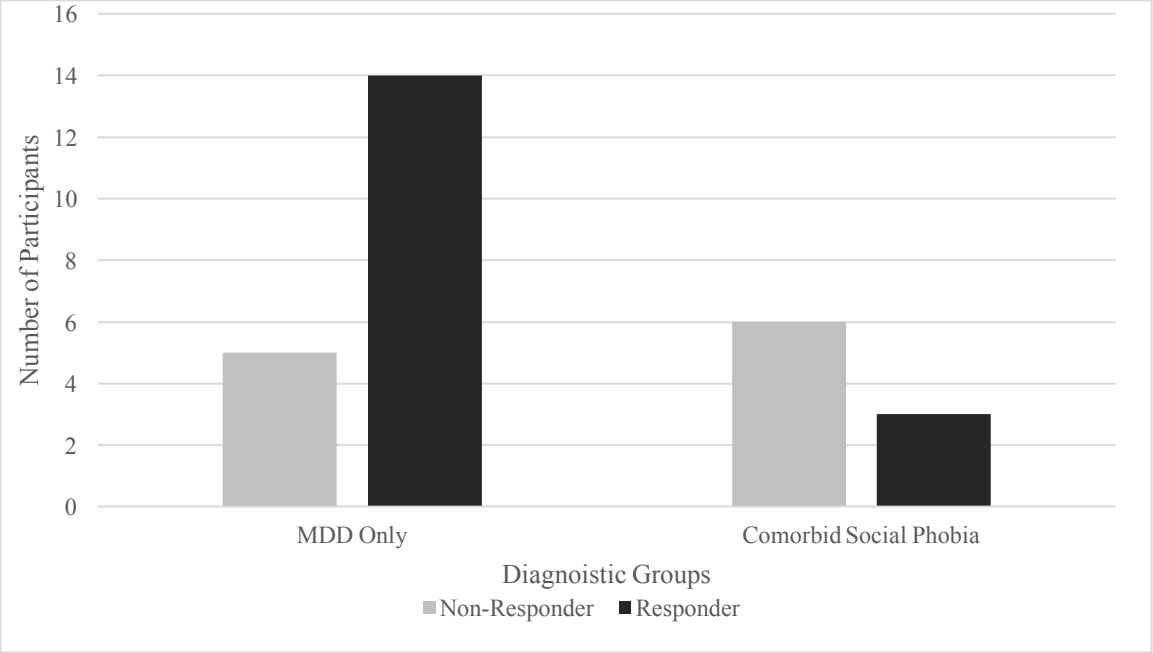

Figure 6. Bar chart demonstrating MDD treatment response based upon social phobia symptom comorbidity

A chi-square test of independence was conducted, examining the relation between social phobia symptom comorbidity and treatment response. A significant relation between the variables was observed between treatment response and whether or not participants had comorbid social phobia symptoms ($\chi^2 = 4.169$, $p = .041$. Based on the odds ratio, the results indicated that participants with MDD who did not have social phobia symptom comorbidity are 0.178 times more likely to experience a significant rTMS treatment response than those who had comorbid social phobia symptoms.

An additional chi-square test of independence was run considering the relation between the two categorical variables: comorbid social phobia symptoms and anxiety treatment response, as defined by a greater than 50% reduction in anxiety symptoms as measured by the Ham-A. There were no significant association between these two variables ($\chi^2 = 0.873$, $p = .35$), such that

there neither the MDD-only or comorbid social phobia symptom participants were more likely than the other to experience a significant anxiety symptom treatment response (see Figure 5).

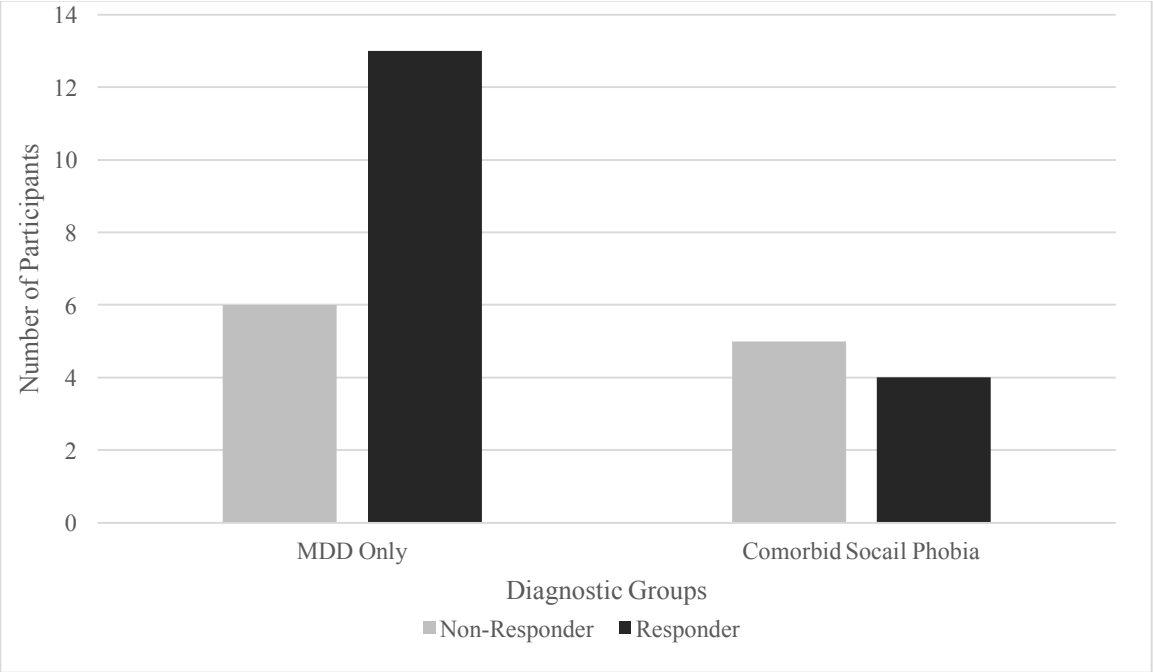

Figure 7. Bar chart demonstrating anxiety symptom treatment response based upon social phobia symptom comorbidity

Question 5: Are there functional connectivity differences between those whose anxiety symptoms significantly decreased following treatment and those whose did not?

Previous research has found potential biomarkers for rTMS response as a treatment for MDD, however, there has been minimal consideration of biomarkers for reduction of anxiety symptoms, despite the fact that this rTMS treatment appears to be indirectly treating anxiety as well as depression. The final research question evaluated whether or not any potential biomarkers do exist by examining differences between participants with and without anxiety

using their rTMS responses. MANOVAs were conducted to identify functional connectivity differences between anxiety responders and non-responders, as determined by a 50% or greater reduction in symptom score. The functional connectivity targets were within the DMN, as well as the left DLPFC and amygdala. The analyses were organized based upon one ROI at a time, and a multivariate analysis of its selected connections.

To explore significant differences between the anxiety responder and non-responder groups, a MANOVA was conducted considering the right posterior parahippocampal gyrus and its ten connectivity variables (see Table 12). The results showed no statistically significant differences between the anxiety responder and non-responder groups, with Wilks' Lambda λ = .805, $F(10,17) = 0.411$, $p = .923$. A MANOVA was also run, examining the left posterior parahippocampal gyrus and its nine connectivity variables (see Table 4). The analysis demonstrated no statistically significant difference between the anxiety responder and non-responder groups, with Wilks' Lambda $\lambda = .514$, $F(9,18) = 1.894$, $p = .119$. However, a follow-up independent samples t-test showed a statistically significant difference between responder and non-responder groups for the left posterior parahippocampal gyrus and left lateral parietal lobe connection ($t = 2.490$, $p < .019$, Cohen's d = 0.519). This shows that the anxiety responder group has greater levels of functional connectivity between these two neural regions than the non-responders. See Table 13.

Table 13.

Significant independent samples t-test results comparing anxiety responders and non-responders on left posterior parahippocampal gyrus functional connectivity

Variable	Group	n	Mean	St. Deviation	*t*	df	*p*
pPaHCL and LLP	Ham-A responder	16	0.425	0.303	2.490	26	.019

	Ham-A non-responder	12	0.136	0.303

Note. pPaHCL = left posterior parahippocampal gyrus. LLP = left lateral parietal lobe. Ham-A = Hamilton Anxiety Rating Scale.

Next, to explore significant differences between the anxiety responder and non-responder groups, a MANOVA was run looking at the right hippocampus and its eight connectivity variables (see Table 5). The results indicated that there is no statistically significant difference between the responders and non-responders in terms of right hippocampal functional connectivity, with Wilks' Lambda $\lambda = .662$, $F(8,19) = 1.213$, $p = .344$.

Additionally, to explore significant differences between the anxiety responder and non-responder groups, a MANOVA was conducted considering the left hippocampus and its seven connectivity variables (see Table 6). The analyses showed a significant difference between the responder and non-responder groups, with Wilks' Lambda $\lambda = .513$, $F(7,20) = 2.711$, $p = .038$, partial $\eta^2 = .487$. An additional follow-up independent samples t test indicated a statistically significant difference between groups for the left hippocampus and left lateral parietal lobe connection ($t = 3.367$, $p = .002$, Cohen's d = 0.630). This finding shows that anxiety responders tended to have greater levels of functional connectivity between the left hippocampus and left lateral parietal lobe than the non-responders. See Table 14.

Table 14.

Significant independent samples t-test results comparing anxiety responders and non-responders on left hippocampus functional connectivity

Variable	Group	n	Mean	St. Deviation	*t*	df	*p*
left hippocampus and LLP	Ham-A responder	16	0.359	0.269	3.367	26	.002

	Ham-A non-responder	12	0.049	0.196

Note. LLP = left lateral parietal lobe. Ham-A = Hamilton Anxiety Rating Scale.

To explore significant differences between the anxiety responder and non-responder groups, a MANOVA was run examining the MPFC its six connectivity variables (see Table 7). The analysis showed no statistically significant difference between the responder and non-responder groups, with Wilks' Lambda $\lambda = .618$, $F(6,21) = 2.165$, $p = .088$. However, follow-up independent samples t tests showed statistically significant group difference for MPFC and left lateral parietal lobe functional connectivity ($t = 2.186$, $p = .038$, Cohen's d = 0.797) and for MPFC and right lateral parietal lobe functional connectivity ($t = 2.292$, $p = .030$, Cohen's d = 1.005). See Table 15 for descriptive and significance statistics for the statistically significant independent samples t tests. These results demonstrate a that anxiety responders tended to have greater levels of functional connectivity between the MPFC and left lateral parietal lobe and the MPFC and right lateral parietal lobe, than the non-responders.

Table 15.

Significant independent samples t-test results comparing anxiety responders and non-responders on MPFC functional connectivity

Variable	Group	n	Mean	St. Deviation	*t*	df	*p*
MPFC and LLP	Ham-A responder	16	0.664	0.378	2.186	26	.038
	Ham-A non-responder	12	0.352	0.366			
MPFC and RLP	Ham-A responder	16	0.614	0.281	2.292	26	.030

	Ham-A non-responder	12	0.363	0.296

Note. MPFC = medial prefrontal cortex. LLP = left lateral parietal lobe. RLP = right lateral parietal lobe. Ham-A = Hamilton Anxiety Rating Scale.

Next, to explore significant differences between the anxiety responder and non-responder groups, a MANOVA was conducted considering the left lateral parietal lobe and its five connectivity variables, as was the right lateral parietal lobe and its four connectivity variables. The results indicated no statistically significant difference between the anxiety responder and non-responder groups for left lateral parietal lobe functional connectivity (Wilks' Lambda λ = .753, $F(5,22) = 1.445$, $p = .248$), nor for right lateral parietal lobe functional connectivity (Wilks' Lambda $\lambda = .982$, $F(4,23) = 0.108$, $p = .978$).

Then, to explore significant differences between the anxiety responder and non-responder groups, a MANOVA was run examining the PCC and its three functional connectivity variables. The results indicated no statistically significant difference between the responder and non-responder groups, with Wilks' Lambda $\lambda = .990$, $F(3,24) = 0.082$, $p = .969$.

To explore significant differences between the anxiety responder and non-responder groups, a MANOVA was completed examining the left DLPFC and its two connectivity variables. This analysis showed no statistically significant difference between the anxiety responder and non-responder groups, with Wilks' Lambda $\lambda = .948$, $F(2,25) = 0.680$, $p = .516$.

Finally, the potential difference between anxiety responder groups in terms of the functional connectivity of the right and left amygdala was analyzed using an independent samples t test. The results of this analysis were not significant ($t = 0.187$, $p = .853$), such that there is no significant difference between responders and non-responders in terms of left and right amygdala functional connectivity.

Chapter 5: Discussion

MDD is a disorder commonly associated with comorbid disorders, and anxiety disorders are one of the most commonly observed comorbidities (APA, 2013). The interaction of these co-existing disorders can both elevate symptom severity and decrease the likelihood of successful treatment responses (Curry et al., 2006). It appears that the traditional MDD and anxiety disorder treatments are not able to address the treatment resistance associated with comorbidity, as they are far less effective within this population (Curry et al., 2006). Thus, for adolescents experiencing MDD-social anxiety comorbidity, it is valuable to consider alternative treatments. rTMS is an increasingly promising alternative treatment option for TRD. This study was intended to add to the current literature surrounding rTMS as a treatment for adolescent depression by providing a focus on comorbid anxiety. As an exploratory study, it seeks to provide insight on the interact between MDD and anxiety, as well as the impacts this interaction may have on rTMS treatment efficacy and adolescents' neurobiology.

When considering rTMS, MDD, and comorbid anxiety, it is necessary to look at both treatment response and neurobiological factors, as the treatment itself targets neurobiological abnormality. Additionally, it is useful to examine both a specific anxiety disorder (i.e., social anxiety disorder) as well as varying levels of anxiety severity. Throughout this study a few key questions were asked: (1) Are there neurobiological markers in terms of functional connectivity for varying levels of anxiety severity? (2) How does anxiety severity impact rTMS treatment

response? (3) Are there neurobiological markers in terms of functional connectivity for comorbid social phobia symptoms? (4) How do comorbid social phobia symptoms impact rTMS treatment response? (5) Are there neurobiological markers in terms of functional connectivity for those who show a significant decrease in anxiety symptoms following the rTMS treatment?

The following is a discussion of each of these five research questions and the implications of their results. As well, there will be a review of the limitations of this particular study. Finally, recommendations will be made for future researchers, how the findings elucidate other areas to explore, and a description of the challenges in doing research using the rTMS methodology.

Are there functional connectivity differences based upon anxiety severity (e.g., mild, moderate, and severe anxiety)?

This first research question considers the potential neurobiological abnormalities in terms of DMN, left DLPFC, and amygdala functional connectivity on adolescents with MDD, based upon varying levels of anxiety severity. Reviewing the various functional connections, one connection demonstrating significant difference was found: The right and left hippocampal connection. Increased hippocampus activity is associated with anxiety disorders, such that increasing levels of anxiety severity would be expected to increase hippocampus activity (Bruhl et al., 2011; Duval et al., 2015).

The post-hoc analyses for this finding did not result in any significant differences at the group level; however, when visually analyzing the functional connectivity levels, an unexpected pattern was observed. It appeared that individuals with moderate levels of anxiety had the lowest levels of functional connectivity. One would typically expect a more linear relationship, with those participants with the most severe anxiety having the highest levels of functional

connectivity, and those with mild anxiety being associated with the lowest levels of functional connectivity (Bruhl et al., 2011; Duval et al., 2015). It is possible that, as with the stress-productivity relation, these moderate levels of anxiety are associated with an ideal level of hippocampal activation, and it is when the anxiety becomes too much that it actually interferes with connectivity and become neurobiologically impairing (Anderson, 1976). There is also potential that the moderate levels of anxiety actually reflect a normative level, as many young adult samples report regularly experiencing stress or anxiety (Beiter et al., 2015). If this is this case, the mild and severe anxiety raters would both be considered to be experiencing abnormal levels of anxiety, which could therefore be associated with increased functional connectivity between the right and left hippocampus (Bruhl et al., 2011; Duval et al., 2015).

Does rTMS treatment response differ by the way of anxiety severity, and if so, in what ways?

This research question considers the potential interaction between anxiety severity and treatment response. This question is of importance when reviewing a possible depression treatment, as anxiety symptoms are so commonly found in individuals with depression (Hirschfeld, 2001). An examination of reduction of both depressive and anxiety symptoms across mild, moderate, and severe anxiety groups was conducted to answer this question. A comparison of the responders and non-responders at each severity level showed no significant differences. This suggests that rTMS treatment response does not vary by way of anxiety severity, at least in terms of symptom scores. This finding is counter to previous research, which indicates that pretreatment anxiety severity is a significant predictor of treatment response (Dadds et al., 1999). As well, the literature shows that comorbid anxiety disorders interfere with treatment response in individuals with MDD (Curry et al., 2006). Since a severe anxiety rating indicates the potential

presence of an anxiety disorder, whereas mild and moderate levels are sub-clinical, one would expect to see treatment response differ based upon anxiety severity, with the treatment responders primarily having mild or moderate levels of anxiety (Shin, Davis, VanElzakker, Dahlgren, & Dubois, 2013; Vitiello, 2003). However, other literature demonstrates some uncertainty surrounding the relation between anxiety severity and treatment response, as well as variability in terms of the potential outcomes associated with levels of anxiety severity (Bomyea et al., 2015). Some theorize that severe anxiety would be associated with greater treatment response, whereas it is also postulated that increased severity is associated with increased risk of relapse (Bomyea et al., 2015). It is possible that the variability of treatment outcomes associated with severe anxiety underlies the lack of significant finding.

Are there functional connectivity differences between adolescents with MDD and those with MDD and comorbid social phobia symptoms?

The study next focused upon comorbid social phobia symptoms. It examined whether or not they interact with functional connectivity within the brain. Potential neurobiological differences were explored through an analysis of functional connectivity group differences, comparing the MDD-only and comorbid social phobia symptom groups. The analyses indicated a number of areas of difference.

Considering functional connectivity, a couple of neurobiological regions stood out. First of all, a significant difference was found between the MDD-only and comorbid social phobia symptoms for the right posterior parahippocampal gyrus, such that MDD-only participants showed greater levels of functional connectivity. The parahippocampal gyrus is associated with episodic memory as well as emotional processing (Aminoff, Kveraga, & Bar, 2013). Additionally, increased parahippocampal gyrus connectivity, particularly with the PCC, is

associated with increased levels of sadness and rumination (Zamoscik, Huffziger, Ebner-Priemer, Kuehner, & Kirsch, 2014). This suggests that those with MDD on its own may actually experience greater levels of sadness and rumination than those with MDD and social phobia symptoms. Follow-up analyses also indicated that the functional connectivity levels between the right posterior parahippocampal gyrus and left lateral parietal lobe were notably higher in the MDD-only participants, further suggesting that the MDD-only participants are experiencing greater levels of sadness than their comorbid peers.

The MPFC showed greater levels of overall functional connectivity for the MDD-only participants. The literature suggests that individuals with MDD have lower than average levels of MPFC functional connectivity (Murrough et al., 2016). Therefore, the finding social phobia symptom group demonstrated even lower levels of MPFC functional connectivity than the MDD-only group, suggests that social phobia symptom comorbidity is even more neurobiologically impairing to the MPFC than MDD on its own (Murrough et al., 2016). Broken down into individual connections, the MDD-only participants showed significantly greater functional connectivity between the MPFC and left lateral parietal lobe, but significantly lower levels of functional connectivity between the MPFC and the left DLPFC as well as the left amygdala. As both the left DLPFC and left amygdala are not part of the DMN, it is possible that the increased neurobiological impairments associated with comorbid social phobia symptoms are focused within the DMN and not its external connections (Raichle, 2015; Murrough et al. 2016).

Do comorbid social phobia symptoms impact rTMS treatment response, and if so, in what ways?

Considering that the comorbid social phobia symptoms interact with neurobiology, one would expect them to also interact with treatment response. The study examined whether or not

social phobia symptoms interact with rTMS treatment response. As well it considered in what ways and to what extent the comorbidity potentially affects treatment response. This question was answered through an examination of participants' pre- and post-test scores on the HAM-D, as well as the Ham-A, with a greater than 50% reduction in symptoms counting as a positive, significant treatment response.

The analyses demonstrated that participants with comorbid social anxiety were significantly less likely to be rTMS treatment responders in terms of depression symptom reduction (as measured using the HAM-D; Hamilton, 1967). This fits with previous findings that comorbidity makes MDD more challenging to treat (Curry et al., 2006). This finding, in combination with the literature indicating comorbidity decreases treatment response, suggests that this comorbidity may actually be interfering with the treatment efficacy of the rTMS (Curry et al., 2006). It is possible that individuals with this comorbidity may still experience some of the benefits of the treatment, but likely to a lesser extent (Garber & Weersing, 2010). This is something that needs to be accounted for in terms of treatment planning, as individuals with MDD and comorbid social anxiety may require their social anxiety to be addressed simultaneously or even treated prior to addressing their depressive symptoms (Gorman, 1996; Ballenger, 2000)

Are there functional connectivity differences between those whose anxiety symptoms significantly decreased following treatment and those whose did not?

It is increasingly clear that anxiety, both in the form of comorbid diagnosis and with regards to single diagnoses varying in symptom severity, is related to neurobiological abnormalities in adolescents with MDD. As well, it appears that while targeting depressive symptoms, rTMS is also able to reduce anxiety symptoms, at least in some participants. Thus,

left open to confirm, there may be something unique about the individuals who see a reduction in anxiety symptoms. Specifically, is there something unique neurobiologically for individuals with comorbid MDD-social anxiety?

Through an examination of functional connectivity differences, areas of significant difference were identified. The anxiety symptom responders showed significantly greater levels of overall functional connectivity in the left hippocampus. Increased hippocampal activation is typically associated with the presence of an anxiety disorder. Combined with this finding, it is possible that increased functional connectivity for the anxiety responders is an indication that those with anxiety disorders may be more likely to experience a significant reduction in their anxiety symptoms. It is possible that this is due to the initial high levels of anxiety symptoms experienced by those with an anxiety disorder, as there somewhere to go: it may be easier to decrease a symptom score of 30 than one of 3. Previous studies have found evidence supporting a positive relation between anxiety scores and change in anxiety score following treatment (Doehrmann et al., 2013). Follow-up analyses also indicated that the left hippocampus and left lateral parietal lobe connection was also significantly greater for the anxiety symptom responders.

Reviewing the other identified regions, there were no significant group differences in terms of overall functional connectivity, but there were a number of specific connections identified. In fact, both the MPFC and right lateral parietal lobe connection and MPFC and left lateral parietal lobe connection were significantly greater for the anxiety responders than the non-responders. There is some discrepancy in the literature in terms of the MPFC and how it appears in individuals with anxiety, such that one cannot be certain what this finding indicates (Liao et al., 2011; Blair et al., 2011; Sripada et al., 2009). However, it is possible that this finding

indicates these participants experienced a less severe combination of anxiety and depression symptoms, as the MPFC is often seen to have lower levels of functional connectivity in those diagnosed with MDD.

Finally, the left posterior parahippocampal gyrus and left lateral parietal lobe functional connectivity was also significantly greater for the anxiety responders. There is a visible trend of anxiety responders having greater functional connectivity in specific connections involving the lateral parietal lobe. The parietal lobe, including the left and right lateral parietal lobe, is associated with personal past and future thinking (Abraham, Schubotz, & Von Cramon, 2008). This may be related to anxious dwelling and future worries, such that those with higher levels of these anxiety symptoms are in a position to benefit from the rTMS as anxiety responders.

Implications

The current study was intended to address a relatively unsearched area: examining the impacts comorbid anxiety has on adolescents undergoing rTMS treatment. Results indicated that there is a relationship between comorbid social phobia symptoms and rTMS treatment response. As well they demonstrated that there are a number of neurobiological correlations associated with comorbid social phobia symptoms, anxiety severity, and a reduction in anxiety symptoms following the rTMS treatment. These findings have valuable implications for adolescents, and their families, who are seeking treatment for MDD, as well as for the healthcare professionals recommending and providing various treatments.

First, considering adolescents with MDD as well as social phobia symptoms, there are significant treatment implications. The finding of a relation between social phobia symptom comorbidity and treatment response, such that those with this comorbidity are less likely to see a significant reduction in depressive symptoms, posits that rTMS may not be a worthwhile

treatment option for this population. At the very least, these exploratory findings suggest that, for adolescents experiencing this MDD-social anxiety comorbidity, it may be worthwhile to consider alternative treatments or even combination treatments.

The finding of neurobiological correlates based upon comorbid social phobia symptoms, anxiety severity, and anxiety symptom reduction also has major implications for both those receiving and providing rTMS. The identification of these neurobiological correlates allows for more accurate prediction of treatment outcomes. With this data, healthcare professionals would be able to better identify those with high chance of receiving anxiety treatment along with the MDD treatment. As well, clinicians would likely be able to identify those at-risk for, or experiencing social phobia, based upon fMRI scans, even in patients only diagnosed with MDD.

The identification of these neurobiological correlates also has strong implications for researchers. Learning more about these neurobiological abnormalities and their relations with MDD as well as anxiety allows for a stronger understanding of how these disorders interact in the brain. This in turn can guide further treatment development, helping to identify ideal targets for neurobiologically based treatments like rTMS, as well as which regions may be most effective for monitoring severity as well as treatment response in adolescents with MDD and anxiety disorders.

Strengths and Limitations

This study makes a small but significant contribution to a relatively under-researched area; however, it also is subject to a number of challenges, a few that ultimately detract from the study itself. The first limitation is one faced by many clinical trials, and likely one of the reasons this field itself is rather lacking: Small sample size. Clinical trials, particularly trials involving such high levels of technology, tend to have small sample sizes (Pagnin, De Queiroz, Battista, &

Battista, 2004; Wall et al., 2011). This is attributable to the high cost of running these studies, as well as the high level of commitment required from the participants themselves. This particular study required every participant to attend daily sessions, Monday to Friday, for three weeks, as well as complete multi-hour pre- and post-test interviews, MRIs, and assessments. These demands can make it challenging to find participants. It can be difficult to administer a large number of the costly, time-consuming trials. Additionally, the trials are restricted by funding and grants. Taken together, these factors can result in a smaller than desired sample size.

Another key limitation is the lack of an official diagnosis. Though all of the participants had a pre-existing MDD diagnosis, their comorbid anxiety diagnoses were based on the results of the K-SADS-PL interview. Unfortunately, the K-SADS-PL is a screener rather than an actual diagnostic tool when administered without use of the supplemental, and used in the extent that it was cannot be used to determine with certainty whether or not an individual qualifies for a diagnosis. Had the anxiety supplemental measure also been administered, a social phobia categorization could have been made as opposed to social phobia symptoms. However, since the anxiety disorder supplemental was not include, the categorization was more of a reflection of multiple social phobia symptoms than social phobia itself.

Additionally, this study is lacking a control group. Though the current group comparisons are informative, this researcher believes that the addition of a control group could make certain analyses even more informative and interesting. For example, being able to compare functional connectivity not only between the MDD-only and comorbid social phobia symptom groups, but also with a control group could be highly beneficial. It would allow one to examine not only where differences lie based upon comorbidity, but how far from the normative population each

group falls. As well, it would allow one to identify whether both groups are diverting from normative levels of functional connectivity in the same direction or not.

Future Research

Going forward, this is an area in need of continued research. Replication and expansion of the current study and those that came before it will further the field and strengthen rTMS as an adolescent MDD treatment option. As well, as researchers continue to explore this area, they may seek to learn from the challenges faced by this study. An increased sample size would provide a greater understanding of rTMS, as well as increase the power of the study. One viable way to achieve this would be to work with researchers from other institutes, combining sample sizes and sharing data.

Additionally, future researchers might consider including a control group. This inclusion will likely provide greater insight into what is occurring. It will allow for more in-depth investigation, and further comparisons. This may be especially beneficial in clinical trials such as this, where the goal is to bring the participants closer to the state of the controls.

Future researchers should also strive to answer the new questions produced by this study. Particularly, there should be consideration given to what to do for those with comorbid social phobia. This study has shown that this comorbidity interferes with treatment response, and thus begs the question: what can be done for those with comorbid social phobia? It may be worthwhile to examine ways of further supporting these individuals, perhaps by simultaneous social phobia treatment, or even addressing the anxiety first.

Finally, it will be important for future researchers to decide upon one rTMS administration method and have that replicated throughout the literature. As it stands, there is

currently inconsistency in the rTMS methods used, which can impact treatment efficacy and even the targets of the treatment.

Conclusion

The current study provides a small but meaningful insight into rTMS as an adolescent MDD treatment. The results, those both significant and nonsignificant, served to elaborate upon and support the current state of the literature examining treatment efficacy. However, it also provided a novel insight into the impacts of comorbid anxiety. This study examined anxiety and its potential influence on many levels. It reviewed social phobia, a commonly occurring comorbidity, and its impacts on both treatment response and neurobiology; considered varying levels of anxiety severity, and how they may impact treatment response and functional connectivity; and examined what may be neurobiologically unique about participants who saw a significant decrease in their anxiety symptoms following treatment.

Findings indicated that comorbid social phobia symptoms significantly interfere with rTMS treatment efficacy. The data showed lower rates of treatment response in the comorbid MDD-social anxiety group than the MDD-only group. Ultimately, it appears that the presence of comorbid social phobia symptoms contributed to decreased treatment efficacy, such that individuals with this comorbidity will need a treatment option addressing not only their MDD symptoms, but also the social phobia symptoms. Additionally, the study demonstrated neurobiological evidence of the effects of comorbid social phobia symptoms, with a number of areas of significant difference in terms of both cortical thickness and functional connectivity.

The findings also demonstrated some neurobiological differences based upon varying levels of anxiety severity. There were no significant differences in terms of treatment response based upon anxiety severity; however, this may be related to the sample size. As previously

stated, a major limitation of this study is its small sample size, and the impact that size can have on statistical power. Based upon this, the impacts of anxiety severity of treatment response, ought to be further examined using a notably large sample.

Finally, this study was able to identify a number of neurobiological areas that were significantly different between those who experienced a significant decrease in anxiety symptoms and those who did not. This finding suggests that there may be neurobiological markers, which indicate a predisposition for indirect treatment of anxiety symptoms through MDD-targeting rTMS. Going forward, this finding has the potential to inform future rTMS trials and treatments. As well, it provides support for the possible use of rTMS as an anxiety treatment, or even a simultaneous MDD and anxiety treatment.

The present study provides new insight into the impacts of co-morbid social phobia, and anxiety in general, on adolescents with MDD, as well as on rTMS as an adolescent MDD treatment. The study is limited by it small sample size, lack of control group, and lack of official anxiety diagnosis, but in spite of this still has a great deal to offer. Going forward, future researchers should seek to expand upon this study, addressing its limitations, and ultimately working toward a greater understanding of comorbid anxiety and how it interacts with MDD and rTMS, as well as how best to address this highly occurring comorbidity.

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