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THE EFFECTS OF REPEATED TRANSCRANIAL MAGNETIC STIMULATION (rTMS) ON THE SPEEDED IDENTIFICATION OF HAPPY FACES IN DEPRESSED ADULTS

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Under the Direction of Sharee N. Light, Ph.D.

Anhedonia (defined as the inability to experience pleasure) is a symptom that is difficult to treat in patients with Major Depressive Disorder (MDD). Prior research suggests that the left dorsolateral prefrontal cortex (DLPFC) is a major underlying mechanism in the pathophysiology of depression. Therefore, we investigated whether repetitive transcranial magnetic stimulation (rTMS) treatment to the left DLPFC would predict a reduction in one facet of anhedonia symptomatology—namely, reward derived from positive social stimuli (i.e., smiling human faces)—in 26 depressed adults. The results revealed no significant effects of rTMS treatment on either accuracy or speeded reaction time during a novel behavioral task that involved identifying positive emotion in human faces. This suggests that although rTMS may be an innovative technique to reduce depressive symptoms in adults with MDD overall, its efficacy may not hinge on a meaningful reduction in this particular aspect of anhedonia.

INDEX WORDS: anhedonia, facial emotion recognition, depression, rTMS, dorsolateral prefrontal cortex (DLPFC), reaction speed, accuracy

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1 INTRODUCTION

Depression is a common mental disorder and is the leading cause of disability worldwide, affecting more than 300 million people of all ages (WHO, 2018). Anhedonia, defined as the reduced capacity to experience pleasure, is a symptom present in several different types of psychiatric disorders and has been recognized as a core feature of depression (Romney & Candido, 2011; Leventhal et al., 2006). In fact, anhedonia has been hypothesized to be a prodrome, and thus a predictor, for the later development of depressive disorder across multiple age groups (Loas, 1996; Gudmundsen et al., 2018). Anhedonia is a particularly difficult symptom to treat, as prior evidence suggests that first-line pharmacotherapies, such as selective serotonin reuptake inhibitors (SSRIs), do not adequately address hedonic deficits in depression (Treadway & Zald, 2011).

The prevalence of anhedonia in depression may be driven by at least two factors. First, individuals with depression are generally biased toward processing negative stimuli *faster* and more efficiently than positive stimuli (Beck, 1972). Specifically, Beck's Cognitive Triad theory postulates that depressed individuals engage in negatively-biased thinking that influences the way they view themselves, the world, and their future. Their lived experiences and schemas become filtered by their negative automatic cognitions, which affects the way they attend to and process information in their environment (Beck, 1967). It is thought that the negative schemas and attitudes held by individuals who are currently depressed and/or are susceptible to depression are maintained by activation of the cognitive triad, which can result in myriad depression symptoms, such as fatigue, amotivation, and anhedonia (Leahy & Dowd, 2002).

However, it is also possible that a more direct deficit in positive affectivity itself may also contribute to the emergence of anhedonia. For example, it may not be just a matter of not attending as well to positive stimuli, but a deficit in the actual interpretation of hedonic information may also exist. This possibility is based on a growing literature that suggests that individuals with depression do not always derive the same *hedonic value* from positive stimuli as healthy controls, even when their general attention is focused appropriately.

Previous research investigating anhedonia in depression has shown significantly reduced responsiveness to, and appraisal of, reward values (Gorwood, 2008). For example, a neuroimaging study conducted by Heller et al. (2009) found that depressed individuals demonstrated a reduction in activation in the nucleus accumbens (NAcc), which, along with the fronto-striatal network, is implicated in reward appraisal and motivation, *over time* during a positive affect evoking task compared to controls. These findings suggest that individuals with depression are unable to adequately sustain a response toward positive stimuli; this anomaly in brain activity patterns may represent an actual loss in reward value across time. This may interfere with depressed individuals' ability to sustain positive mood across time in everyday life, making it more probable—given their negative schemas and hypersensitivity to negative stimuli—that a negative mood can take hold and be maintained.

Thus, anhedonia not only encompasses a reduction in the capacity to subjectively experience pleasure from activities that most people find enjoyable (e.g., a good meal or a good book), but also is characterized by an inability to sustain neural activity in regions that are thought to support positive affect over time (Tomarken and Keener,

1998). In another neuroimaging study, Keller et al. (2013) assessed trait anhedonia via a questionnaire in healthy adults without prior history of Axis I diagnoses and had them rate the pleasantness of various pieces of music. Individuals who initially endorsed higher trait anhedonia levels rated the music pieces as less pleasant; greater trait anhedonia was also associated with reduced activity in various brain regions that are integral to reward processing, such as the NAcc.

Together, these findings suggest that anhedonia in depressed patients involves neural networks that are involved in: a) negative schemas, b) general reward processing, and c) the ability to sustain a neural response over time following positive stimulation, with disruptions in the underlying fronto-striatal networks resulting in difficulties in responding appropriately to positive stimuli.

Anhedonia also has a very social component, in that individuals who are anhedonic may (or may not) show deficits in the number and quality of their positive relationships. Indeed, there is a subtype of anhedonia termed “social anhedonia” that is characterized by a reduced ability to derive pleasure from social situations. However, given that the broader construct of anhedonia, which includes both social and non-social aspects, has not yet been investigated using repetitive transcranial magnetic stimulation (rTMS), one aim of the current work was to determine how anhedonia proper (encompassing both social and non-social aspects of the construct), may relate to a particular aspect of social anhedonia (i.e., response to smiling faces) that we chose to measure using a facial emotion recognition task.

The human face conveys detailed information about the emotional state of other people, and we interpret others’ emotions in part by analyzing facial displays at both

conscious and unconscious levels. Here, our interest was in how depressed people read the happy facial displays of other people. We conceptualize this activity—subjective interpretation of pleasure on the face of another human being—as one narrow proxy for how people may take in and experience joy themselves. Indeed, researchers have already identified an association between the ability to accurately read happy facial expressions and the experience of anhedonia (broadly construed). For example, the presence of anhedonia has been linked to a *slowed* ability to accurately identify positive facial emotions (Vrijen et al., 2016), which may, in turn, relate to a reduced subjective experience of positive emotion in response to the joy of another human being (generally a rewarding event under normal circumstances).

Furthermore, there is a probable relationship between the ability to experience pleasure as a result of seeing a smiling face and the ability to discriminate among positive faces eliciting varying intensities. In fact, although it may be easy to read a frank smile and derive pleasure from it, it may be more difficult for individuals to read and subjectively experience pleasure in response to a slight smile. Here, it is hypothesized that individuals who are genetically or biologically prone to accurately perceive subtle positive emotion may be less vulnerable to anhedonic symptoms, whereas individuals who are poor at this particular ability may be more likely to experience anhedonia.

Efforts to combat the deleterious effects of depression have primarily focused on how to decrease sadness. Furthermore, the use of antidepressant medications, including SSRIs, has resulted in inconsistent findings, and these medications often fail to address anhedonic symptoms and amotivation in patients with MDD (Nutt et al.,

2007; Shelton & Tomarken, 2001). Behavioral Activation (BA), a psychotherapeutic approach that aims to increase engagement in adaptive activities and to solve problems that limit an individual's access to rewards, has been commonly used to treat depression symptoms overall; yet, the research in the use of BA as a therapeutic method to ameliorate symptoms of anhedonia is inconsistent (Strauss, 2013). Given inconsistencies in the literature regarding the efficacy of currently available treatments for depression, there is an increasing demand to identify and test the efficacy of alternative treatment modalities that may prove to be more efficient in addressing specific symptoms such as anhedonia. rTMS represents a novel treatment that could potentially address these concerns.

1.1 Depression and Anhedonia

A diagnosis of MDD, as stated in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), requires the presence of either a depressed mood or a loss of interest/pleasure that contributes to a change from prior functioning (DSM-5, 2013). Previous studies have estimated that more than two-thirds of all individuals diagnosed with MDD experience clinically significant levels of anhedonia (Buchwald & Rudick-Davis, 1993). The occurrence and manifestation of anhedonia in depressed individuals can be affected by a variety of factors such as race, ethnicity, and socioeconomic status (SES); Liu and Tronick (2014) found a greater likelihood for Hispanic, African-American, and Asian/Pacific Islander women to endorse symptoms of postpartum anhedonia than White women. However, after accounting for SES, postpartum anhedonia was more likely to be reported by Asian/Pacific Islanders than members of any other racial group (Liu & Tronick, 2014).

The cognitive model of depression proposed by Aaron Beck (1979) is grounded in the concept of the “cognitive triad,” in which the depressed individual tends to have negative views of him/herself, to interpret ongoing experiences in a negative way, and to have negative views about the future. Consistent with these theories, depressed individuals tend to exhibit a predilection to attend to, remember, and process negative stimuli in their environment more efficiently than positive stimuli that contradict their schemas (Blaney, 1986; Clark & Teasdale, 1982; Kuiper & Derry, 1982).In Disner et al.’s (2011) cognitive model of depression (Figure 1), depressed self-referential schemas in a vulnerable individual trigger biased attention, biased processing, and biased memory of internal and external stimuli. The depressed individual filters perceived information in a manner that over-represents the schema-consistent elements of the experience. This biased focus toward schema-related elements in the environment, in turn, maintains depressive symptoms. The presence of depressive symptoms continues to strengthen and validate the vulnerable individual’s negative schema, thus reinforcing the cycle of biased processing of perceived experiences.

Importantly, the depressive cognitions and negatively-biased worldviews central to Beck’s cognitive model of depression are often accompanied by symptoms of anhedonia and thoughts of hopelessness (Beck et al., 2003). Though models have varied across time, the most current models suggest that a complex neural circuit mediates the processing of hedonic information and emotional stimuli. Indeed, reduced activity in many areas of the prefrontal cortex have been implicated in anhedonia, with abnormal activity observed in regions such as the dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VMPFC), and orbitofrontal cortex (OFC) (Der-

Avakian & Markou, 2011). The reward-processing neural circuitry recruits inputs and outputs from both cortical (i.e., VMPFC, DLFC) and subcortical structures (i.e., anterior cingulate cortex (ACC), NAcc), and disruptions and abnormal activity in these neural circuits can result in anhedonia-like symptoms and hedonic deficits (Der-Avakian & Markou, 2011).

Addressing negative biases and cognitions alone does not generally bring positive emotions online. Increasing research suggests that treatment of depression should involve not only dismantling negative schemas and the cognitive triad, but also directly intervening to modulate the positive affect system in the brain. These different systems can be activated separately, and currently available treatments may be more or less efficacious for one or the other aspect of emotionality. For example, previous research has already identified associations among anhedonia, trait emotionality (i.e., positive and negative mood), and social functioning. Blanchard et al. (1998) used multiple questionnaires to assess anhedonia, positive and negative affectivity, and overall social functioning in individuals with schizophrenia. They found a negative correlation between anhedonia and trait positive affect. Additionally, individuals with greater anhedonia reported greater negative affect and poorer social functioning than controls (Blanchard et al., 1998). Given that anhedonia is considered a trans-diagnostic symptom, it offers a meaningful avenue for research in MDD samples as well.

Another study used a mediation analysis to demonstrate a link between social anhedonia and social functioning by assessing activity in brain regions associated with Theory of Mind (ToM), or the ability to explain and predict other people's mental states. Individuals who experienced greater social anhedonia exhibited hypoactivation in the

medial prefrontal cortex and impaired activity in the ToM neural circuitry. These anomalies likely contributed to a hampered ability to understand and reason about the mental states of others in everyday life (Dodell-Feder et al., 2014). These studies highlight the negative effects of anhedonia, which not only contribute to a decreased response to pleasurable rewards, but also negatively impact people's ability to function in social settings.

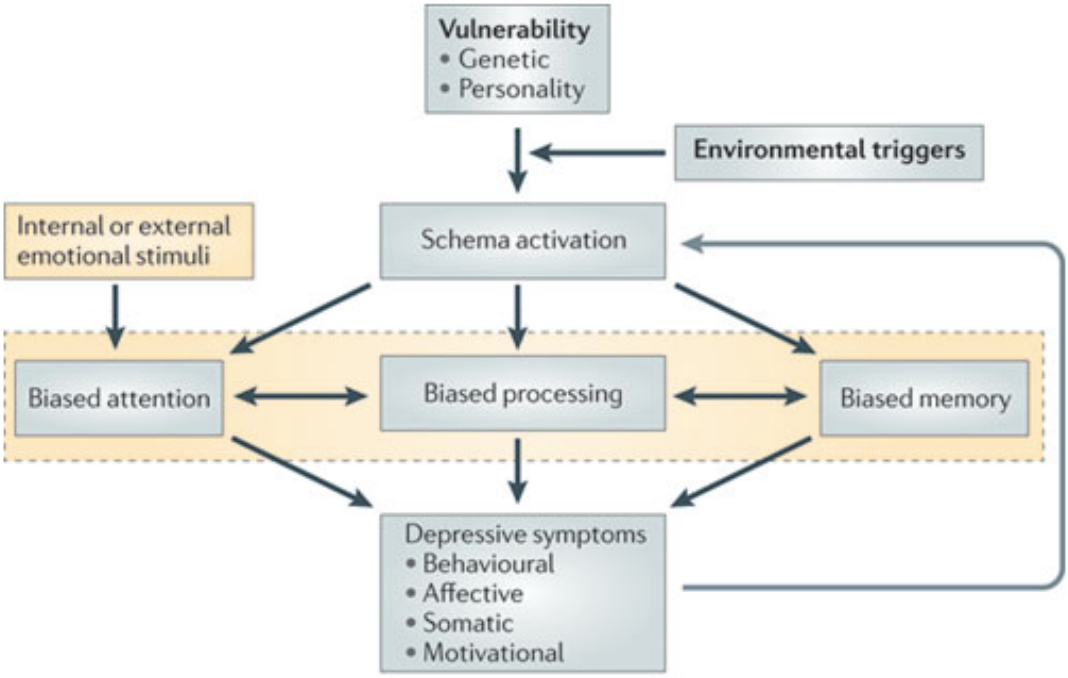

Figure 1.1. Information processing in the cognitive model of depression proposed by Disner et al. (2011)

1.2 Facial Emotion Recognition

An important bottom-up process that plays a crucial role in vicarious emotional processing is the ability to detect emotional valence in facial expressions. Facial expressions help convey emotionally salient information about an individual's internal state; they also help us communicate emotions to others, which facilitates appropriate social behavior (Knutson, 1996). Although the interpretations of different facial

expressions may vary across cultural groups, the detection of emotions from facial expressions is a universal skill observed among members of both literate and illiterate cultures (Ekman & Friesen, 1971; Ekman et al., 1987).

The ability to recognize, decode, and discriminate among emotional facial expressions develops with age. Whereas correct identification of happiness, sadness, and anger from facial expressions develops early in childhood, the ability to identify facial expressions of fear, disgust, and surprise continues to develop over the course of late childhood and adolescence (Lawrence, Campbell, & Skuse, 2015). The ability to accurately recognize facial expressions predicts likeability among peers and social competence through later childhood and adolescence (Izard et al., 2001; Miller et al., 2005; Mostow, Izard, Fine, & Trentacosta, 2002). Individuals interpret human faces to avoid conflict, predict the attitudes of other people, and to monitor and appropriately respond to social interactions with others (Hess, Kappas, & Scherer, 1988; Salovey & Mayer, 1990). This process may be disrupted in the context of depression. In particular, depressed individuals, with their negatively biased internal schema, who display a predisposition toward heightened processing of negative stimuli and reduced processing of positive stimuli in their environment, may also exhibit a response bias when attending to faces eliciting negative emotions compared to faces that display positive emotions.

Indeed, individuals with MDD show difficulties in the efficient and accurate recognition of both positive and negative emotions in faces. Specifically, Surguladze et al. (2004) showed that—compared with healthy volunteers—depressed patients demonstrated a bias away from the accurate identification of happy and positive

expressions. Similarly, Demenescu et al. (2010) found, in a meta-analytic study, that patients with MDD exhibited significant biases in overall emotional facial identification. Another study found that depressed patients, compared to healthy controls, were slower and more inaccurate at recognizing neutral faces; they also reported a higher incidence of sad responses to neutral faces. These findings further highlight the tendency among depressed individuals to misinterpret neutral emotions as negative (Leppanen et al., 2004; Gur et al., 1992). Further, Joorman and Gotlib (2006) found that individuals with MDD required *significantly greater* intensity of positive emotion to accurately identify happy faces compared to faces that displayed emotions such as fear and sadness, indicating reduced reward responsiveness. Taken together, the evidence suggests that individuals with MDD struggle to identify emotions from facial stimuli accurately.

Differences in the speeded identification of emotion from facial stimuli have also been identified between patients with MDD and healthy controls. In one recent prospective study, reduced speed in identifying happy faces relative to sad faces prospectively predicted the onset of depressive disorder and symptoms of anhedonia in adolescence (Vrijen et al., 2016). This finding adds credence to the hypothesis that individuals are faster at identifying stimuli that are congruent with their emotional state in the moment; therefore, individuals who are at risk for MDD, who display symptoms of anhedonia, or who are currently diagnosed with MDD all are likely to react faster to negative stimuli (sad faces) than to positive stimuli (happy faces). However, current research looking at the speeded responses to facial stimuli is scarce, and what remains to be more fully elucidated is whether response speed varies across different intensities of positive stimuli.

Given the importance of speeded processing of affective information in the ability to respond appropriately to environmental and social demands, depressed individuals who exhibit a bias in speeded processing of positive stimuli of various intensities may also produce more errors in emotion recognition, which could negatively impact their ability to function normally in social contexts in everyday life (Gross, 1998; Gollan et al., 2008). Research focused on the speeded identification of positive facial expression in patients with MDD is sparse. Further research is warranted to help us better understand mechanisms that underlie identification of positive facial emotion in individuals with MDD. This understanding could also help improve emerging treatments.

1.3 Repetitive Transcranial Magnetic Stimulation

Relapse in treated individuals with MDD, even following acute interventions such as electroconvulsive therapy (ECT), is common (Coppen et al., 1981; Grunhaus, Dolberg, & Lustig, 1995). To address this problem, clinicians and researchers have begun to explore new pharmacologic and nonpharmacologic approaches, including rTMS, to ameliorating depression (Mantovani et al., 2012). Several meta-analyses of placebo-controlled trials have indicated that rTMS is effective in providing acute, clinically significant antidepressant effects; further, additional studies have investigated the safety and efficacy of TMS as an acute antidepressant form of treatment (Mantovani et al., 2012; Moreines, McClintock & Holtzheimer, 2010).

Studies have also investigated neural mechanisms of depression and the antidepressant effects of rTMS. For example, research has strongly implicated the DLPFC, particularly the left DLPFC, in the pathophysiology of depression (Davidson, 2004; Taylor & Liberzon, 2007). Specifically, the lateral prefrontal cortex has been

implicated in eudemonia (i.e. well-being; Heller et al., 2013) and anhedonia (Light et al., 2011) during attempts to up-regulate (DLPFC) or down-regulate (ventrolateral prefrontal cortex (VLPFC)) positive affect. It is thought that hypo-activation of the DLPFC in particular relates to the reduced experience of positive emotions (Davidson, 2004; Heller et al. 2013), whereas increased VLPFC activity relates to the suppression of positive emotion often seen in depressed individuals (Light et al., 2011).

Prior research also indicates that those individuals with MDD who respond to antidepressant treatment showed increases in activity in DLPFC pre- to post-treatment (Taylor & Liberzon, 2007; Brody et al., 2001). Thus, because depression is associated with a decrease in left DLPFC activity, studies have successfully used high-frequency rTMS to induce greater cerebral blood flow in this region to induce a clinical antidepressant effect (Nahas et al., 2001; Gross et al., 2007; Rumi et al., 2005). Further, Avery et al. (2006) found that the clinical effects of rTMS to the left DLPFC increased with the duration of the treatment, highlighting a linear effect between the number of rTMS sessions and depression score reduction. Importantly, the efficacy of rTMS to the left DLPFC may also lie in its indirect effects on other brain regions; for example, it may initiate or enhance negative connectivity between DLPFC and the a) subgenual cingulate (Taylor et al., 2018) and b) frontopolar prefrontal cortex (Downar & Daskalakis, 2013). Regardless of the pathways along which it operates, we hypothesize that rTMS targeting the left DLPFC is a promising region approach to anhedonia reduction in depressed individuals.

Further, advancement in individualizing rTMS treatment to particular patients may spring from specifically investigating the effectiveness of rTMS on one or more specific

aspects of anhedonia. Given that the two key symptoms present in depression are anhedonia and/or sad mood, determining the effectiveness of rTMS on anhedonia in particular (versus global depression symptomatology), and a very specific aspect of anhedonia at that—positive emotion recognition in human facial stimuli—may help identify rTMS treatment protocols that are better or more poorly suited to target this specific symptom. Indeed, the efficacy of rTMS varies depending on site of stimulation, and not all patients who receive the treatment respond. Therefore, by using a novel behavioral task to look for distinct relationships between performance on the task and rTMS treatment response at the symptom level (rather than looking for a relationship simply between self-reported anhedonia and response to rTMS treatment), we may provide a means by which to ascertain whether this aspect of the disorder changes pre- to post- rTMS.

In the current study, individuals with MDD underwent a series of either active or sham rTMS sessions targeting the left DLPFC and completed a novel behavioral task that required each participant to identify various intensities of positive emotion in a series of human faces, pre- to post-treatment. Previous studies have identified a significant correlation between increased accuracy in recognition of happy faces and clinical improvement after six-weeks of antidepressant medication treatment (Tranter et al., 2009). Although multiple studies have yielded evidence of improvements in the accurate identification of positive emotions in facial stimuli post-treatment, few studies have examined associations between the accurate identification of varying intensities of positive emotion and the effects of treatment on how quickly people accurately detect happiness in human faces. Considering that depressed individuals demonstrate a

predilection toward identifying negatively-valenced faces quickly and are typically less accurate and slower in identifying faces that express positive emotion, successful treatment of both of these positive and negative affective symptoms of depression may help shift these individuals' emotional predispositions and result in better, more accurate interpretations of positive emotion in human faces post-treatment (Leppanen et al., 2004; Gur et al., 1992). Additionally, as previous research has suggested that individuals with MDD are typically faster at detecting negative faces than positive faces, treatment with rTMS may result in faster response speeds to positive emotion in faces if rTMS is able to influence neural mechanisms associated with positive affectivity (Suslow & Junghanns, 2001). Given the utility of rTMS as an innovative and low-risk technique to alleviate symptoms of depression, the proposed study aims to identify beneficial effects of rTMS on the left DLPFC on the speed and accuracy with which depressed people identify positive emotion in human faces, a skill that is often impaired in anhedonic individuals and thus may serve as one behavioral marker of the symptom.

1.4 Specific Aims and Hypotheses

Despite research on the utility of rTMS as a therapeutic technique to decrease general symptoms of depression, questions remain regarding its long-term efficacy, as well as its effects on the perceptual biases of individuals with MDD. The current study serves to address this issue by observing whether multiple sessions of rTMS will have an effect on an individual's performance on a task that requires accurate and speeded identification of positive emotion. As rTMS has been previously shown to provide antidepressant effects for individuals with MDD (Mantovani et al., 2012), and given that depressed individuals tend to exhibit a negative processing bias in interpreting neutral

faces as sad and are typically slower, less accurate, and require higher intensity happy faces to accurately categorize human faces as happy, we hypothesized that rTMS to the left DLPFC would impact the speed and accuracy of identification of positive emotions in human faces. This hypothesis is based on prior literature and the idea that individuals who are more anhedonic have two problems that may make it difficult for them to attend to and interpret positive information in their environment: 1) a negative processing bias, and 2) an intensity bias, such that it takes exposure to more intense positive stimuli for them to register and interpret a conveyed positive emotion. We were most interested the intensity bias in our investigation of rTMS to the left DLPFC.

The current study focused on a sample of adults diagnosed with MDD and used a novel behavioral measure of positive emotional identification (i.e. the "Happy Faces" task) to investigate the effectiveness of rTMS on this social aspect of anhedonia. The study could have direct impacts on the fields of psychiatry, clinical neuropsychology, and positive psychology; further, this study will contribute to the growing body of work on the role of emotional processing in depression.

1.4.1 ***Specific Aim 1***

Determine the effect of rTMS to the left dorsolateral prefrontal cortex on the <u>speeded</u> identification of various intensities of happy emotional faces.

Hypothesis 1: Individuals in the active rTMS group would be faster in the identification of faces, specifically to low-intensity faces on the Happy Faces Task, by post-treatment than individuals who underwent the sham treatment.

1.4.2 *Specific Aim 2*

Determine the effect of rTMS to the left dorsolateral prefrontal cortex on the accurate identification of various intensities of happy emotional faces.

Hypothesis 1: Individuals who underwent active treatment will show statistically significant improvement in their performance at post-treatment relative to pre-treatment (compared to individuals in the sham group). In particular, we expected patients to make gains in accurately identifying low intensity happy faces (relative to high intensity happy faces, where we anticipated no gains pre-post treatment).

2 METHODS

2.1 Procedures

2.1.1 Participants

Twenty-six adults (M_{age} = 45.21, *SD* = 11.21, 63% women) were recruited for the study. Of these adults, 97% identified themselves as non-Hispanic white; one participant self-identified as Asian. To be enrolled, participants had to be between the ages of 22 and 65 years, and to meet DSM-IV diagnostic criteria for MDD, as assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). In addition, they had to obtain a score of 18 or higher on the Montgomery-Asberg Depression Rating Scale (MADRS), a 9-item questionnaire that includes questions about sadness, inner tension, reduced sleep, an inability to feel, pessimistic and suicidal thoughts, and concentration difficulties. Finally, participants were required to have experienced failure of at least one antidepressant treatment at adequate dose/duration or have failed to achieve adequate dose/duration due to intolerable side effects, and to have been on a current stable dose of medication for at least four weeks prior to rTMS

therapy. Medications had to be maintained on a stable dosage for one month prior to and during the double-blinded phase. Potential participants were excluded if they reported presence of bipolar disorder (I/II), obsessive-compulsive disorder, post-traumatic stress disorder, any psychosis, or serious suicidal ideation/behavior; previous repetitive Transcranial Magnetic Stimulation (rTMS) treatment; previous ECT, and contra-indications to rTMS or MRI. Table 1 shows the means and standard deviations for age, number of medications used, and MADRS prescreen scores for each group.

Table 1

Demographics and Participant Characteristics

	Active rTMS Group	Sham rTMS Group
Gender		
n	12	14
% Female	75	57.1
% Male	25	42.9
Age	45.25	44.78
SD	10.88	10.71
Number of Medications	2.75	2.28
SD	1.48	1.33
MADRS Scores	24.5	21.64
SD	5.38	3.67
Range	18-33	18-25
SHAPS Scores**	31.83	35.21
SD	3.79	4.92
Range	28-38	28-43

Note: MADRS = Montgomery-Asberg Depression Rating Scale;
SHAPS = Snaith Hamilton Pleasure Scale
**Based on Franken et al. (2007), a score equal to or greater than 29 indicates clinically significant anhedonia using the 2-standard deviation rule

2.1.2 Measures

The Montgomery-Asberg Depression Rating Scale (MADRS), a 9-item questionnaire that includes questions about sadness, inner tension, reduced sleep, an inability to feel, pessimistic and suicidal thoughts, and concentration difficulties. The score range is 0-27 points, and a score at baseline on the MADRS of 18 or greater was

required for study entry. The MADRS has been found to have high internal consistency (Cronbach's alpha = 0.85), construct validity, and concurrent validity relative to other depression screeners such as the Beck Depression Inventory – II (BDI-II) and the Hamilton Depression Scale (Kjærgaard et al., 2014; Davidson et al., 1986).

The Snaith-Hamilton Pleasure Scale (SHAPS) is a 14-item self-report scale that assesses the respondent's ability to feel pleasure in response to stimuli that typically elicit positive emotions. The SHAPS covers four domains: interests/pastimes, social interaction, sensory experience, and food/drink. The inter-item reliability for this test is 0.857 and higher scores are indicative of greater anhedonia (Snaith et al., 1995; Nakonezny et al., 2015). Published normative data indicate that healthy controls who are not anhedonic exhibit a mean score of 20.4 (Franken et al., 2007), whereas the sample of confirmed depressed patients had a mean score of 34.4 (Franken et al., 2007). Using a cut-off of two standard deviations above the mean of healthy controls to indicate clinically significant anhedonia, these data suggest that a score of 29 or greater indicates clinically significant anhedonia.

The Happy Faces Task is designed to ascertain levels of anhedonia (Mirabito et al., 2019). During the task, patients are asked to look at human faces (balanced by gender) evincing varying degrees of positive emotion. The task consists of 20 low-intensity trials and 33 high-intensity trials presented in random order, with 22 neutral trials interspersed. When the task was developed, researchers selected stimulus faces from the well-validated Cohn-Kanade dataset, which includes hundreds of images of human faces expressing neutral and varying degrees of spontaneous positive emotion (Cohn, Ziochower, Lien & Ambadar, 1999; Ambadar, Cohn & Reed, 2009). They then

identified faces that elicited “low-intensity” positive emotions (i.e., subtle smiles) or “high-intensity” positive emotions (i.e., frank smiles) (Mirabito et al., 2019). Specifically, faces that showed only zygomaticus activity (facial muscles that control mouth-based actions of smiling) were identified as low intensity, and faces that showed both orbicularis (facial muscles that control the eyelid region) and zygomaticus activity were identified as high intensity. Whereas some task paradigms use facial stimuli that span a broad range of discrete emotions, the Happy Faces Task focuses simply on the presence or absence of positive emotion of any type.

During the Happy Faces Task, participants were instructed to indicate by button press whether any positive emotion was present on the face they were viewing in “yes” or “no” format. Importantly, the face remained on the screen until the participant made a response and their reaction time was recorded. Task duration was approximately 10 minutes for each participant. In a recently published study that used the Happy Faces Task during fMRI scanning, findings yielded evidence that the Happy Faces Task is a valid measure of consummatory anhedonia and may have clinical utility in anhedonic populations (Mirabito et al., 2019).

2.1.3 Procedure

The protocol was a sham-controlled, randomized, double-blind study. A research assistant conducted a psychiatric assessment (the MADRS, a MINI-Structured Clinical Interview for DSM-IV disorders, and a psychiatric interview) with each potential participant before study enrollment. Patients who met study inclusion criteria then provided informed consent to take part in the full study. They then underwent an assessment process, which included the completion of the SHAPS and the pre-

treatment Happy Faces Task. Participants also underwent MRI scanning to identify target locations for rTMS treatment. All patients eventually received rTMS treatment, but at study entry, they were randomly assigned to a sham treatment or active treatment group.

Following screening and assessment, subjects entered phase one of the study. In this blinded phase, subjects had 20 sessions of rTMS therapy or sham treatment, delivered on five days per week for four weeks by a licensed psychiatrist. rTMS treatments were delivered at 10 Hz frequency at 120% of motor threshold, with 3000 pulses/session to the left DLPFC at a location determined by neuronavigation from each participant's initial Magnetic Resonance Imaging (MRI) session. TMS was delivered with the NeuroStar XPLOR system in research mode. Whereas the coil in the active rTMS group was active, the sham coil, which was identical in shape and weight to the active coil, did not deliver any magnetic energy. A speaker on the coil gantry delivered a 10Hz pulsed sound that mimicked acoustic characteristics of the active coil. At the end of phase one, five taper TMS sessions over two weeks were performed for those in the active arm and five sham taper sessions were delivered over two weeks to sham participants (phase two). Participants from both groups completed the Happy Faces Task at the end of their respective treatment. Subjects who received sham stimulation had the option of receiving active TMS in the second, open-label phase of the study.

2.1.4 Analytic Plan

In order to determine the effect of rTMS to the left DLPFC on the speeded and accurate identification of various intensities of happy emotional faces over time, we conducted two repeated-measures ANCOVAs for each dependent variable. A repeated-

measures ANCOVA was used given our interest in examining group differences in performance as a function of time (pre-treatment and post-treatment) and intensity of the happy face (i.e., high, low, neutral). In our analyses, accuracy and reaction speed on the Happy Faces Task served as dependent variables, while group membership (i.e., active vs. sham treatment) was included as the independent variable.

ANCOVA, rather than ANOVA, was a preferable approach because we included a number of covariates in our analysis. First, age and sex were included, given evidence from epidemiological studies that these factors such as age and sex can influence the prevalence of MDD, such that depressive symptoms are more common in females in young adulthood and less common in patients aged 65 years (Gallo et al., 1994; Bebbington et al., 1998; Stordal et al., 2001). Second, we included indices of depression severity (i.e., number of medication, MADRS score) as covariates in the analysis to control for the possibility that effects of treatment on task performance might be attributable to baseline depression severity (Nakonezny et al, 2010). Koenig et al. (1998) found that the number of medications taken, akin to illness severity, was significantly related to depression severity in an elderly population. Finally, in order to control for the possibility that effects of treatment on task performance might be attributable to baseline subjective experience of anhedonia (which may not be an accurate indicators of their behaviorally observed/measured anhedonia), we included pretest SHAPS scores as an additional covariate.

We also decided to run two separate ANOVAs looking at group effects on both dependent variables (i.e., accuracy and reaction speed) with the exclusion of these covariates. Given the small sample size and low power in the study, we conducted

these analyses in order to see if the exclusion of these variables would have any effect on the statistical output.

In additional exploratory analyses, we also ran two ANCOVAs without including the baseline levels of anhedonia (SHAPS score) as a covariate in order to increase the statistical power of the analysis and to examine whether baseline self-reported SHAPS scores would meaningfully affect performance on the Happy Faces Task.

Prior to conducting the main analyses, we examined the data for potential sources of biases. First, we generated boxplots to identify outliers in the data. We identified three univariate outliers in the dataset; we therefore winsorized the data by replacing outliers with the next highest score that was not an outlier. We then conducted Levene's tests for each of the dependent variables in order to check for assumptions of homogeneity of variances; results were not significant for any variables, indicating that the assumption of homogeneity of variances was met. Finally, we conducted Mauchly's test to assess for the presence of sphericity (the variation within the experimental conditions is roughly equal). Violation of sphericity may create a loss of power and an inaccurate test statistic. Results of the Mauchly tests were not significant, which indicates that data met the assumptions of sphericity.

3 RESULTS

The patients' pre- and post-treatment performance based on group membership on speeded reaction times (ms) and accuracy scores relative to the corresponding facial stimuli (low-intensity, neutral, or high-intensity) are presented in Table 2.

Table 2

Participant Performance on Reaction Speed and Accuracy to Different Intensities of Happy Faces based on Group and Type of Facial Stimuli

	Group			
	Active		Sham	
Measure	Mean	SD	Mean	SD
Rx to low-intensity 1	2083.00	870.22	1661.63	916.78
Rx to low-intensity 2	1646.88	476.92	1354.30	386.47
Acc to low-intensity 1	13.08	3.92	12.07	4.98
Acc to low-intensity 2	13.92	4.08	12.71	4.75
Rx to high-intensity 1	1266.86	563.17	1068.12	385.49
Rx to high-intensity 2	1200.88	346.49	976.60	180.16
Acc to high-intensity 1	31.42	2.07	31.43	2.56
Acc to high-intensity 2	32.17	1.34	32.43	1.02
Rx to neutral 1	1729.68	746.87	1569.67	851.45
Rx to neutral 2	1785.17	468.71	1450.25	591.49
Acc to neutral 1	18.17	2.48	18.50	2.14
Acc to neutral 2	18.17	2.25	17.50	3.32

Note: 1 = pre; 2 = post; Rx = Reaction Time, Acc = Accuracy

3.1 Reaction Speed

As shown in Table 3, results from a repeated-measures one-way ANCOVA, with reaction speed as the dependent variable and number of medications, age, SHAPS scores, MADRS scores, and gender included as covariates, yielded no evidence of statistically significant main effects of treatment group, time, or face type. The interaction between time and group membership was also non-significant.

Results did, however, indicate a significant effect of pre-treatment SHAPS scores on reaction speed ($F(1,20) = 4.76$, $p = .04$, $\eta_p^2 = .19$). A correlation matrix presented in Table 4 shows that pre-treatment SHAPS scores were negatively correlated with reaction times to low intensity faces prior to treatment and neutral faces post-treatment. In other words, contrary to our predictions, participants who endorsed higher levels of anhedonia on the SHAPS responded faster to low intensity and neutral faces.

Table 3

Repeated-Measures ANCOVA with Reaction Speed as the Dependent Variable

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	20610.49	1	.04	.85	.00
Facial Intensity	853393.08	1	2.67	.08	.12
Time * Group	337679.74	1	.58	.46	.03
Tests of Between-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Intercept	5340569.89	1	5.60	.03	.22
Gender	185402.72	1	.19	.66	.01
MADRS	1687844.76	1	1.77	.20	.08
Medications	290780.49	1	.31	.59	.02
SHAPS	450113.63	1	4.76	.04*	.19
Group	49348.42	1	.05	.82	.00
Error	19071053.80	20			

*$p < .05$

Table 4

Correlation Matrix (SHAPS and Rx)

Correlation Matrix		
Measure		**SHAPS Score**
Rx to low intensity 1	Pearson Correlation	-.44*
	Sig. (2-tailed)	.03
Rx to low intensity 2	Pearson Correlation	-.37
	Sig. (2-tailed)	.06
Rx to neutral 1	Pearson Correlation	-.38
	Sig. (2-tailed)	.06
Rx to neutral 2	Pearson Correlation	-.49*
	Sig. (2-tailed)	.01
Rx to high intensity 1	Pearson Correlation	-.30
	Sig. (2-tailed)	.14
Rx to high intensity 2	Pearson Correlation	-.27
	Sig. (2-tailed)	.18

Note: 1 = pre; 2 = post; Rx = Reaction Time
**Correlation is significant at the .05 level (2-tailed)*

Main effects of group membership and time remained non-significant at a significance threshold of $p = .05$ when covariates were excluded (see Table 5).

However, there was a significant main effect of facial intensity ($F(2, 48) = 21.41$, $p < .01$, $\eta_p^2 = .55$). Consistent with what we expected, the participants, regardless of group, reacted the slowest when asked to identify faces that elicited low intensity positive emotions and responded the fastest to high intensity faces. Pairwise comparisons among the three face types can be seen in Table 6. As shown in Figure 3.1, participants' reaction times to neutral faces were marginally faster than their reaction speed to low intensity faces. The interaction between time and group membership was also non-significant.

Table 5

Repeated-Measures ANOVA with Reaction Speed as the Dependent Variable

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	1002638.02	1	1.82	.19	.07
Facial Intensity	9823864.74	2	21.41	<.01*	.55
Time * Group	5526.00	1	.01	.92	.00
Tests of Between-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Intercept	340945398.00	1	314.08	.00	.93
Group	2867968.81	1	2.64	.12	.10
Error	26053151.20	24			

*$p < .05$

Table 6

Pairwise Comparisons Among Facial Intensities (Reaction Speed)

Pairwise Comparisons					
Facial Intensity	Mean (ms)	Comparison	Mean Differences	Standard Error	*p*
Low Intensity	1686.45	High Intensity	558.34	86.77	<.01*
		Neutral	52.76	65.73	.43
Neutral	1633.69	Low Intensity	-52.76	65.73	.43
		High Intensity	505.58	86.38	<.01*
High Intensity	1128.11	Low Intensity	-558.34	86.77	<.01*
		Neutral	-505.58	86.38	<.01*

*$p < .05$

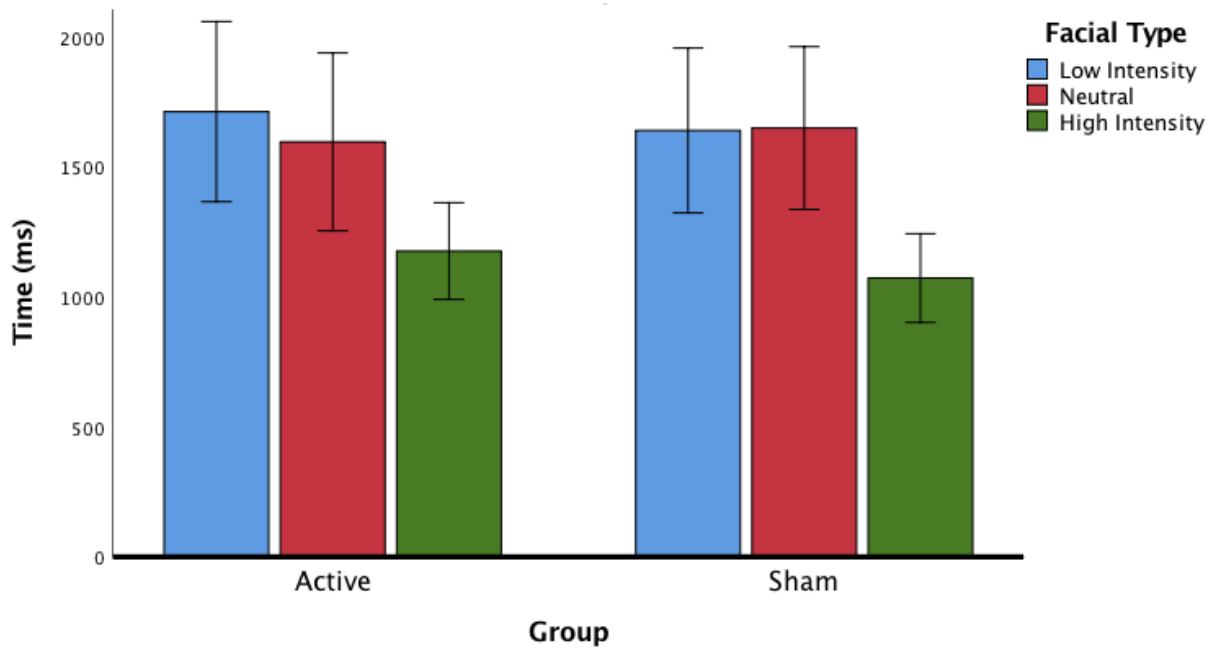

Figure 3.1 Performances on Reaction Times Based on Group Membership and Intensity of Facial Stimuli

3.2 Accuracy

Results of a repeated-measures one-way ANCOVA, with accuracy as the dependent variable and number of medications, age, pre-treatment SHAPS scores, MADRS scores, and gender included as covariates, indicated no statistically significant main effects of treatment group, time, or face type. The interaction between time and group membership was also non-significant. No other significant main effects or interactions were observed (see Table 7).

Table 7

Repeated-Measures ANCOVA with Accuracy as the Dependent Variable

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	.89	1	.22	.64	.01
Facial Intensity	89.12	1	2.77	.07	.12

Time * Group	1.30	1	.33	.58	.02
Tests of Between-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Intercept	672.211	1	59.29	.00	.75
Gender	25.19	1	2.22	.15	.10
MADRS	1.19	1	.11	.75	.01
Medications	17.08	1	1.51	.23	.07
SHAPS	16.49	1	1.45	.24	.07
Group	5.93	1	.52	.48	.03
Error	226.76	20			

Similarly, when a repeated-measures one-way ANOVA was conducted with the exclusion of the covariates, results indicated no statistically significant main effects of group or time; however, there was a significant difference in performance in the accurate identification of different *intensities* of positive faces ($F(1,24) = 309.65$, $p < .05$, $\eta_p^2 = .93$) (See Table 8). All participants, regardless of group membership, were the most accurate when asked to identify high intensity positive faces, and they performed the worst when asked to accurately identify the faces eliciting low intensity positive emotions (Figure 3.2). Table 9 shows pairwise contrasts that indicate significant differences in accuracy across all facial comparisons. No other significant main effects or interactions were observed. The interaction between time and group membership was also non-significant.

Table 8

Repeated-Measures ANOVA with Accuracy as the Dependent Variable

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	5.34	1	1.29	.27	.05
Facial Intensity	9889.00	1	309.65	<.01*	.93
Time * Group	.95	1	.23	.64	.01
Tests of Between-Subjects Effects					

	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Intercept	68150.06	1	5875.95	.00	.99
Group	5.57	1	.48	.50	.02
Error	278.36	24			

*$p < .05$

Table 9

Pairwise Comparisons Among Facial Intensities (Accuracy)

Pairwise Comparisons					
Facial Type	Mean	Comparison	Mean Differences	Standard Error	*p*
Low Intensity	12.95	High Intensity	-18.91	.59	<.01*
		Neutral	-5.14	1.10	<.01*
Neutral	18.08	Low Intensity	5.14	1.10	<.01*
		High Intensity	-13.78	.55	<.01*
High Intensity	31.86	Low Intensity	18.91	.59	<.01*
		Neutral	13.78	.55	<.01*

* $p < .01$

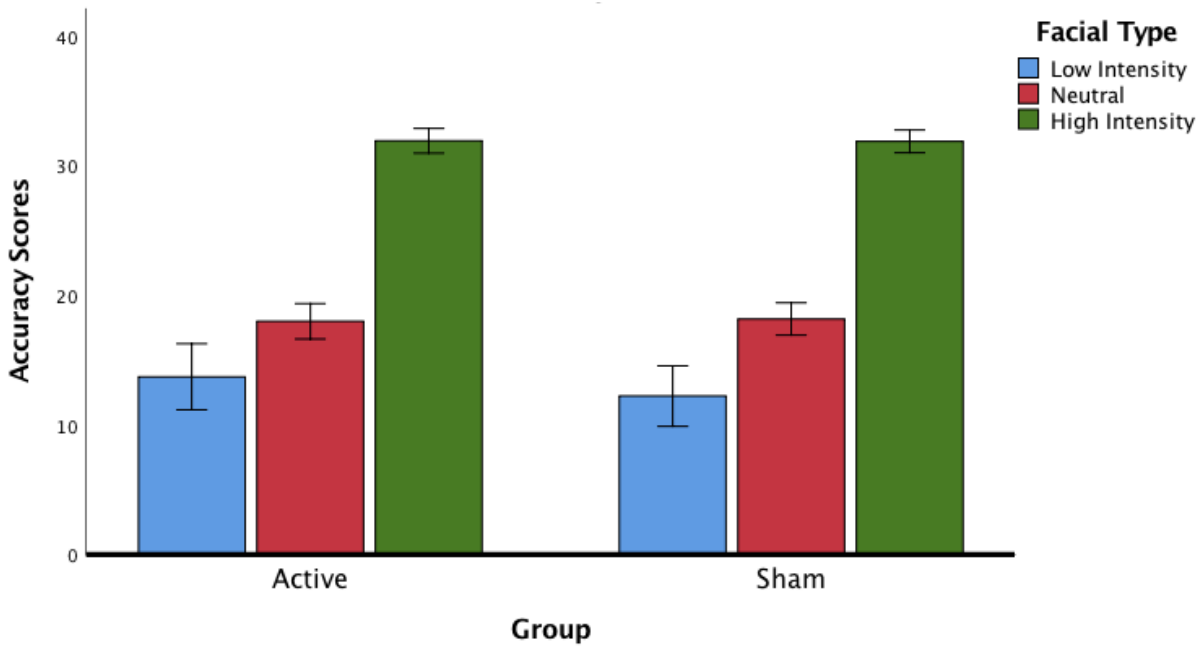

Figure 3.2 Performances on Accuracy Based on Group Membership and Intensity of Facial Stimuli

3.3 Exploratory Analysis

When SHAPS score was removed as a covariate, results of the initial analyses did not change. The repeated-measures ANCOVA conducted with reaction time as the dependent variable indicated no significant main effects of group, time, or facial intensity (Table 10). However, as shown in Table 11, although the repeated-measures ANCOVA with accuracy as the dependent variable indicated no significant main effects of group membership or time, there was a significant main effect of facial intensity on the participant's ability to accurately respond ($F(1,21) = 5.71$, $p = .01$, $\eta_p^2 = .21$). Similarly as before, participants were the most accurate when asked to quickly identify positive emotions in high intensity faces; however, they performed significantly worse when asked to identify positive emotions in more ambiguous faces (e.g., low intensity, neutral faces).Further, there were no significant time by group interactions on either reaction time or accuracy.

Table 10

Repeated-Measures ANCOVA on Reaction Time (Without SHAPS)

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	367970.90	1	.64	.43	.03
Facial Intensity	6251.02	2	.02	.98	.00
Time * Group	165588.43	1	.29	.60	.01
Tests of Between-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	Partial Eta Squared
Intercept	997266.03	1	.89	.36	.04
Gender	1040687.38	1	.93	.35	.04
MADRS	1165552.62	1	1.04	.32	.05
Meds	108670.35	1	.10	.76	.01
Group	888897.95	1	.79	.38	.04
Error	23611167.40	21			

Table 11

Repeated-Measures ANCOVA on Accuracy (Without SHAPS)

Tests of Within-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	η_p^2
Time	5.23	1	1.25	.28	.06
Facial Intensity	182.17	1	5.71	.01*	.21
Time * Group	.07	1	.02	.90	<.01
Tests of Between-Subjects Effects					
	Type III Sum of Squares	*df*	*F*	*p*	Partial Eta Squared
Intercept	1485.29	1	128.23	< .01	.86
Gender	16.84	1	1.45	.24	.07
MADRS	2.34	1	.20	.66	.01
Meds	7.57	1	.65	.43	.03
Group	15.34	1	1.32	.26	.06
Error	243.25	21			

DISCUSSION

This study of the effects of rTMS treatment on how quickly and accurately adults with MDD identified positive emotions in an array of faces extends previous research on the utility of rTMS to combat symptoms of depression, particularly when it is administered to the left DLPFC (Davidson, 2004; Taylor & Liberzon, 2007). Given previous research on the beneficial effects of rTMS for acute depression, we hypothesized that rTMS treatment would have an ameliorating effect on one behaviorally-measured aspects of anhedonia. Specifically, we predicted that depressed participants who underwent 20 active high frequency rTMS sessions would react faster and more accurately in identifying positive emotions, especially low-intensity positive faces, on the Happy Faces Task than would participants who underwent sham treatment.

We did not find any significant treatment effects on the participants' ability to quickly and accurately identify different facial intensities on the Happy Faces Task. Yet, as predicted, we found that individual's speed and accuracy varied as a function of stimulus face emotional intensity. We had anticipated that depressed individuals would more accurately identify faces that elicited low intensity positive emotions than faces showing high intensity positive emotions. Results from the analyses were consistent with this idea, and participants were significantly better at identifying faces that exhibited evident positive emotions than more subtle faces that displayed more ambiguous expressions (neutral and low intensity faces), suggesting that depressed individuals may demonstrate difficulties in quickly deciphering between neutral faces and faces that exhibit low levels of positive emotions.

Interestingly, we found a significant effect of SHAPS score on participants' reaction speed to the different facial stimuli, such that individuals who endorsed greater levels of anhedonia were faster in identifying low intensity faces and neutral faces. This observation deviated from our hypotheses, in which we assumed that more anhedonic individuals would be slower in processing happiness in faces, especially faces eliciting low intensity positive emotions. Subjective factors, such as alertness, level of attention and focus, and impulsivity may have played a role in these findings. Although depression-related anhedonia has been associated with reduced levels of arousal, research focusing on attentional processes in individuals with anhedonia is sparse (Amr & Volpe, 2013). However, given the small sample size and resulting low power of the study, caution is warranted in interpreting this finding unless it is replicated. Future studies focused on anhedonia and facial expression identification would benefit from

recruiting larger samples and from including measures to assess subjective levels of attention/alertness and impulsivity.

Overall, these findings indicate that although rTMS to the left DLPFC has been shown to provide moderate general antidepressant effects for individuals with depression, it may not induce changes in the behaviorally measured aspect of social anhedonia presented here (i.e., identification of positive emotion in others' faces). Given that all patients were also taking psychoactive medications at the time of the study (on a stable dose), it is possible that these patients may not have demonstrated a measurable change in performance with active rTMS because symptoms were dampened or relieved by concurrent psychoactive medication usage. Future studies should better rule out this possibility by excluding participants that are medicated at the time of the study or comparing medicated and unmedicated individuals.

Current neuroimaging models of depression suggest that disruptions in the interactions among emotion-regulating regions such as the DLPFC, VLPFC, dorsomedial prefrontal cortex (DMPFC), VMPFC, and the dorsal and ventral ACC contribute to the onset of depressive symptoms (Seminowicz et al., 2004; Greicius et al., 2007; Price & Drevets, 2012; Johnstone et al., 2007; Davey et al., 2012). Further, researchers propose that different clinical subtypes and depression profiles based on symptomatology may depend on underlying patterns of network disruption (Downar et al., 2014). Multiple studies have postulated that dopamine (DA) pathway impairment—with circuitry coursing through the ACC, amygdala, and the prefrontal cortex—contributes to the prevalence of anhedonia (Martin-Soelch, 2009). In the "endophenotype concept" model of MDD (Figure 4.1), Gorwood (2008) suggests that

anhedonia is an intermediate endophenotype, defined as a heritable mechanism that bridges the gap between clinical phenotypes and genetics, that results from a deficit in reward processing, which can be influenced by either a genetic predisposition or the presence of environmental risk factors (Gottesman, Hon, & Gould, 2003).

Other evidence suggests that hedonic processing is not a unitary construct but rather consists of both anticipatory (motivation to pursue an impending reward) and consummatory (in-the-moment aspects of pleasure) phases; reduced activations and disruptions in brain areas that process either consummatory and/or anticipatory aspects of reward processing (such as prefrontal subregions, thalamus, insula, and the ventral striatum) can result in an anhedonic presentation (Sherdell et al., 2012; Höflich et al., 2019). Nestler and Carlezon (2006) suggested that the mesolimbic dopamine system, which is dependent on dopaminergic connections between subcortical areas of the brain such as the NAcc and ventral tegmental area (VTA) of the midbrain, contribute to the interpretation of reward and hedonic processing; disruptions of this system can also result in anhedonia-like symptoms. The mesolimbic dopaminergic system also includes projections from the VTA to the medial PFC, and a reduction or interruption of dopamine release along this pathway can also result in amotivation and an anhedonic profile (Drevets, Price & Furey, 2008).

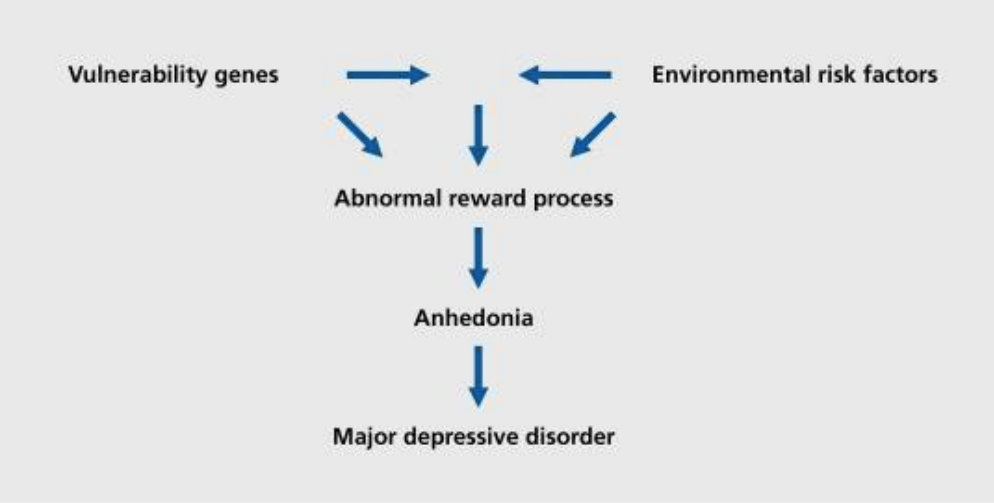

Figure 4.1. The role of anhedonia as an endophenotype between risk factors and depression as proposed by Gorwood et al. (2008)

Downar et al. (2014) posited that different treatment modalities, whether invasive or noninvasive, could be used to target specific brain regions that are involved within these neural systems in order to intervene more efficaciously. Invasive techniques such as high-frequency deep brain stimulation (DBS) of subcortical brain regions, such as the subgenual cingulate gyrus and the NAcc, have been incorporated as an effective technique for reducing depression-like symptoms in treatment-resistant depression (Mayberg et al., 2005; Delaloye & Holtzheimer, 2014). With respect to noninvasive techniques, current studies primarily use rTMS to reduce depressive symptoms. However, given the current results, questions remain open regarding the efficacy of rTMS treatment targeting the left DLPFC for adequately addressing the social aspect of anhedonia measured in this study.

While the treatment of depression with active rTMS has consistently centered on the DLPFC, emerging evidence suggests that other cortical brain regions may play a central role in depression. For example, a neuroimaging study looking at the effects of

rTMS found that the VMPFC, an area that is often linked with reward learning and interpretation of rewards, acts as a “bottleneck” region in depressed patients with anhedonia, who demonstrate poorer connectivity between areas of the mesolimbic dopaminergic system (i.e. VTA and left caudate nucleus). This observation suggests that VMPFC may be a potential future target for effective rTMS treatment of hedonic processing (Downar et al., 2014). Another study found that abnormal VMPFC and striatal activity was present in anhedonic populations when they responded to positive stimuli; anhedonic participants who found it difficult to respond happily to positive stimuli displayed a greater VMPFC response, which is the reverse of the pattern often observed in healthy adults (Keedwell et al., 2005). The effects on anhedonic symptoms of rTMS to the VMPFC region might thus be worthwhile to examine.

Another brain region in which to explore the utility of rTMS is the VLPFC, a cortical area that has been shown to exhibit abnormal patterns of hyperactivity in depressed individuals during positive affect inhibition. In one study, individuals who were respondent to antidepressant medication and showed the greatest reduction in anhedonia after 8 weeks of treatment exhibited lower levels of VLPFC activity when asked to suppress positive affect (Light et al., 2011). Other studies found that depressed patients exhibited greater activity in the VLPFC while processing positive stimuli, which may result in the experience of excessive negative affect and an overall reduction to experience pleasure and positive affect (Light et al., 2001; Keedwell et al., 2005; Kumari et al., 2003). Given the role of VLPFC in hedonic processing and the experience of positive affect, rTMS treatment targeting the suppression of activity in the VLPFC in depressed individuals may be a potential alternative to pursue. Moreover,

researchers could compare the effects of rTMS to the DLPFC and VMPFC on both self-reported and behaviorally measured anhedonia.

An important limitation of this study is that the sample sizes in both groups were very small, which may have obscured significant relationships. It will be helpful for future researchers to replicate this study using a larger sample, which will increase the study's power and increase the likelihood of detecting true relationships. Another limitation of this study is the lack of racial diversity in the sample; there was only one Asian participant in the sample, and the rest were Caucasian. Studies have shown that the diagnosis and treatment of depression in both adult populations can be influenced by racial and ethnic differences; this relationship is mediated by the presence of life factors such as socioeconomic status, social support, and exposure to poverty that vary across ethnic and racial groups (U.S. DHHS, 2001; Plant & Sachs-Ericsson, 2004; Holahan et al., 1999). Thus, the presentation and severity of depression and anhedonia may manifest differently as a function of racial and ethnic disparities (Dunlop et al., 2003; Akincigil et al., 2012). Inclusion of participants from a variety racial/ethnic backgrounds would be useful for evaluating the generalizability of rTMS treatment effects.

Of note, anhedonia can manifest in different ways and can include physical, social, appetitive, and consummative features (Ho & Sommers, 2014). Whereas physical anhedonia refers to decreases in ability to experience pleasure from physical activities (i.e. eating, sex), social anhedonia refers to reduction in ability to experience pleasure with loved ones and friends (Blanchard et al. 2011; Reise et al., 2011; Ho & Sommers, 2014). Studies have found that individuals experiencing anhedonia can have intact anticipatory pleasure and a deficit in consummatory pleasure, the reverse trend,

or deficits in both (Martin et al., 2011; Strauss et al., 2011; Der-Avakian & Marou, 2012). Thus, although the results of the study implied that rTMS treatment did not have any beneficial effect on the depressed individuals' facial processing skills, which may tap aspects of consummatory and/or social pleasure, these results cannot decisively rule out potential treatment effects to other facets of anhedonia, including physical or anticipatory pleasure. Future studies might further explore the utility of rTMS to the left DLPFC for treating other facets of anhedonia.

In conclusion, our results suggest that rTMS treatment to the left DLPFC in depressed patients does not significantly improve speed of or accuracy in identifying positive emotions in facial stimuli. Hedonic processing of positive stimuli in one's environment, whether personal or social, requires one to learn and assess its reward value. Given that these skills are often compromised in anhedonic adults, future studies might examine how rTMS modulation of activity in regions the brain—such as the VMPFC—that support reward learning may reduce both anhedonic and more traditional depressive symptoms.

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