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Master Thesis

The Effects of Repetitive Transcranial Magnetic Stimulation on Anhedonia Symptoms in Treatment Resistant Major Depressive Disorder

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Anhedonia is one of the core features of major depressive disorder, but treatment has proven to be difficult. Effects of antidepressants on symptoms of anhedonia may be related to their ability to alter dopamine neurotransmitter reward-systems. This warrants research to search for therapies that can specifically target these neuronal pathways. Repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) has this ability and might therefore be a promising therapy for anhedonia. Current study examines the effects of rTMS over the left DLPFC on anhedonia symptoms in a series of patients with moderate to severe, unipolar, treatment resistant depression. This randomized controlled trial involved an intervention of 8 weeks of rTMS treatment and subsequent follow-up six months later. Severity of depression and anhedonia symptoms (measured with the HDRS-17 and SHAPS respectively) were assessed as baseline, after the treatment and at the six-month follow-up. Primary results were analyzed using a linear mixed model, with SHAPS scores as dependent variable. Secondary outcomes include calculations response and recovery rates regarding anhedonia symptoms after treatment. The analysis revealed a significant main effect of treatment group and time on the SHAPS-scores, with a significant decrease in SHAPS scores after 8 weeks of treatment rTMS treatment. Effect were long-lasting as the same results were seen at the 6 month follow-up. 45% of patients showed considerable decline in anhedonia (>50%) after rTMS treatment, and 27% even reached full recovery. This study therefore indicates that rTMS could be a effective treatment for reducing anhedonia symptoms in MDD, but more extensive research is needed before it can be used in clinical practice.

Acknowledgements

In front of you lies my thesis on the effectiveness of repetitive transcranial megnetic stimulation on anhedonia symptoms in major depressive disorder, which is written as part of my internship at the departments of Psychiatry and Intensive Care of the Radboudumc in Nijmegen.

During this internship of in total 7 months, I have been examining the use of non-invasive brain stimulation as therapy for psychiatric disorders. Aside from the writing of this thesis, this project included setting up a clinical pilot that examined the feasibility of transcranial direct current stimulation in the prevention of delirium in critically ill patients. The project showed me first-handedly how modern-day technology can be of influence in improving healthcare and how important it is to search for non invasive therapies for psychiatric disorders.

Throughout the writing of this thesis I have received a great deal of support and assistance. I would first like to thank my supervisor, Professor dr. Indira Tendolkar, for all of the opportunities I was given to further my research. I would also like to acknowledge the other colleagues from my internship for their wonderful collaboration. dr. Monica Pop-Purceleanu, thank you for your interest in this project and all the time you put into it. Harmke Duindam, your clinical expertise was invaluable in this process. dr. Farid Abdo, without your desire to improve on current therapies on the intensive care, this project would have never excisted. My appreciation also goes out to Iris Dalhuizen, who acquired the data used in this thesis as part of the DETECT study and to prof. dr. Slooter, who took the time to read and grade my thesis. Lastly, my boyfriend, Ilian, deserves a special note of thanks: you kept me sane during the most stressful times.

I hope this thesis will reflect how much I have learned from all of you.

Enjoy the reading.

Emma Visser
October 5, 2021

Summary

On this page, you can find a summary of my thesis. In my thesis I tested if a treatment called repetitive transcranial direct current stimulation could treat anhedonia.

What is anhedonia?

Anhedonia is the inability to feel pleasure. It's a common symptom of depression as well as other mental health disorders. Most people expect certain things in life to make them happy. Maybe you enjoy playing sports, eating delicious food, or just having a chat with your friends. But when you have anhedonia, the things that once liked are no longer fun or enjoyable. For patients, having anhedonia is frustrating, it makes going about their life hard. Unfortunately, there is no clear way to treat anhedonia. The medication that is currently used to treat depression does not seem to work properly for anhedonia. Therefore, we are working on other therapies to treat this symptom. One of these therapies is called repetitive transcranial magnetic stimulation, or rTMS for short.

How does rTMS work?

During a rTMS treatment we deliver a series of short magnetic pulses through your skull. This can make specific regions of the brain more or less active. In this study, we targeted a part of the brain that plays a role in feelings of reward. We hope that activating this regions results in the decrease of anhedonia.

Wat did we do to test the effectiveness of rTMS?

At the start, we asked all patients to complete a questionnaire that assesses anhedonia. This way, we would know how much anhedonia they had before the treatment. Then, we divided our patients into two groups. One group received rTMS treatment and the other group did not. After 8 weeks, we gave them the anhedonia questionnaire again. Now we could measure the change in anhedonia during this time. We saw that anhedonia levels decreased in the group of patients that got rTMS treatment, but that there was no change in anhedonia in the group that did not receive rTMS treatment. 1 out of 2 patients that received rTMS experienced at least half as much anhedonia after the treatment and almost 1 out of 3 patients even recovered completely from anhedonia. This lead us to believe that the treatment had worked.

How does this help patients?

In this study we proved that rTMS could treat anhedonia. Unfortunately, this does not mean it will get used immediately. More studies will need to find the same results. That way we can be absolutely sure. If that happens, we will finally have a way to treat anhedonia and make the life of patients with depression much easier.

Contents

List of Abbreviations

AD	**A**nti**d**epressants
ANOVA	**An**alysis **o**f **Va**riance
ATHF	**A**ntidepressant **T**reatment **H**istory **F**orm; (Sackeim, 2001)
CBT	**C**ognitive **B**ehavior **T**herapy
DLPFC	**D**orso**l**ateral **Pref**rontal **C**ortex
ECT	**E**lectro**c**onvulsion **t**herapy
HDRS-17	**H**amilton **D**epression **R**ating **S**cale; (Hamilton, 1960)
MDD	**M**ajor **D**epressive **D**isorder
MEP	**M**otor **E**voked **P**otential
rMT	**r**esting **m**otor **t**hreshold
rTMS	**r**epetitive **T**ranscranial **M**agnetic **S**timulation
SCID-5	**S**tructured **C**linical **I**nterview for **D**SM**-5** disorders (First et al., 2015)
SHAPS	**S**naith-**Ha**milton **P**leasure **S**cale; (Snaith et al., 1995)
TAU	**T**reatment **a**s **U**sual

1 Introduction

Major Depressive Disorder (MDD) is an heterogeneous mental disorder, with anhedonia drawing attention as one of it's core features. Recent reports are estimating that almost 70% of individuals diagnosed with MDD experience clinically significant anhedonia (Shankman et al., 2014), which is defined by The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as having 'markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day' (American Psychiatric Association et al., 1980).

Treatment of anhedonia has proven to be particularly difficult, and residual anhedonic symptoms persist in almost all patients even when MDD is in remission (Di Nicola et al., 2013). Moreover, recent evidence suggests that current first-line antidepressants do not effectively reduce anhedonic symptoms (Dichter et al., 2012). This is deeply concerning, as anhedonia has a tremendous impact on patient quality of life and functional outcomes in MDD (Hatzigiakoumis et al., 2011; Uher et al., 2012; Vrieze et al., 2013; Vinckier et al., 2017). Next to the burden for patients and those who care for them, this has a substantial economic affect consisting of direct costs for health care and costs due to productivity losses. A thorough understanding of the effects of other antidepressant treatments on measures of anhedonia is therefore essential.

The effects of antidepressants on symptoms of anhedonia may be related to their ability to alter dopamine neurotransmitter reward-systems (Dichter et al., 2012). Individuals with anhedonia have been shown to display disturbances in the mesolimbic and mesocortical reward circuit pathways (Argyropoulos and Nutt, 2013), which lead to the disruption of reward-based learning and valuation (Satterthwaite et al., 2015; Whitton et al., 2015). This evidence warrants research to examine interventions that are able to to specifically target these reward circuits.

Non-invasive brain stimulation might be a promising treatment option in this regard, because of it's ability to regionally modulate neuronal excitability. One of the major modalities of brain stimulation is repetitive transcranial magnetic stimulation (rTMS), which is widely available as a neurostimulation treatment for MDD. It involves stimulating the brain by using magnetic fields to induce small currents in the cerebral cortex, which could have an excitatory of inhibitory effect. Currently, rTMS is mainly applied excitatory over the left dorsolateral prefrontal cortex (DLPFC) or inhibitory over the right DLPFC, whereby the former is tested the most (Downar and Daskalakis, 2013; Teng et al., 2017; Yadollahpour et al., 2016).

The DLPFC is an interesting target for rTMS treatment, given it's strong connections to areas heavily involved in mood regulation including the insula, anterior cingulate, and amygdala (Margulies et al., 2007; Stein et al., 2007; Yuan et al., 2020). The earliest functional imaging studies of depression compared the resting state brain activity (e.g. blood flow or glucose metabolism) of depressed patients to that of non-depressed comparison subjects and associated depression with abnormally low levels of DLPFC activity (Baxter et al., 1989; Biver et al., 1994; Galynker et al., 1998). Findings like these have caused the DLPFC to become the main target for rTMS treatment, with large clinical trials displaying significantly reduced depressive symptoms significantly in about 40% of MDD patients (Fitzgerald et al., 2016).

For the treatment of anhedonia, an attractive feature of the DLPFC is the connectivity it has with the parietal, prefrontal- and deeper subcortical structures of the brain (e.g. the striatum) that are involved in the mesolimbic and mesocortical reward circuit pathways (Downar et al., 2014). Emerging evidence from primate neurophysiological studies and human neuroimaging studies suggests that the DLPFC is involved in encoding reward-related information to enhance cognitive control functions (Kouneiher et al., 2009; Krawczyk et al., 2007; Szatkowska et al., 2011). Furthermore, the DLPFC might contribute to successful regulation of reward via increased promotion of low-reward responses (Staudinger et al., 2011). Given this relation of the DLPFC to reward-processing, it is highly likely that it plays a central role in anhedonia. Consequently, stimulation of the DLPFC using rTMS might potentially be used to improve hedonic capacity. Therefore, in the current study we examine the effects of excitatory rTMS over the left DLPFC on anhedonia symptoms in a series of patients with MDD.

In recent years, studies examining the efficacy of existing antidepressant therapies in treating anhedonia have been conducted, though only in small numbers and primarily focused on the effects of pharmacological interventions. Moreover, outome measures in these studies are highly heterogeneous, as various measures of hedonic capacity were used. In current research, we will use The Snaith-Hamilton Pleasure Scale (SHAPS, (Snaith et al., 1995)) to assess anhedonia, which measures anhedonia extensively and is used regularly in research. A review by Rizvi et al. (2016) considered the SHAPS to be the gold standard for measuring anhedonia in depression. In addition, the SHAPS has a practical validity, because of it's correlation with patient's quality of life and societal functioning (Nakonezny et al., 2010).

We aim at testing the effectiveness of rTMS on anhedonic symptoms in terms of clinical improvement and persistence of anhedonic symptoms (as measured with the SHAPS) over the course of six months, in a randomized controlled trial involving an intervention of 8 weeks of rTMS treatment and continued antidepressants (AD) with a control condition receiving treatment as usual. Understanding the effects of rTMS on anhedonic symptoms, would ideally result in a specific treatment for anhedonia in MDD, and thereby a substantial improvement of patient quality of life.

2 Methods

2.1 Design Overview

This study investigated the effects repetitive transcranial magnetic stimulation (rTMS) over the left DLPFC on anhedonia symptoms in a series of patients with moderate to severe, non-psychotic, treatment resistant, unipolar depression. It constitutes an interim assessment of data acquired by DETECT study (Dalhuisen et al., 2021). This open-label randomized controlled trial involved an intervention of 8 weeks of rTMS treatment on top of cognitive behavior therapy (CBT) and continued antidepressants (AD) and a control condition of protocolled pharmacological treatment described within the Dutch guidelines, augmented with CBT. Patients were randomly assigned to the rTMS or control condition, while stratifying for setting, number of depressive episodes, and current depression severity.

After inclusion into the study, participants underwent an initial clinical assessment to determine the severity of depression (Hamilton Depression Rating Scale (HDRS-17); Hamilton (1960)) and anhedonia symptoms (Snaith–Hamilton Pleasure Scale (SHAPS); Snaith et al. (1995)). A detailed description of these questionnaires can be found in appendix A. To examine the effects of the intervention, anhedonia symptoms were again assessed directly post-treatment and at a follow-up assessment six months later. All study procedures were approved by the local institutional review boards.

2.2 Subjects

32 Subjects were included in this study (9 male, 21 female, age = 42.2 $\pm$ 14.6), recruited from 4 specialized outpatients clinics and through the national patient association in the Netherlands. All patients met the DSM-V criteria for non-psychotic unipolar depression, as established through the administration of the Structured Clinical Interview for DSM-5 disorders (SCID; First et al. (2015)). The current episode of the subjects was classified as moderate to severe (corresponding to a HDRS-17 score higher than 16), with a duration of less than two years, and included a failure to respond to at least two adequate dose-duration trials with antidepressants.

Regarding the exclusion criteria, no patients with a lifetime diagnosis of bipolar disorder, schizophrenia or schizoaffective disorder, current substance abuse disorder or organic brain syndrome participated in the study. Patients with potential contraindications to rTMS, including a history of seizures, implanted pacemaker or

neurostimulator, foreign metal bodies or the presence of a concurrent medical condition, were excluded from the study, just like patients undergoing pregnancy, or patients that were previously treated with rTMS or electroconvulsion therapy. All patients included into the study provided written informed consent.

2.3 rTMS Treatment Parameters

rTMS treatment was delivered at the department of psychiatry of the Radboudumc as well as at the neuroCare clinic in Nijmegen using a Magstim Rapid 2 (Radboudumc) or a Deymed duomag Pro machine (neuroCare). The coil vertex was placed over the left-DLPFC, which was located with the use of freely available software (BeamF3). The details of the localization procedure can be found in supplement B. Patients in the intervention arm of the study received 25 sessions of rTMS over the course of 8 weeks, following a schema of 4,4,4,3,3,3,2,2, sessions per week.

At the beginning of every treatment week, the resting motor threshold (rMT) was determined in each participant. The rMT was defined as the minimal stimulation intensity evoking a Motor Evoked Potential (MEP) of ≥ 0.05 mV in 50% of the trials in the muscle of the right thumb (M. abductor pollicis brevis). Stimulation was delivered at 120% of the rMT, at 10Hz, with a duty cycle of 5 seconds on and 25 seconds off, for a total of 3000 pulses in 60 trains per session.

2.4 Cognitive Behavior Therapy

All patients in both treatment arms received weekly sessions of cognitive behavioral therapy for 8 weeks, either in groups or individually at the location of inclusion. The exact manifestation of the treatment differed between patients, as it would during usual care.

2.5 Statistical Analyses

Patients in both treatment arms (rTMS and TAU) were compared on demographic and clinical variables such as age, gender and level of anhedonia and depression using a Pearson's Chi-Square (categorical variable), independent samples t- test (continuous, normally distributed variables), and Mann-Whitney tests (continuous, non-normally distributed variables).

For the primary aim, the effects of rTMS on anhedonia were examined via a linear mixed model analysis (LMM), which was constructed with the SHAPS as dependent variable, the treatment group as a fixed factor (two levels including rTMS and TAU) and repeated measures on time (three levels including, baseline, post-treatment and 6-month follow-up). The two-tailed significance level was set at $\alpha = .05$. Post hoc pairwise comparison of the estimated marginal means of SHAPS scores was conducted within treatment groups between baseline and each subsequent time

point and between treatment groups within time points, adjusting for multiple comparisons using the bonferroni correction.

For a more detailed assessment of the effectiveness of the rTMS treatment in reducing anhedonic symptoms, the percentage of participants that showed more than 50% reduction in SHAPS-scores between baseline and follow-up (8 weeks and 6 months) was calculated and defined as the response rate. Additionally, the proportion of patients that achieved complete recovery from anhedonia was defined as showing a 100% reduction in SHAPS-scores between time points. Response- and recovery rates were compared between the treatments using Pearson's Chi-Square.

All statistical analyses were performed using R Statistical Software (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Participant Characteristics

In total, 30 patients suffering from Major Depressive Disorder were included in the study, from which 22 patients were assigned to the rTMS treatment, and 8 patients received TAU. Since this study constitutes an interim assessment of the data, 9 patients did not complete the 6-months post-treatment assessment before completing the analyses of this study. Of these patients, 8 were assigned to the rTMS treatment and 1 to TAU.

Table 1 – Sample characteristics for patients receiving rTMS treatment and treatment as usual

	rTMS treatment (n = 22)	Treatment as usual (n = 8)	Test Statistic	df	p-value
Male, n (%)	7 (31.8%)	2 (25.0 %)	$\chi^2 = 0.08$	1	$p = 1.00$
Age, y mean (SD)	44.05 (15.81)	37.13 (9.46)	$t = 1.46$	21	$p = .16$
HDRS-17, median (range)					
pre-treatment	22 (17 – 34)	20 (17 – 26)	$U = 102$	–	$p = .53$
post-treatment	12 (1 – 24)	21 (18 – 26)	$U = 12.5$	–	$p = .001^*$
follow-up	12 (0 – 23)	19 (9 – 27)	$U = 11.5$	–	$p = .30$
SHAPS, mean (SD)					
pre-treatment	9.4 (3.1)	11.5 (1.6)	$t = -2.40$	28	$p = .08$
post-treatment	5.09 (4.5)	11.6 (2.4)	$t = -5.03$	23.3	$p < .001^*$
follow-up	4.36 (4.1)	10.9 (4.4)	$t = -3.31$	19	$p = .004^*$

rTMS, repetitive Trancrianial Magnetic Stimulation; HDRS-17, Hamilton Rating Scale for Depression; SHAPS, Snaith-Hamilton Pleasure Scale; Treatment consisted of 8 weeks, with the follow-up assessment conducted 6 months post treatment.

Table 1 displays an overview of the demographic and clinical characteristics of each of the two treatment groups. Before treatment, patients in both treatment arms displayed moderate depression as measured with the HDRS-17 and anhedonia levels in the groups were high. At the post treatment and follow-up assessments, severity of depression and anhedonia symptoms decreased in the rTMS group, but remained stable in the TAU group. Significant differences in depression symptoms were seen between treatment groups at the post treatment assessment, but not at baseline or follow-up. Regarding level of anhedonia, treatment groups differed significantly from each other at both the post-treatment assessment as well as the follow-up. Patients receiving rTMS or TAU did not differ on gender distribution, mean age, or baseline clinical characteristics.

3.2 The Effect of the Treatments on Anhedonia Levels

The effects of rTMS on anhedonia were examined via a linear mixed model analysis, which was constructed with the SHAPS score as dependent variable, and with a fixed effect of Treatment group (rTMS or TAU) and repeated measures of time (three levels including, baseline, post-treatment and 6-month follow-up). A boxplot depicting the SHAPS-scores of the groups over time is displayed in figure 1.

The analysis revealed a significant main effect of treatment group ($F1, 25.189 = 18.92, p < 0.001$) and time ($F2, 24.072 = 4.86, p = .017$) on the SHAPS-scores. In pairwise comparisons between baseline and subsequent time points, there was a significant reduction in mean anhedonia score in the rTMS group between baseline and post-treatment ($p = .019$), and between baseline and 6-month follow-up ($p = .044$), but not between post-treatment and follow-up ($p = .073$). In the TAU group, SHAPS scores did not differ significantly from each other between baseline, post-treatment assessment and followup ($p = 1.00$ for all pairwise comparisons). At both post-treatment assessment and follow-up SHAPS scores of the rTMS group were significantly lower than those from the TAU group ($p < .001$ and $p = .004$ respectively).

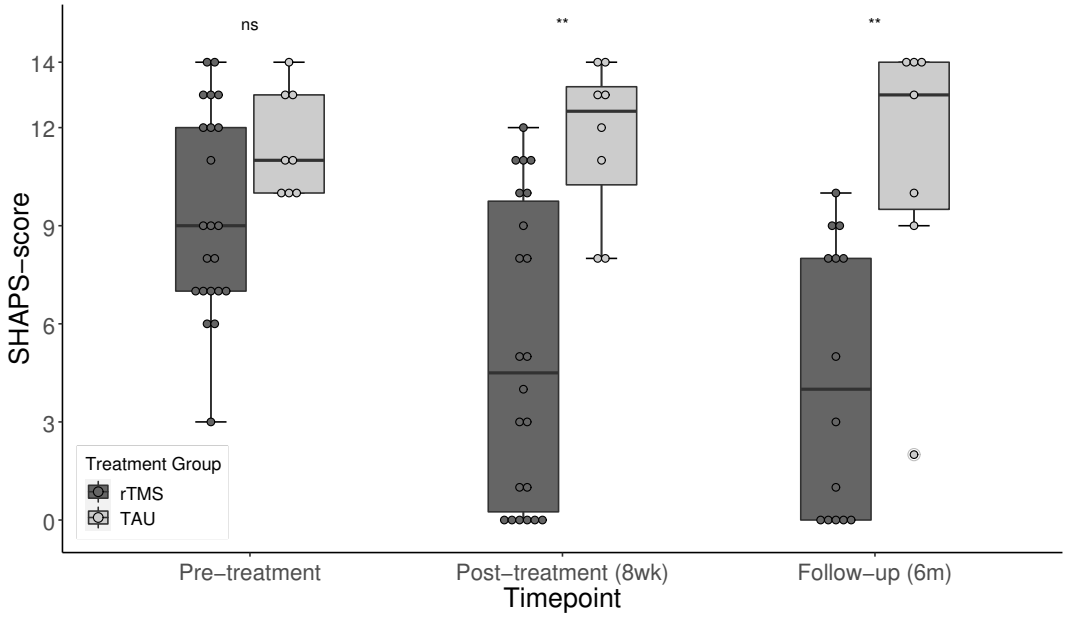

Figure 1: Level of anhedonia symptoms of patients receiving rTMS treatment or Treatment as Usual (TAU) *Error bars depict the 95% confidence interval; Significance of the differences in anhedonia scores between the treatment groups is indicated by either ns (not significant) or ** ($p < 0.001$); rTMS, repetitive Transcranial Magnetic Stimulation; SHAPS, Snaith-Hamilton Pleasure Scale*

3.3 The effectiveness of rTMS in reducing anhedonia symptoms

To assess the effectiveness of the rTMS treatment, the level of response to the treatment was calculated using the percentage of participants that showed more than 50% reduction in SHAPS-scores between baseline and one of the follow-up assessments (8 weeks and 6 months). Additionally, the proportion of patients that achieved complete recovery was defined as showing a 100% reduction in SHAPS-scores between time points. Table 2 displays the level of response and recovery for each treatment at the two time points.

Directly after the 8-week intervention, a significantly higher proportion of patients in the rTMS group responded to the treatment compared to the TAU group. Of the patients receiving rTMS treatment, 45.5% responded to the treatment, whereas 0% of the patients in the TAU group showed a 50% reduction in SHAPS scores. The level of recovery did not differ significantly between the two treatment groups, even though the proportion of recovered patients in the rTMS group (27%) was considerably higher than that of the TAU group (0%).

6 Months post-treatment, no significant difference was found comparing the response rates of the two treatment groups. Response was achieved for 50.0 percent of patients in the rTMS group and 14.3 percent of patients in the TAU group. The reported recovery rate of the patients receiving rTMS was higher (35.7%) than that of the patients receiving TAU (0%), but this difference was not significant.

Table 2 – Calculation of response and recovery to rTMS treatment and treatment as usual

		rTMS treatment	Treatment as usual	Test Statistic	df	p-value
Response, n (%)	after 8 weeks	10 (45.5%)	0 (0 %)	$\chi^2 = 5.46$	1	$p = 0.02^*$
	after 6 months	7 (50.0%)	1 (14.3%)	$\chi^2 = 2.52$	1	$p = 0.11$
Recovery, n (%)	after 8 weeks	6 (27%)	0 (0%)	$\chi^2 = 2.73$	1	$p = 0.099$
	after 6 months	5 (35.7%)	0 (0)	$\chi^2 = 3.28$	1	$p = 0.07$

*Response was defined as more than 50% reduction of the anhedonia symptoms; Recovery was defined as 100% reduction of anhedonia symptoms; Anhedonia levels were measured using the Snaith-Hamilton Pleasure Scale; rTMS, repetitive Trancrianial Magnetic Stimulation; 8 patients of the rTMS group, and 1 patient of the treatment as usual group did not complete the 6 months follow-up asessment; * indicates significance*

4 Discussion

To our knowledge this is the first study that investigated the effects of rTMS over the DLPFC on anhedonia symptoms in MDD. We tested the effectiveness of rTMS on anhedonic symptoms in terms of clinical improvement and persistence of anhedonic symptoms (as measured with the SHAPS) over the course of six months, in a randomized controlled trial. This trial involved an intervention of 8 weeks of rTMS treatment over the left DLPFC and a control condition in which patients continued their antidepressant treatment as prescribed by the Dutch guidelines.

4.1 The effects of rTMS on anhedonia

The effects of 8 weeks of rTMS treatment on anhedonia symptoms in patients with MDD were examined using a linear mixed model analysis which revealed that the treatment group was of influence of the anhedonia scores. A post-hoc analysis indicated that patients in the rTMS group showed significantly lower levels of anhedonia after 8 weeks of treatment compared to their baseline assessment, with mean scores ultimately ending up being sub-clinical (see Trøstheim et al. (2020) for reference values regarding anhedonia severity as measured with the SHAPS). Effects were long-lasting, as the decreased anhedonia levels in the rTMS group were also seen 6 months after treatment. These findings points to the effectiveness of rTMS over the left-DLPFC in reducing anhedonia symptoms, and should be replicated in larger clinical trials.

The decrease in anhedonia that was seen in the rTMS group, was considerable, as 45.5% of the patients displayed least 50% decrease in anhedonia symptoms after 8 weeks of treatment. Remission rates were also high, with 35.7% of patient reaching complete recovery from anhedonia symptoms. These response and remission rates are comparable to those reported for rTMS as treatment for depressive symptoms in treatment resistant depression. A study by Levkovitz et al. (2015) reported a 43% response rate and 36.6% remission rate of rTMS for patients after one to two failed medication therapies. While a direct comparison of response and remission rates between these studies cannot be made, it appears rTMS may provide at least comparable outcomes for anhedonia symptoms as for depressive symptoms. No data is available on response rates of antidepressants regarding anhedonia symptoms, but given that anhedonia symptoms almost always occur even after MDD is in remission, these could be substantially lower than those of rTMS (Di Nicola et al.,

2013). The response rates found in this study are therefore promising, and provide opportunity to use rTMS in clinical practice as treatment for anhedonia symptoms.

No differences in anhedonic symptoms were seen in the control group of patients continuing antidepressant therapy as described by the Dutch guidelines. This is somewhat surprising, as these treatments are expected to reduce anhedonia at least to some extent. A recent review on pharmacological interventions targeting anhedonia by Cao et al. (2019), indicates that monoaminergic antidepressants, glutamatergic agents, psychedelics, and stimulants have all been associated, to varying degrees, with improvements in anhedonia. Among the antidepressive treatments investigated, only the combination therapy of escitalopram and riluzole was found to be ineffective in improving measures of anhedonia in MDD. However, this review focused mainly on treatment naive patients, whereas in our study, treatment resistant participants were included. Those patients might only show limited decrease in anhedonia symptoms after switching antidepressants. Taken together with the small sample size and the heterogeneity of the received treatments, these findings should be viewed in the light of an under powered study.

4.2 Therapeutic mechanism

The underlying mechanism by which magnetic stimulation of the left-DLPFC leads to a decrease in anhedonia levels is still unclear, although convincing explanations could be given. One credible hypothesis is that the rTMS treatment modified activity in brain regions associated with the mesolimbic and mesocortical reward-circuits. Relevant pathways could be originating from the connectivity between the DLPFC and brain regions like the frontopolar prefrontal cortex, subgenual cingulate cortex, striatum, ventral tegmental area and nucleus accumbens (Avissar et al., 2017; Ballard et al., 2011; Fettes et al., 2018; Fox et al., 2013). A previous study by Strafella et al. (2001) for example showed that stimulation of the left-DLPFC induced dopamine release in the caudate. It should however be noted that although we have linked hedonic capacity with the left DLPFC, we cannot say with absolute certainty whether or not the effect on anhedonia symptoms was actually mediated by the DLPFC. It is possible that another brain area, also affected by rTMS, is responsible for this change in anhedonia symptoms.

4.3 Limitations

Interpretation of the present findings must be placed in the context of some major limitations. First, it is important to note that this was an exploratory study with a relatively small sample size, as this study constitutes an interim assessment of data collected by Dalhuisen et al. (2021). It is critical to reproduce current findings in adequately-powered data-sets before making definitive claims about the effectiveness of rTMS in reducing anhedonia symptoms. Considering the small sample size

and the heterogeneity of the treatments received by the control group, no reliable comparison can be made between the use of rTMS treatment and currently used antidepressant treatments, although our results seem to favor rTMS.

Second, our findings could be influenced by the patients' attitudes towards rTMS treatment. This study only included patients with treatment resistant depression and it can be hypothesized that those patients will look more favorable upon a new treatment than they do on continuing with antidepressants, which could explain the absence of change in anhedonia symptoms in the control condition. In addition, the reduction of anhedonic symptoms in the rTMS group could be partly explained by a placebo effect caused by the positive outlook on rTMS. This effect is enhanced by a possible inclusion bias of patients looking favorably upon rTMS, as a large part of the included patients applied for the study after reading about the possible antidepressant effects online. To ascribe the anti-anhedonic effects of rTMS directly to the treatment, future studies should include a sham-condition to correct for possible placebo effects.

Lastly, our study uses the SHAPS to measures hedonic capacity, which is lacking a standard scoring method or reference values. However, a recent meta-analysis by Trøstheim et al. (2020) reported that patients with MDD would not enjoy, on average, 6 of the 14 items and in contrast to healthy participants who reported, on average, 1 unenjoyable SHAPS item. In our study, we used these values as reference and concluded that mean levels of anhedonia in our patients before treatment was high and reduced to sub-clinical after rTMS treatment. When comparing our outcomes to other studies using the SHAPS, it should be kept in mind that they might have used different scoring methods or reference values. Nonetheless, the SHAPS is considered the gold standard for measuring anhedonia in depression (Rizvi et al., 2016), with outcome measures correlating with both patient's quality of life and societal functioning (Nakonezny et al., 2010).

4.4 Conclusion

In summary, 8 weeks of rTMS over the left-DLPFC had a favorable and long-term effect on anhedonia symptoms in patients with moderate to severe, treatment resistant depression, with a response rate of 45.5% and a remission rate of 30%. These results provide a first indication for the usability of rTMS in the treatment of anhedonia symptoms in clinical practice, especially given the correlation between anhedonia and patients quality of life and functional outcomes of MDD. However, due to the small sample size and absence of a sham condition, no definitive claims on the effectiveness of rTMS treatment can be made based on these findings.

For generalizability of these results, future studies should examine the effects of rTMS on anhedonia in other psychiatric disorders. Given that rTMS directly targets underlying neurobiolgy of anhedonia, which is most likely similar across diagnoses, rTMS could eventually be used trans-diagnostically to treat anhedonic symtoms.

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A Description of the questionnaires used for clinical assessment

Participants in our study underwent clinical assessments to determine the severity of depression and anhedonia symptoms as measured with the Snaith–Hamilton Pleasure Scale and the Hamilton Depression Rating Scale respectively. In this appendix a detailed description of those two questionnaires can be found.

A.1 Snaith-Hamilton Pleasure Scale

The Snaith–Hamilton Pleasure Scale (SHAPS; Snaith, 1993) is a self-administered questionnaire that assesses the respondents' hedonic capacity. It consists of 14-items, covering four domains, being interests/pastimes, social interaction, sensory experience, and food/drink. Each of the 14 items includes four response categories; Definitely Agree, Agree, Disagree, and Strongly Disagree. Either of the Disagree responses are assigned a score of 1 and either of the Agree responses are assigned a score of 0. The total SHAPS score is calculated as the sum of the scores on the individual items, resulting in a total SHAPS score between 0 and 14. A higher total SHAPS score indicated higher levels of present state of anhedonia. The inter-item reliability (Cronbach's alpha) for this test is 0.8571,28.

A.2 Hamilton Depression Rating Scale

The HDRS (also known as the Ham-D) is the most widely used clinician-administered depression assessment scale. The original version contains 17 items (HDRS-17) pertaining to symptoms of depression experienced over the past week. Items are being scored on either a 3-point or 5-point Linkert-like scale depending on the question. Four additional questions not added to the total score are used to provide additional clinical information about the subtype of depression. Scores on the HDRS-17 are calculated as a sum of the individual items and fall between 0 and 52, with scores of 0–7 being considered normal, 8–16 suggesting mild depression, 17–23 indicating moderate depression and scores over 24 are indicative of severe depression. Although the scale was designed for completion after an unstructured clinical interview, there are now semi-structured interview guides available.

B Localization Procedure for the rTMS treatment

In the current study, rTMS treatment was delivered over the left DLPFC, which was located with the use of BeamF3 software (Beam et al., 2009). This appendix explains the localization procedure.

B.1 The International 10-20 system

The International 10–20 system is a method for standardized placement of electroencephalogram (EEG) electrodes, which is widely used in research and clinical practice. Skull locations and underlying cortical areas are correlated using a mathematical approach to account for variability of patient's skull size. The desired skull locations are found by using percentages of the patients circumference and the distance between nasion and inion and the left and right earlobe as displayed in figure 2. The DLPFC is believed to correspond to the F3 location given by the 10–20 system.

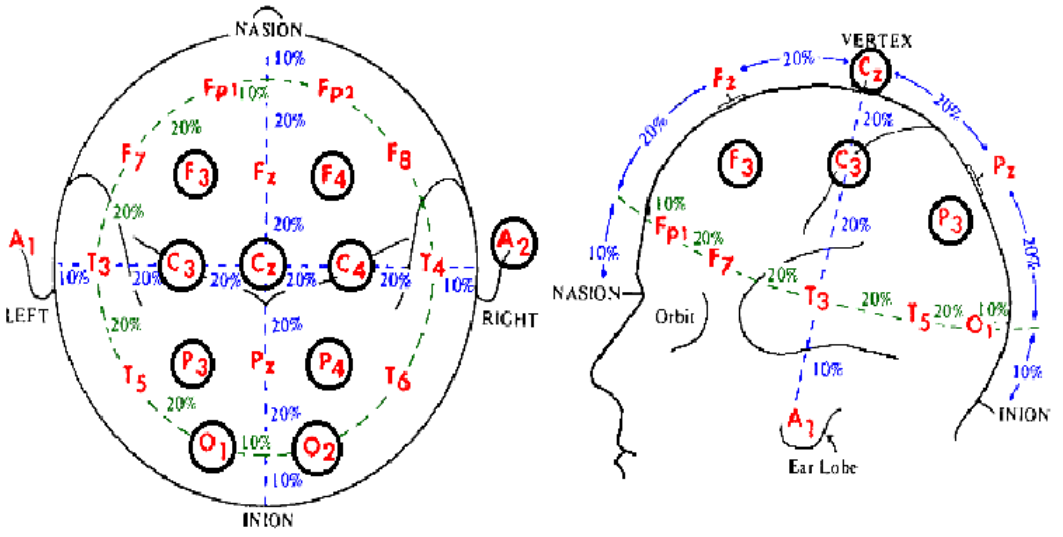

Figure 2: Calculation of skull locations using the International 10-20 system *Skull locations are calculated using percentages of the patient's skull circumference and distance between nasion and inion and the left and right earlobe. Figure adapted from a publication by Abhang and Gawali (2015).*

B.2 BeamF3

The freely available software, BeamF3, was used to find the F3 location. This computer program can be downloaded from the ClinicalResearcher website (`https://clinicalresearcher.org/software.htm`) or used as a web based interface (`http://clinicalresearcher.org/F3/`). BeamF3 provides instructions on how to find the F3 location based on the patient's specific measurements. Distances between anatomic landmarks are measured using a tape measure in centimeters, while the patients is wearing a swimming cap. See figure 3 for an illustration of the system in practice.

Figure 3: Locating the F3 location using BeamF3 software *[1] The the distance between the left and right preaurical point is measured and the halfway point is marked on the patients swimming cap. [2] The distance between nasion and inion is measured and the halfwaypoint is marked on the swimming cap. [3] The vertex is located using the intersection of the two halfway points. [4] The circumference is measured with the tape measure over the eyebrows and inion. After this step, measurements are given as input to the BeamF3 program, which provides an x and a y distance to locate the F3 position [5] After the x distance over the circumference is measured, the F3 location can be found be going y cm from the vertex to the x location. [6] The F3 location is marked on the swimming cap. Figure is adapted from a publication by Beam et al. (2009)*

The first measurement is that of the distance from nasion to inion, which is entered into the BeamF3 software. The halfway point on this line is marked on the swimming cap, to later find the vertex. Then the distance from the left preaurical point to the right preaurical point is calculated. This measurement is also entered into the program and the administrator marks the halfway point on this line as well.

The vertex of the patient is located on the intersection of the two marked halfway-points. The last measurement the administrator takes is the circumference, measured at the level of the eyebrow and passing over the inion. Once this value has been given to the BeamF3 program, it produces two output values. The first is the distance from the center line to a point called 'x', which is located along the circumference. The second the distance from the vertex to F3, located on the line from the vertex to point 'x'. Using these two output measured the F3 locatation can be found, and will then be used as the target for the rTMS treatment.