Psychiatry Research 279 (2019) 55–61

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Cognitive profiles in major depressive disorder: Comparing remitters and non-remitters to rTMS treatment

Mohamed Abo Aoun[a], Benjamin P Meek[a], Mandana Modirrousta[a,b,*]

[a] St Boniface General Hospital, Winnipeg, MB, R2H2A6, Canada
[b] University of Manitoba, Department of Psychiatry, Winnipeg, MB, Canada

ARTICLE INFO

Keywords:
rTMS
Cognition
Remission
MDD
Task Switching
Reaction time

ABSTRACT

Major Depressive Disorder (MDD) is typically accompanied by cognitive impairment. Repetitive Transcranial Magnetic Stimulation (rTMS) treatment for MDD involves stimulation of the dorsolateral prefrontal cortex which plays an important role in cognition. This study aimed to identify differences in cognitive profiles between remitters and non-remitters to rTMS at baseline and across treatment. 25 patients with MDD performed cognitive tasks at baseline and after 6, 12 and 30 sessions of rTMS. At baseline, there was no difference in simple reaction time (RT) between groups, but remitters (n = 13) showed faster RTs than non-remitters (n = 12) in the Switch and No-Switch conditions of Task Switching. Across sessions, remitters showed a decrease in 3-Back omission errors and RTs to 3-Back, Stroop's Congruent and Incongruent, and Task Switching's Switch and No-Switch conditions, whereas non-remitters only showed improvements in Stroop Congruent and Incongruent RTs. Baseline and final scores on the Hamilton Depression Rating Scale were positively correlated with Switch and No-Switch RTs. This study demonstrates that eventual remitters to rTMS treatment for MDD perform better in cognitive tasks requiring shifting attention, and this difference is observable prior to the start of treatment. Remitters also show improvement in both their mood and cognitive performance.

1. Introduction

Major Depressive Disorder (MDD) is a pervasive, multidimensional disorder that is diagnosed in 14% of individuals during their lifetime (Kessler et al., 2012) and is associated with high rates of non-recovery and recurrence (van Randenborgh et al., 2012). In addition to affective symptoms, subjective complaints of cognitive decline from patients are common (Dotson et al., 2008). Indeed, in two thirds of cases, MDD is associated with cognitive dysfunction (Bhalla et al., 2006; Reppermund et al., 2009), which acts as a crucial mediator of adverse psychosocial outcomes (Buist-Bouwman et al., 2008; Conradi et al., 2011; Jaeger et al., 2006) and is associated with poor response to antidepressant treatment (Roiser et al., 2012). Functional impairment caused by MDD, especially with regards to workforce participation, disproportionately accounts for the costs incurred by the disorder (Kessler et al., 2008; Reppermund et al., 2009).

Broadly, the cognitive domains found to be impaired in MDD include executive functioning, memory, and attention (Rock et al., 2014). Although no 'gold standard' psychometric cognitive tests exist for MDD assessment, cognitive deficits are fairly consistent and easily replicable, especially with regards to executive functioning, working memory, attention, and sensorimotor or cognitive processing speed (Lee et al., 2012). Successful treatment of affective symptoms in MDD using antidepressants is not always accompanied by an improvement in cognitive functions, with studies reporting mixed results (Conradi et al., 2011; Constant et al., 2005).

Previous studies have attempted to use the cognitive profiles of patients with MDD to predict treatment response to antidepressants. For example, it has been observed that non-responders to fluoxetine tend to show more baseline perseveration in the Wisconsin Card Sorting Test (Dunkin et al., 2000) as well as psychomotor slowing on oral word association and Stroop tests compared to responders (Taylor et al., 2006). Similarly, in geriatric patients, abnormal scores on the initiation/perseveration subscale of the Mattis Dementia Rating Scale are associated with poor response to citalopram (Alexopoulos et al., 2005). Logistic regression has also been used to identify neuropsychological indices able to predict SSRI responsiveness using the results of clinical and neuropsychological assessment (Kampf-Sherf et al., 2004).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of producing an intense, localized magnetic field using an electromagnetic coil held over the scalp in order to excite or inhibit focal cortical areas. rTMS is now accepted and approved as standard of

* Corresponding author at: St Boniface General Hospital, M4-McEwen Building, 363 Tache Ave, Winnipeg, MB, R2H2A6, Canada
E-mail address: mmodirrousta@sbgh.mb.ca (M. Modirrousta).

https://doi.org/10.1016/j.psychres.2019.07.007
Received 14 December 2018; Received in revised form 2 July 2019; Accepted 3 July 2019
Available online 04 July 2019

care for treatment resistant MDD in many countries (McClintock et al., 2018). The most common cortical region targeted in the treatment of depression using rTMS is the left dorsolateral prefrontal cortex (DLPFC), which has been shown to have decreased activation in functional neuroimaging studies of depression (George et al., 1999). The DLPFC plays a significant role in the dorsal executive system, where it is involved in cognitive control during emotional regulation (Iordan et al., 2013; Mayberg, 1997). Dopaminergic dysfunction in fronto-striatal structures, including the DLPFC, is thought to contribute to the psychomotor performance deficits seen in MDD (Taylor et al., 2006).

Given the role of DLPFC in cognitive control and the associated cognitive dysfunctions in patients with MDD, especially those with treatment resistant depression, this study sought to explore the differences in cognitive profiles of remitters and non-remitters to rTMS treatment at baseline as well as how these cognitive profiles change across a full course of treatment.

2. Methods

This study was approved by the University of Manitoba's Research Ethics Board and the Research Review Committee at Saint Boniface General Hospital.

25 patients who were scheduled to receive rTMS treatment for depression were recruited from the Neuromodulation and Neuropsychiatry Unit at Saint Boniface General Hospital. Informed consent was obtained from all participants. All participants were over 18 years of age and had a diagnosis of Major Depressive Disorder as established by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Association, 2013). Additional inclusion criteria required that participants i) not be actively receiving psychotherapy and ii) currently be taking no more than one antidepressant and willing to keep their antidepressant dosage stable throughout their participation in the study. Exclusion criteria eliminated potential participants with: i) any history of a psychotic episode, ii) neurological illness, iii) previous major head injury (e.g. concussion with loss-of-consciousness), iv) active alcohol or substance abuse, v) history of a seizure disorder, vi) current pregnancy.

Depression symptoms were assessed by the study psychiatrist (MM) using the Hamilton Depression (Ham-D) Scale (Hamilton, 1960) at baseline and after 10, 20, and 30 sessions of treatment. Patients were discontinued from treatment after 20 sessions if they failed to show any improvement in mood. rTMS treatment was administered using a Magstim® Rapid^2 stimulator attached to an AirFilm® Figure-Eight Coil (The Magstim Company Ltd., Whitland, UK). Treatment consisted of 30 sessions of high-frequency (HF) stimulation over the left dorsolateral prefrontal cortex (DLPFC). The DLPFC was defined at Brodmann areas 9 and 46 using Brainsight software (ver 2.3.7; Rogue Research, QC), and precise targeting of the treatment site was achieved using on-line neuronavigation combining Brainsight with a mounted Polaris Vicra camera (Northern Digital Inc., ON). The treatment coil was held perpendicular to the scalp over the center point of the previously defined target region, with the coil oriented at a 45°angle to the parasagittal plane. 60 trains of 10 Hz pulses were administered in 5 s trains with a 25 s inter-train interval, for a total of 3000 pulses per session. Stimulation power was set at 120% of each participant's resting motor threshold (MT), which is considered safe for a broad spectrum of patients receiving rTMS (Johnson et al., 2013). Resting MTs were established using the criterion of lowest intensity of stimulation that resulted in a visible movement of the dominant thumb (targeting the abductor pollicis brevis muscle) on 5 of 10 sequential pulses. MTs were not re-measured after the initial session, so each patient's treatment intensity remained the same throughout the length of their treatment. Two sessions of stimulation were administered each working day (Monday-Friday) with a 15 min break between sessions. This twice-daily treatment protocol has been found to be as effective as once-daily stimulation for the treatment of depression (Loo et al., 2007; Modirrousta et al., 2018).

Following 30 sessions of rTMS treatment, patients were determined to have reached remission if their Ham-D scores were less than or equal to 7.

2.1. Tasks

Participants performed four computer-based tasks at baseline, and then after receiving 6, 12 and 30 sessions of rTMS: Simple Reaction Time, 3-Back, Stroop, and Task-Switching. All of these tasks were reported *a priori* as part of the task battery. Participants also completed an emotion-judgement task at the end of each testing session, the results of which were not intended to be part of this analysis and are not reported here. The timing of mid-treatment testing (i.e. following sessions 6 and 12 rather than 10 and 20) was chosen in an effort to specifically detect changes in cognitive functioning early in rTMS treatment with the intent of observing whether early cognitive changes may be an indicator of treatment response. Baseline testing was performed prior to participants receiving any rTMS treatments, while subsequent testing sessions were performed immediately following the 6th, 12th, and 30th rTMS session (which was always the second treatment session of the day). The task battery took an average of 30 min to complete. All tasks were programmed using E-Prime software version 2.0 (Psychology Software Tools, Inc.) and were presented on a desktop computer with a 24″ monitor. Responses were collected using a Serial Response Box (Psychology Software Tools, Inc.) with an attached microphone.

The Simple Reaction Time tasks required participants to press a designated key on the response box in response to the appearance of a target stimulus (a red circle) over 25 trials. The stimulus always appeared at the location of the fixation cross in the center of the screen. No distractor or non-target stimuli were used. The target stimulus appeared at random intervals of between two and five seconds following the previous stimulus. The outcome variable of interest was response time (RT), measured as the difference in time between the appearance of the red circle on the screen and the pressing of the response key, which is a measure of psychomotor speed.

In the 3-Back task (Braver et al., 1997), white, lower-case letters were presented sequentially, one at a time in the center of the screen. Each letter was visible for one second with a 250 ms inter-stimulus-interval. Participants were instructed to press a key on the response box whenever the current letter on the screen matched the letter presented three before it. Participants saw 120 stimuli, of which 20 were target stimuli. Outcome variables of interest were RT (average time taken to press the response key following the appearance of target stimuli), commission errors (number of responses to non-target stimuli), and omission errors (number of non-responses to target stimuli). N-back tasks can be used as a measure for working memory (Jaeggi et al., 2010), which has been shown to be impaired in MDD patients (Lee et al., 2012).

In the Stroop task (Stroop, 1935), participants were shown the name of a color on the screen, e.g. 'GREEN', and instructed to name the color of the font used to display the word. Words could be either congruent (i.e. the font color matched the name) or incongruent (i.e. the font color did not match the name). Words were presented one at a time, but split into groups of two such that each pair of words contained both a congruent and incongruent stimulus. After each pair of words, the participant was asked to identify whether the first or second word was incongruent by speaking their response into the microphone. E-Prime software recorded the onset time of their vocal response as the RT for that trial. All trials were vetted by a research assistant to ensure accuracy of the automated timing system. Data from trials with erroneous readings were discarded. Participants responded to 30 pairs of stimuli. Outcome variables of interest were RT on congruent trials, RT on incongruent trials, and Stroop Effect (difference in RT between incongruent and congruent trials). Response times on incorrect-response trials were excluded from these analyses. The Stroop task allows for a

measure of cognitive inhibition, as participants are required to suppress the reading response to instead focus on the font color of the word in incongruent stimuli (MacLeod, 1991). Cognitive inhibition has been demonstrated to be affected in patients with MDD (Mitterschiffthaler et al., 2008).

The Task-Switching task presented participants with a letter and a number (e.g. 'G5') inside a colored square. Participants were instructed to name the letter if the square was blue or name the number if the square was yellow. Trials were structured such that the color of the square would switch after every two stimuli. Participants completed 128 trails with a break at the half-way point. E-Prime software recorded the onset time of participants' vocal responses into the microphone as the RT for that trial. All trials were vetted by a research assistant to ensure accuracy of the automated timing system. Data from trials with erroneous readings were discarded. Outcome variables of interest were RT on switch trials, RT on no-switch trials, and Switch-Cost (difference in reaction time between switch and no-switch trials). Response times on incorrect-response trials were excluded from these analyses. This task is designed to test executive function and cognitive flexibility, processes which several studies have shown to be impaired in patients with MDD (Biringer et al., 2005; Yu et al., 2019).

2.2. Statistical analysis

Statistical analysis was carried out using SPSS version 21. A Shapiro-Wilk test was performed in order to test of the normality of data for each test at each time point. For tests with normal data, independent t-tests or chi-squared tests were performed for baseline comparisons. For tests with data points deviating from normality, non-parametric tests were performed, namely Friedman ANOVA for repeated measures and Wilcoxon Signed Rank Test for post-hoc analysis with Bonferroni adjustment for multiple comparisons. The Bonferroni adjusted alpha level was 0.0167 to account for the number of comparisons..

3. Results

Following rTMS treatment, 13 participants were defined as remitters (having post-rTMS Ham-D scores of ≤7), while 12 were non-remitters. Five participants who were discontinued from treatment after session 20 due to non-response did not complete the final, post-treatment session of cognitive testing.

The Shapiro-Wilk test for normality showed that all baseline data was normally distributed ($p > 0.05$), allowing for the use of parametric tests for baseline comparisons. With regards to trends over time, some data were not normally distributed ($p < 0.05$), so the non-parametric Friedman ANOVA and Wilcoxon-Signed Rank post-hoc were run.

3.1. Demographics

Demographic characters are listed in Table 1. No significant differences were identified between the groups in terms of age, years of education, or sex ($p > 0.05$).

3.2. Baseline testing

Ham-D scores at baseline were significantly different between treatment-outcome groups, with remitters (16.23 ± 3.56) showing lower Ham-D scores than non-remitters (21.08 ± 4.12; $t_{23} = 3.156$, $p < 0.01$).

At baseline, remitters were faster than non-remitters in both Switch RT (901.6 ms ± 195.7 ms versus 1141.3 ms ± 474.8 ms) and No-Switch RT (895.4 ms ± 203.9 ms versus 1134.1 ms ± 451.2 ms) for the Task Switching task ($p < 0.0167$; Fig. 1). The two groups were not statistically different in their scores on the Simple RT, 3-back, or Stroop tasks, nor in their Switch Cost on the Task Switching task ($p > 0.0167$).

3.3. Changes over time

Friedman ANOVA highlighted significant improvements for remitters, but not non-remitters, over time on several cognitive tasks which were revealed using a Wilcoxon Signed-Rank post-hoc analysis with Bonferroni correction. Significant changes can be seen in Fig. 2.

3.3.1. Simple RT

No significant changes over time were noted for remitters or non-remitters with respect to simple reaction time ($p > 0.05$).

3.3.2. 3-back

Remitters demonstrated significant improvements in number of omission errors and RT across sessions ($p < 0.0167$). Post-hoc analysis revealed improvements between baseline and 30 sessions for omission errors, and between baseline and sessions 12 and 30 for RT ($p < 0.0167$; Fig. 2a-b). No significant changes were noted in commission errors for remitters ($p > 0.0167$). There were no significant changes across the sessions for non-remitters ($p > 0.0167$)

3.3.3. Stroop

RT for congruent trials improved significantly across testing sessions in both remitters and non-remitters ($p < 0.0167$; Fig. 2c). For remitters, post-hoc analysis showed improvements between baseline and sessions 12 and 30, while non-remitters showed an improvements between baseline and session 12 ($p < 0.0167$).

RT for incongruent trials also improved significantly across testing sessions in both remitters and non-remitters ($p < 0.0167$; Fig. 2d). For remitters, there was a difference in RT between baseline and session 12 ($p < 0.0167$). Non-Remitters showed a difference in RT between baseline and 12 sessions ($p < 0.0167$)

There was no significant change in Stroop Effect across testing sessions for remitters or non-remitters ($p > 0.0167$)

3.3.4. Task switching

Remitters showed a significant improvement in Switch RT across testing sessions ($p < 0.0005$), with post-hoc analysis indicating a difference between all sessions ($p < 0.0167$), with the exception of between sessions 12 and 30 ($p > 0.0167$). Non-remitters did not show any significant change in Switch RT over time ($p > 0.0167$; Fig. 2e).

Remitters also showed a significant improvement in No-Switch RT across testing sessions ($p < 0.0167$), with post-hoc analysis showing a difference between baseline and all subsequent measurements ($p < 0.0167$). No improvements were noted in No-Switch RT across sessions for non-remitters ($p > 0.0167$; Fig. 2f).

There was no significant change in Switch-Cost across sessions for either remitters or non-remitters ($p > 0.0167$). Error bars represent standard error.

3.4. Correlations

Baseline Ham-D scores showed a significant moderate positive correlation with both Switch RT ($r = 0.406$; $p = 0.044$), and No Switch RT ($r = 0.459$; $p = 0.021$). Final Ham-D scores after session 30 showed a significant strong positive correlation with both Switch RT ($r = 0.64$; $p = 0.002$) and No-Switch RT ($r = 0.638$; $p = 0.002$) in the Task Switching task.

4. Discussion

In this study, we sought to determine the differences in cognitive profiles between remitters and non-remitters to high frequency (10 Hz) rTMS over the left DLPFC for MDD at baseline and over the course of their treatment.

The results of our study show that despite similar psychomotor speeds (as measured using the Simple RT task) between the two groups,

Table 1
Comorbid diagnoses and concomitant medications for each participant, all of whom had major depressive disorder as their primary diagnosis. Averaged demographic data (Standard Deviation) is presented for each response group separately (remitters and non-remitters).

	Remission	Comorbid diagnosis	Antidepressants	Mood Stabilizers/ Anticonvulsants	Antipsychotics	Benzodiazepines	Other Medications
1	No	Nil	Imipramine	Nil	Nil	Clonazepam	Nil
2	No	Nil	Venlafaxine	Nil	Nil	Clonazepam	Nil
3	No	Nil	Fluoxetine	Lamotrigine	Nil	Lorazepam	Zopiclone, Trazodone
4	No	Nil	Nil	Nil	Quetiapine	Clonazepam	Nil
5	No	Nil	Nil	Nil	Quetiapine	Diazepam	Zopiclone
6	No	Nil	Citalopram, Mirtazapine	Nil	Nil	Nil	Nil
7	No	Nil	Mirtazapine	Nil	Nil	Nil	Nil
8	No	Nil	Nil	Nil	Nil	Lorazepam	Nil
9	No	Nil	Nil	Nil	Nil	Nil	Nil
10	No	Nil	Mirtazapine, Sertraline	Nil	Quetiapine, Aripiprazole	Lorazepam	Nil
11	No	GAD	Citalopram	Nil	Nil	Diazepam	Nil
12	No	Nil	Venlafaxine, Mirtazapine	Sodium Valproate	Risperidone	Diazepam	Nil
	Non-remitters	Sex (female/ male)	4/8	Age (years)	52.17 (16.93)	Years of Education	14.5 (2.97)
13	Yes	Nil	Nil	Nil	Nil	Nil	Nil
14	Yes	Nil	Duloxetine	Nil	Nil	Nil	Nil
15	Yes	Nil	Nil	Nil	Nil	Nil	Dextroamphetamine, Trazodone
16	Yes	Nil	Sertraline	Nil	Nil	Nil	Nil
17	Yes	Nil	Sertraline	Nil	Quetiapine	Nil	Nil
18	Yes	Nil	Escitalopram	Nil	Nil	Clonazepam	Trazodone
19	Yes	Nil	Imipramine	Nil	Nil	Clonazepam	Nil
20	Yes	Nil	Nil	Nil	Nil	Lorazepam, Clonazepam	Zopiclone, Zolpidem
21	Yes	Nil	Sertraline, Bupropion	Nil	Nil	Clonazepam	Nil
22	Yes	Nil	Nil	Nil	Nil	Nil	Nil
23	Yes	Nil	Venlafaxine	Nil	Aripiprazole	Nil	Nil
24	Yes	Nil	Sertraline, Trazodone	Nil	Nil	Nil	Nil
25	Yes	Nil	Sertraline	Nil	Nil	Clonazepam	Zopiclone
	Remitters	Sex (female/ male)	7 / 6	Age (years)	42.85 (14.7)	Years of Education	15.04 (2.77)

PTSD = Post-Traumatic Stress Disorder; GAD = Generalized Anxiety Disorder; OCD = Obsessive Compulsive Disorder.

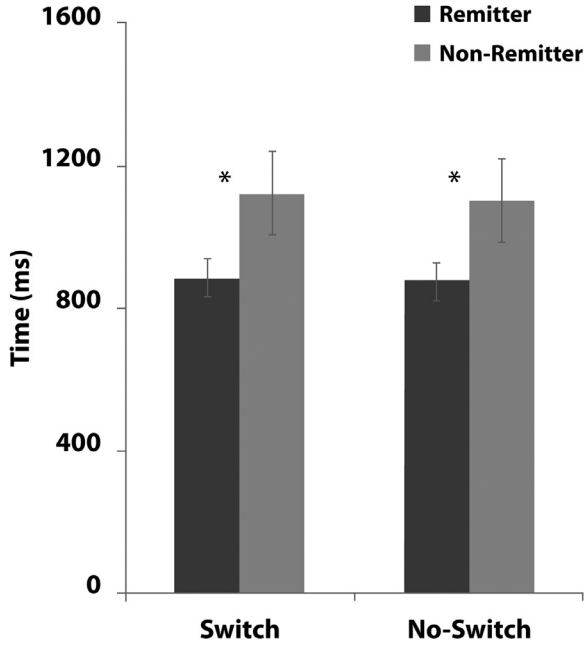

Fig. 1. Switch and No-Switch RTs on the Task Switching task at baseline. Error bars represent standard error.
*significance at $p < 0.0167$.

remitters were faster when performing a cognitively demanding task such as Task Switching at baseline. This finding suggests that patients presenting with better cognitive control, specifically between two or more competing tasks, show a more positive response to rTMS treatment. Similar findings have previously been described in studies using Trail Making Tests (Kampf-Sherf et al., 2004; Kaur et al., 2019). Comparing the simple reaction time of both groups at baseline helps demonstrate that the differences in reaction times in the cognitive tasks between remitters and non-remitters can be attributed mainly to cognitive processing time and not merely motor speed, similar to what has been shown in previous studies looking at simple RT, the Stroop task, and the Controlled Word Association Test (COWAT) (Harvey et al., 2004; Kampf-Sherf et al., 2004; Taylor et al., 2006).

It has been proposed that aberrant Default Mode Network (DMN) response in MDD is responsible for negative and passive self-relational ruminations. It is postulated that rTMS exerts its antidepressant mechanism by regulating the functional connectivity between the DMN and the Task Positive Network (TPN) – a network that recruits executive control and working memory resources (Fox et al., 2005; Richieri et al., 2017). In addition, HF rTMS applied to the left DLPFC has been shown to improve cognitive performance over 10–15 sessions (Guse et al., 2010). Our results corroborate these findings in some domains for remitters, namely in 3-Back omission scores and RT, Stroop Congruent and Incongruent RTs, and Task Switching Switch and No-Switch RTs. These tasks tested for working memory, cognitive flexibility, and retrieval, which have been reported to improve with rTMS treatment (Fabre et al., 2004; Hausmann et al., 2004; Martis et al.,

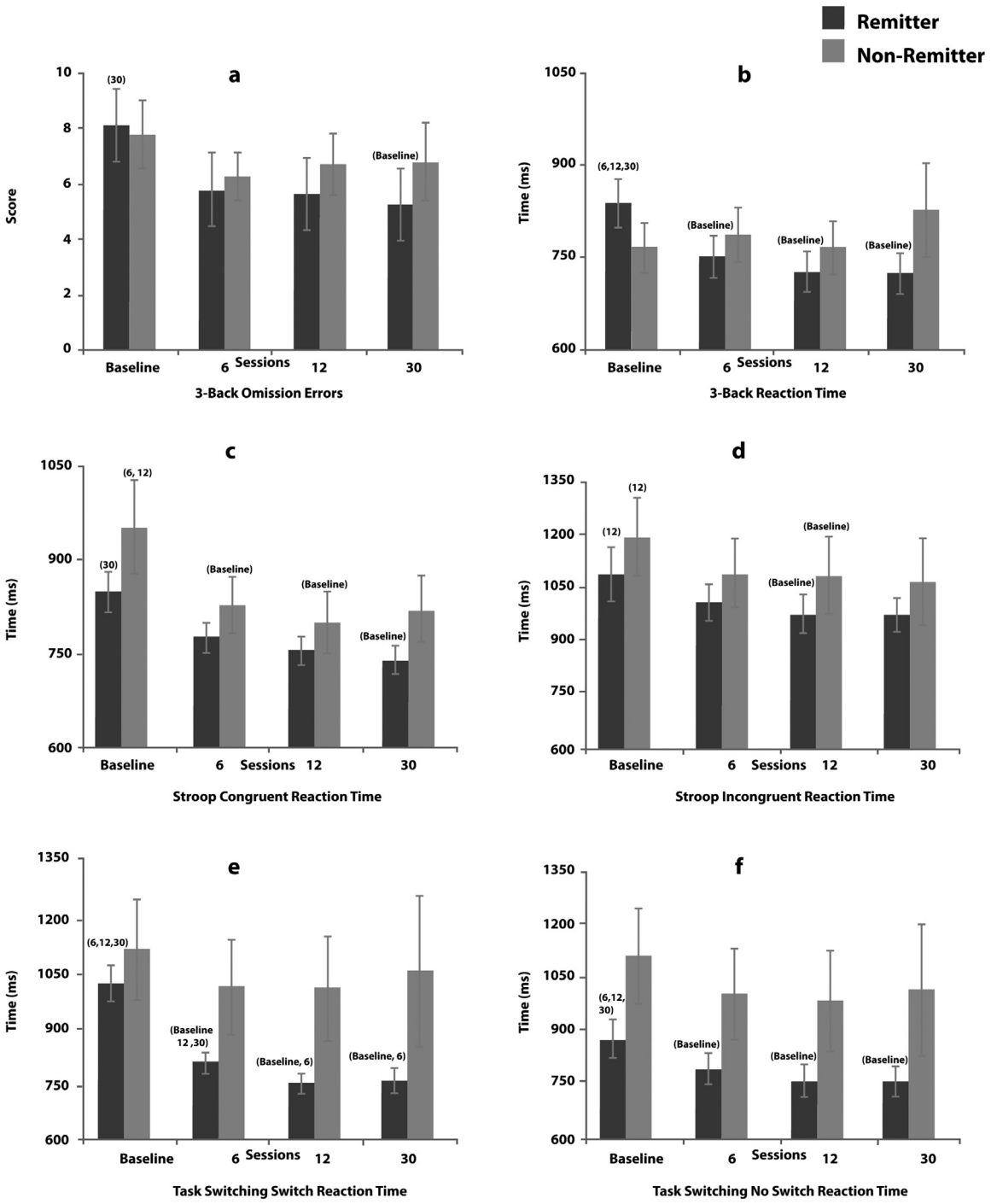

Fig. 2. Significant changes over time in (a) 3-Back omission scores, (b) 3-Back reaction time, (c) Stroop congruent condition reaction time, (d) Stroop incongruent condition reaction time, (e) Task Switching switch condition reaction time, (f) Task Switching no-switch condition reaction time. Numbers in parentheses refer to sessions with significantly different scores with Wilcoxon Signed Rank Test post-hoc and Bonferroni correction ($p < 0.0167$).

2003). The observed improved cognitive control in remitters in our study could be the result of the direct modulatory effect of HF rTMS over the DLPFC as part of the TPN and executive control network.

In the present study, remitters, on average, had lower baseline Ham-D scores (16.23) than non-remitters (21.08). This is in line with previous studies showing that patients with mild to moderate depression tend to respond better to rTMS treatment (Grammer et al., 2015). There were positive correlations between depression severity and reaction times in the Task Switching test both at baseline and at the end of treatment suggesting that, at least partially, the observed cognitive dysfunction in our study could be explained by the severity of depressive symptoms. Studies have shown that recurrent episodes of depression are associated with hippocampal atrophy (Schmaal et al., 2016; Sheline et al., 1996), potentially accounting for some of the observed cognitive dysfunctions in patients with MDD. In addition, anhedonia and lack of motivation are common symptoms in MDD that can affect task performance especially on tasks with more reliance on cognitive effort.

It is also possible that improvement of affective symptoms and cognitive impairment in MDD are not directly linked and may be independently mediated. In support of this assertion, a recent analysis of pooled cognitive results from different clinical trials found no link

between cognitive changes and mood improvements (Martin et al., 2017). While some previous studies have shown that successful treatment of depression by medications is associated with improvement in cognitive function (Constant et al., 2005), several others have demonstrated that MDD patients receiving pharmacological treatments targeted at improving their mood still show cognitive deficits even after going into remission (Conradi et al., 2011; Jaeger et al., 2006; Xu et al., 2012). Therefore, the degree of cognitive improvement during MDD treatment may depend on the treatment modality. In the present study, the strength of the correlation between Ham-D score and Task Switching RTs went from moderate at baseline to strong post-treatment, suggesting a potential decoupling of the improvement of depression and cognitive symptoms. rTMS may represent a treatment modality that can improve both depressive and cognitive symptoms in MDD, directly mediating cognitive improvement through stimulation of the left DLPFC while achieving its antidepressant effects through regulation of functional connectivity between the DMN and TPN. Future studies should address the possibility of decoupling of affective and cognitive symptoms in MDD and the mechanisms by which treatment modalities differentially affect their improvement.

The observed cognitive improvement across rTMS sessions could be due to a learning effect or increased task familiarity over time. Indeed, a practice effect in completing the Stroop task more rapidly has been well documented by several studies (Lemay et al., 2004; Salinsky et al., 2001), which may explain our observed improvement in Stroop RT for both remitters and non-remitters. However, observed improvements on other cognitive assessments are unlikely to be solely related to task familiarity given that non-remitters did not show similar improvements to those observed in remitters.

5. Limitations and future directions

Limitations of this study include the small sample size which prevents us from further analysis including the possible correlation between different sub-scores of the Ham-D scale and the cognitive task results. The baseline difference in Ham-D scores between remitters and non-remitters has additionally played a confounding role; With our current study design, it is difficult to ascertain decoupling between the potential role of rTMS vs. depression severity in improvement of cognitive function. Due to the small sample size we are limited in predicting treatment response to rTMS using cognitive measures, which is something that is highly sought-after due to the minimal cost and non-invasive nature of such tasks (Taylor et al., 2006). Future studies could look into employing tasks testing similar cognitive domains with a larger sample size and longitudinally tracking remitters after treatment in case of relapse.

6. Conclusion

In summary, our study shows a very distinct difference in baseline cognitive functions of eventual remitters to rTMS treatment. Patients with MDD who entered remission following rTMS treatment scored better on measures of cognitive control and shifting attention prior to treatment compared to non-remitters, and these observations were not attributable to differences in simple motor reaction time. Additionally, following successful treatment, remitters benefited from improvement in some aspects of their cognitive function in addition to an alleviation of their depressive symptoms. Future cohort studies with larger sample size will be helpful to identify the cognitive predicting factors of treatment outcome, which could potentially help with identifying good rTMS candidates before starting the time-consuming and labor intensive rTMS treatment.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

We would like to gratefully acknowledge the contributions of our sponsors including the University of Manitoba Start-Up Fund and the St. Boniface Hospital Foundation. We would also like to acknowledge Dr. Benjamin Prasad for his useful commentary and Sara Wikstrom for her role in patient care.

References

Alexopoulos, G.S., Kiosses, D.N., Heo, M., Murphy, C.F., Shanmugham, B., Gunning-Dixon, F., 2005. Executive dysfunction and the course of geriatric depression. Biol. Psychiatry 58 (3), 204–210.
Association, A.P., 2013. Diagnostic and Statistical Manual of Mental disorders: DSM-5, 5th ed. American Psychiatric Publishing, Arlington, VA [2013]©2013.
Bhalla, R.K., Butters, M.A., Mulsant, B.H., Begley, A.E., Zmuda, M.D., Schoderbek, B., Pollock, B.G., Reynolds, C.F., Becker, J.T., D.o.G.R.E.C.C.o.t.P.V.A.H.S.P.P., 2006. Persistence of neuropsychologic deficits in the remitted state of late-life depression. Am. J. Geriatr. Psychiatry 14 (5), 419–427.
Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., Lund, A., 2005. Executive function improvement upon remission of recurrent unipolar depression. Eur. Arch. Psychiatry Clin. Neurosci. 255 (6), 373–380.
Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5 (1), 49–62.
Buist-Bouwman, M.A., Ormel, J., de Graaf, R., de Jonge, P., van Sonderen, E., Alonso, J., Bruffaerts, R., Vollebergh, W.A., 2008. Mediators of the association between depression and role functioning. Acta Psychiatr. Scand. 118 (6), 451–458.
Conradi, H.J., Ormel, J., de Jonge, P., 2011. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol. Med. 41 (6), 1165–1174.
Constant, E.L., Adam, S., Gillain, B., Seron, X., Bruyer, R., Seghers, A., 2005. Effects of sertraline on depressive symptoms and attentional and executive functions in major depression. Depress. Anxiety 21 (2), 78–89.
Dotson, V.M., Resnick, S.M., Zonderman, A.B., 2008. Differential association of concurrent, baseline, and average depressive symptoms with cognitive decline in older adults. Am. J. Geriatr. Psychiatry 16 (4), 318–330.
Dunkin, J.J., Leuchter, A.F., Cook, I.A., Kasl-Godley, J.E., Abrams, M., Rosenberg-Thompson, S., 2000. Executive dysfunction predicts nonresponse to fluoxetine in major depression. J. Affect. Disord. 60 (1), 13–23.
Fabre, I., Galinowski, A., Oppenheim, C., Gallarda, T., Meder, J.F., De Montigny, C., Olie, J.P., Poirier, M.F., 2004. Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: an open trial. Int. J. Geriatr. Psychiatry 19 (9), 833–842.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U.S.A. 102 (27), 9673.
George, M.S., Lisanby, S.H., Sackeim, H.A., 1999. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch. Gen. Psychiatry 56 (4), 300–311.
Grammer, G.G., Kuhle, A.R., Clark, C.C., Dretsch, M.N., Williams, K.A., Cole, J.T., 2015. Severity of depression predicts remission rates using transcranial magnetic stimulation. Front. Psychiatry 6, 114.
Guse, B., Falkai, P., Wobrock, T., 2010. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J. Neural Transm. (Vienna) 117 (1), 105–122.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23 (1), 56–62.
Harvey, P.O., Le Bastard, G., Pochon, J.B., Levy, R., Allilaire, J.F., Dubois, B., Fossati, P., 2004. Executive functions and updating of the contents of working memory in unipolar depression. J. Psychiatr. Res. 38 (6), 567–576.
Hausmann, A., Pascual-Leone, A., Kemmler, G., Rupp, C.I., Lechner-Schoner, T., Kramer-Reinstadler, K., Walpoth, M., Mechtcheriakov, S., Conca, A., Weiss, E.M., 2004. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. J. Clin. Psychiatry 65 (6), 772–782.
Iordan, A.D., Dolcos, S., Dolcos, F., 2013. Neural signatures of the response to emotional distraction: a review of evidence from brain imaging investigations. Front. Hum. Neurosci. 7, 200.
Jaeger, J., Berns, S., Uzelac, S., Davis-Conway, S., 2006. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res. 145 (1), 39–48.
Jaeggi, S.M., Buschkuehl, M., Perrig, W.J., Meier, B., 2010. The concurrent validity of the N-back task as a working memory measure. Memory 18 (4), 394–412.
Johnson, K.A., Baig, M., Ramsey, D., Lisanby, S.H., Avery, D., McDonald, W.M., Li, X., Bernhardt, E.R., Haynor, D.R., Holtzheimer 3rd, P.E., Sackeim, H.A., George, M.S., Nahas, Z., 2013. Prefrontal rTMS for treating depression: location and intensity results from the OPT-TMS multi-site clinical trial. Brain Stimul. 6 (2), 108–117.
Kampf-Sherf, O., Zlotogorski, Z., Gilboa, A., Speedie, L., Lereya, J., Rosca, P., Shavit, Y., 2004. Neuropsychological functioning in major depression and responsiveness to selective serotonin reuptake inhibitors antidepressants. J. Affect. Disord. 82 (3), 453–459.
Kaur, M., Naismith, S.L., Lagopoulos, J., Hermens, D.F., Lee, R.S.C., Carpenter, J.S., Fitzgerald, P.B., Hoy, K.E., Scott, E.M., Hickie, I.B., 2019. Sleep-wake, cognitive and clinical correlates of treatment outcome with repetitive transcranial magnetic stimulation for young adults with depression. Psychiatry Res. 271, 335–342.

Kessler, R.C., Merikangas, K.R., Wang, P.S., 2008. The prevalence and correlates of workplace depression in the national comorbidity survey replication. J. Occup. Environ. Med. 50 (4), 381–390.
Kessler, R.C., Petukhova, M., Sampson, N.A., Zaslavsky, A.M., Wittchen, H.-U., 2012. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int. J. Methods Psychiatr. Res. 21 (3), 169–184.
Lee, R.S., Hermens, D.F., Porter, M.A., Redoblado-Hodge, M.A., 2012. A meta-analysis of cognitive deficits in first-episode major depressive disorder. J. Affect. Disord. 140 (2), 113–124.
Lemay, S., Bedard, M.A., Rouleau, I., Tremblay, P.L., 2004. Practice effect and test-retest reliability of attentional and executive tests in middle-aged to elderly subjects. Clin. Neuropsychol. 18 (2), 284–302.
Loo, C.K., Mitchell, P.B., McFarquhar, T.F., Malhi, G.S., Sachdev, P.S., 2007. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol. Med. 37 (3), 341–349.
MacLeod, C.M., 1991. Half a century of research on the stroop effect: an integrative review. Psychol. Bull. 109 (2), 163–203.
Martin, D.M., McClintock, S.M., Forster, J.J., Lo, T.Y., Loo, C.K., 2017. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with depression: a systematic review and meta-analysis of individual task effects. Depress. Anxiety 34 (11), 1029–1039.
Martis, B., Alam, D., Dowd, S.M., Hill, S.K., Sharma, R.P., Rosen, C., Pliskin, N., Martin, E., Carson, V., Janicak, P.G., 2003. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin. Neurophysiol. 114 (6), 1125–1132.
Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. 9 (3), 471–481.
McClintock, S.M., Reti, I.M., Carpenter, L.L., McDonald, W.M., Dubin, M., Taylor, S.F., Cook, I.A., O'Reardon, J., Husain, M.M., Wall, C., Krystal, A.D., Sampson, S.M., Morales, O., Nelson, B.G., Latoussakis, V., George, M.S., Lisanby, S.H., 2018. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry 79 (1).
Mitterschiffthaler, M.T., Williams, S.C., Walsh, N.D., Cleare, A.J., Donaldson, C., Scott, J., Fu, C.H., 2008. Neural basis of the emotional stroop interference effect in major depression. Psychol. Med. 38 (2), 247–256.
Modirrousta, M., Meek, B.P., Wikstrom, S.L., 2018. Efficacy of twice-daily vs once-daily sessions of repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: a retrospective study. Neuropsychiatr. Dis. Treat. 14, 309–316.
Reppermund, S., Ising, M., Lucae, S., Zihl, J., 2009. Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. Psychol. Med. 39 (4), 603–614.
Richieri, R., Jouvenoz, D., Verger, A., Fiat, P., Boyer, L., Lancon, C., Guedj, E., 2017. Changes in dorsolateral prefrontal connectivity after rTMS in treatment-resistant depression: a brain perfusion SPECT study. Eur. J. Nucl. Med. Mol. Imaging 44 (6), 1051–1055.
Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med. 44 (10), 2029–2040.
Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive mechanisms of treatment in depression. Neuropsychopharmacology 37 (1), 117–136.
Salinsky, M.C., Storzbach, D., Dodrill, C.B., Binder, L.M., 2001. Test-retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12-16-week period. J. Int. Neuropsychol. Soc. 7 (5), 597–605.
Schmaal, L., Veltman, D.J., van Erp, T.G., Samann, P.G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W.J., Vernooij, M.W., Ikram, M.A., Wittfeld, K., Grabe, H.J., Block, A., Hegenscheid, K., Volzke, H., Hoehn, D., Czisch, M., Lagopoulos, J., Hatton, S.N., Hickie, I.B., Goya-Maldonado, R., Kramer, B., Gruber, O., Couvy-Duchesne, B., Renteria, M.E., Strike, L.T., Mills, N.T., de Zubicaray, G.I., McMahon, K.L., Medland, S.E., Martin, N.G., Gillespie, N.A., Wright, M.J., Hall, G.B., MacQueen, G.M., Frey, E.M., Carballedo, A., van Velzen, L.S., van Tol, M.J., van der Wee, N.J., Veer, I.M., Walter, H., Schnell, K., Schramm, E., Normann, C., Schoepf, D., Konrad, C., Zurowski, B., Nickson, T., McIntosh, A.M., Papmeyer, M., Whalley, H.C., Sussmann, J.E., Godlewska, B.R., Cowen, P.J., Fischer, F.H., Rose, M., Penninx, B.W., Thompson, P.M., Hibar, D.P., 2016. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. Mol. Psychiatry 21 (6), 806–812.
Sheline, Y.I., Wang, P.W., Gado, M.H., Csernansky, J.G., Vannier, M.W., 1996. Hippocampal atrophy in recurrent major depression. Proc. Natl. Acad. Sci. U. S. A. 93 (9), 3908–3913.
Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18 (6), 643.
Taylor, B.P., Bruder, G.E., Stewart, J.W., McGrath, P.J., Halperin, J., Ehrlichman, H., Quitkin, F.M., 2006. Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. Am. J. Psychiatry 163 (1), 73–78.
van Randenborgh, A., Hüffmeier, J., Victor, D., Klocke, K., Borlinghaus, J., Pawelzik, M., 2012. Contrasting chronic with episodic depression: an analysis of distorted socio-emotional information processing in chronic depression. J. Affect. Disord. 141 (2–3), 177–184.
Xu, G., Lin, K., Rao, D., Dang, Y., Ouyang, H., Guo, Y., Ma, J., Chen, J., 2012. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J. Affect. Disord. 136 (3), 328–339.
Yu, Y., Yu, Y., Lin, Y., 2019. Anxiety and depression aggravate impulsiveness: the mediating and moderating role of cognitive flexibility. Psychol. Health Med. 1–12.