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Moving away from depression: Physical activity changes in patients undergoing r-TMS for major depressive disorder

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A B S T R A C T

Background: Physical activity (PA) may predict or mark successful treatment from major depressive disorder after repeated-transcranial magnetic stimulation (r-TMS).
Objectives: To explore if r-TMS treatment responders were more physically active than non-responders at baseline, and to determine if treatment responders increased PA compared to non-responders post-treatment.
Methods: Thirty subjects were included in the study. PA was measured through Actical accelerometers. Baseline PA levels were compared through separate independent t-tests, whereas post-treatment changes were compared through separate ANCOVAs.
Results: There were no differences in PA at baseline between groups. Controlling for baseline PA levels, ANCOVAs identified a non-significant treatment effect between moderate-to-vigorous physical activity levels post-treatment between groups [$p = 0.276$, $\eta^2 = 0.044$]. A significant treatment effect was found between groups for light physical activity favouring responders [$p = 0.009$, $\eta^2 = 0.226$].
Conclusion: Responders' LPA significantly increased in comparison to non-responders receiving r-TMS for major depressive disorder.

1. Introduction

Major depressive disorder (MDD) is common and debilitating to everyday life (Ravindran et al., 2016; World Health Organization, 2018). According to the World Health Organization, over 300 million people are affected by depression globally (World Health Organization, 2018). Depression is commonly treated through antidepressant medication and/or psychological therapy. However, approximately 30% of people with depression do not respond to first-line treatments (Fava, 2003). Treatment-resistant depression is a major clinical concern with a significant burden for patients, their families, and the health care system.

Repeated transcranial magnetic stimulation (r-TMS) has shown success in treating traditional treatment-resistant individuals with MDD (Sehatzadeh et al., 2019). Furthermore, levels of habitual physical activity (PA) before starting treatment may predict the success of MDD treatment, and through treatment, habitual PA may increase and serve as a marker of successful treatment (Hallgren et al., 2016). These possibilities have received little research attention. A systematic review of RCTs of psychological treatments for depression found that PA was not assessed as an outcome in any of the identified trials (Cuijpers, Wit, & Taylor, 2014). A recent study reported that patients who routinely engaged in high levels of self-reported physical activity at baseline responded more favourably to cognitive behavioral therapy focused depression treatment compared to adults who engaged in low-to-moderate levels of activity (Hallgren et al., 2016). Changes in physical activity over the course of treatment were not assessed.

In the context of r-TMS treatment, an open-label study found an increase in mean steps per day measured by the FS-750 actigraph between baseline and the first week of treatment, but no difference between baseline and end of treatment after three weeks (Nishida, Kikuchi, Nisijima, & Suda, 2017). As Cuijper and colleagues (2014)

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Table 1
Demographic and clinical characteristics.

	Non-Responders	Responders	Total	P value
Age [a]	44.21 (11.26)	43.25 (13.21)	43.70 (12.09)	.729
Percent Female [b]	50	56.25	53.33	.732
Duration of Education (years) [a]	15.29 (2.13)	15.50 (2.58)	15.4 (2.34)	.808
Percent receiving iTBS [b]	42.86	56.25	50	.464
LPA Baseline [a]	390.92 (135.23)	332.36 (84.88)	362.90 (112.95)	.157
LPA Post-Treatment [c]	338.32 (102.34)	380.58 (83.17)	360.86 (93.45)	**.009**
MVPA Baseline [a]	35.44 (27.17)	24.99 (34.41)	29.57 (25.62)	.269
MVPA Post-Treatment [c]	21.62 (23.16)	25.39 (28.99)	23.63 (26.06)	.276
17-HRSD Baseline [a]	21.86 (1.70)	22 (3.74)	21.93 (2.92)	.897
17- HRSD Post Treatment [a]	15.57 (3.57)	3.81 (2.63)	9.30 (6.70)	**.000**
Age at Onset [a]	23.14 (9.60)	24.25 (12.21)	23.73 (10.90)	.787
Number of Years with Depression [a]	21.07 (9.15)	19.06 (10.27)	20.00 (9.80)	.553
Length of Current Episode [a]	25.61 (22.01)	29.63 (32.09)	27.83 (27.62)	.705
Percent on Benzodiazepine [b]	42.85	13.33	26.66	.057
Equivalent Escitalopram Dose [a] (mg)	12.50 (14.85)	25.26 (18.41)	19.54 (17.82)	.054

NOTE. Data are presented in mean (SD) or percent of total. iTBS = intermittent theta burst stimulation. The 17-HRSD = 17-item Hamilton Rating Scale for Depression. LPA = light physical activity. MVPA = moderate to vigorous physical activity. Equivalent escitalopram dose standardizes different antidepressants to one comparable measure and is based on dose equivalent antidepressant reviews (Hayasaka et al., 2015; Inada & Inagaki, 2015). **Bold font** = statistically significant result. [a] = independent *t*-test to detect significance. [b] = chi-squared test to detect significance. [c] = ANCOVA to detect significance.

noted, it is remarkable that there is so little evidence on whether treatments for depression among adults have an impact on physical activity and whether changes in physical activity mediate the outcomes of these treatments. Further research is required in understanding the co-variation of PA with depression treatment response.

2. Objectives

The objectives of this study were to explore if treatment responders were more physically active than non-responders at baseline and to determine if treatment responders increased PA compared to non-responders who were receiving r-TMS for MDD.

3. Methods

The current study is a secondary analysis from a subset of participants from the University of British Columbia site of the THREE-D randomized control trial (standard high frequency vs. intermittent theta burst stimulation (iTBS; Blumberger, Vila-Rodriguez, Feffer, & Noda, 2018)). As indicated by Blumberger et al. (2018) two separate meta-analyses have provided evidence for the superiority of iTBS over a sham condition in the treatment of depression (Berlim, McGirr, Rodrigues dos Santos, Tremblay, & Martins, 2017; Daskalakis et al., 2016). As such, the THREE-D non-inferiority randomized control trial did not include a sham condition. The THREE-D trial (ClinicalTrials.gov, number NCT01887782) was approved by the institutional ethics board, and all patients provided informed consent. Participants were randomized to either receive four to six weeks of conventional r-TMS or iTBS. In the standard r-TMS treatment arm, individuals received the most common form of r-TMS (10 Hz; 4 s ON and 26 s OFF, for a total of 3000 pulses per session; 37.5 min in duration) to the left dorsolateral prefrontal cortex (L-DLPFC). In the iTBS arm, participants underwent triplet 50 Hz bursts repeated at 5 Hz; 2 s ON and 8 s OFF for a total of 600 pulses per session; 3 min and 9 s in duration) to the L-DLPFC.

Depression was measured pre and post using the 17-item Hamilton Rating Scale for Depression (17-HRSD; Hamilton, 1967). Actical accelerometery data assessing the intensity and duration of PA was collected at two separate time points. First, a "baseline" measurement was obtained during the first 10 treatments (2 weeks) and for a week post-treatment (after approximately 6 weeks). Accelerometry analysis was performed in RStudio (v1.1.453; R v3.4.4) with package "PhysicalActivity" (v0.2.2) to apply a wear validation algorithm (Choi, Liu, Matthews, & Buchowski, 2011) and "acc: Exploring Accelerometer Data" (v1.3.3) to quantify PA intensity.

Only days with ≥600 min of wear time were analyzed. PA was characterized as either light physical activity (LPA) which is classified by any waking behaviour in the 1.5–3 metabolic equivalents (METs) range (Haskell et al., 2007) or moderate-to-vigorous physical activity (MVPA) which is any waking behaviour greater or equal to 3.0 METs (Haskell et al., 2007). PA intensity cut points for accelerometry were set to 100–1534 counts per minute for LPA and ≥1535 for MVPA in line with Actical analysis performed with the Canadian Health Measures Survey (Colley et al., 2011).

Demographic comparisons between groups were conducted with a chi-squared test for categorical data (e.g. sex) or an independent *t*-test for continuous data (e.g. age and baseline PA). Separate ANCOVAs were completed to examine if the light physical activity (LPA) or moderate to vigorous physical activity (MVPA) were different post-treatment between the responders and non-responders controlling for baseline PA levels. Furthermore, demographic comparisons between groups were conducted through a chi-squared test for categorical data (e.g. sex) or an independent *t*-test for continuous data (e.g. age and baseline PA). The significance level was set at $\alpha < 0.05$.

4. Results

Thirty patients at the UBC site were compared. All demographic information can be found in Table 1. There were no significant differences between the two groups. Responders (n = 16) were classified as individuals who had at least a 50% reduction in depressive symptoms at the end of treatment (with a baseline score of ≥18 on the 17-HRSD); therefore, fourteen patients were classified as non-responders based on the THREE-D trial protocol. The mean (*sd*) treatment length for responders was 6 (*0*) weeks and 5.29 (*0.99*) for the non-responders. A significant difference in treatment length was observed between groups [t (28) = 2.880, p = 0.008, d = 1.015]. The mean (*sd*) for wear time for responders was 1232.06 (*131.71*), and non-responders was 1281.99 (*67.81*). This difference was non-significant [*t* (31) = 1.356, p = 0.146, d = 0.476].

MVPA was not significantly different between groups at baseline [*t* (29) = 1.128, *p* = 0.269, d = 0.405]. LPA was not significantly different between groups at baseline [*t* (29) = 1.454, *p* = 0.157, d = 0.519]. Controlling for baseline PA levels, ANCOVAs identified a non-significant treatment effect between MVPA levels post-treatment between groups [F (1,28) = 1.238, *p* = 0.276, $\eta^2 = 0.044$] (see Fig. 1). A significant treatment effect was found between groups for LPA favouring the responders [F (1,28) = 7.887, *p* = 0.009, $\eta^2 = 0.226$] with an increase of approximately 55 min per day of LPA (see Fig. 2).

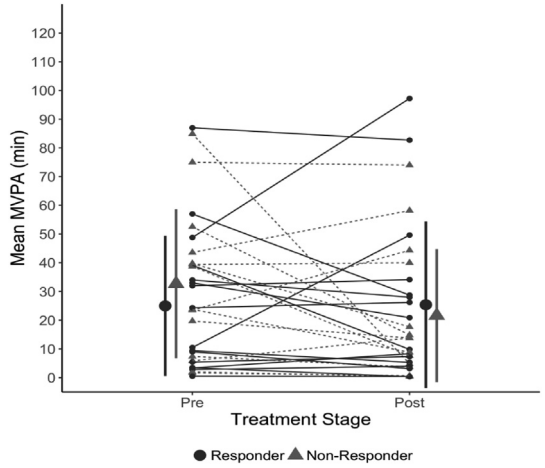

Fig. 1. MVPA patterns at baseline and post r-TMS treatment for responders and non-responders.

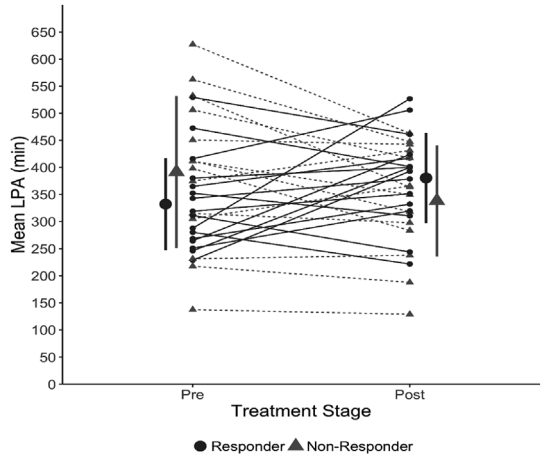

Fig. 2. LPA patterns at baseline and post-rTMS treatment for responders and non-responders.

5. Discussion

This study quantified PA changes throughout r-TMS treatment between responders and non-responders with treatment-resistant depression. There were no baseline PA differences (for LPA or MVPA) between the responders and non-responders. Notably, both groups were quite active at baseline with most meeting Canadian PA guidelines of 150 min per week of MVPA (m = 34.16 min/day for non-responders and m = 24.99 min/day for responders; Tremblay et al., 2011). This is atypical as individuals with MDD frequently report low levels of MVPA (Schuch et al., 2016). It is speculated that the high levels of MVPA may be due to active transportation to the laboratory five out of seven days a week for treatment. However, data on mode or timing of physical activity was not collected and could be further explored moving forward. Responders to r-TMS treatment significantly increased participation in LPA but not MVPA, and the effect was large. This is in contrast to findings described by Nishida et al. (2017) where after an initial increase in steps there was no difference compared to baseline after treatment. Simply, our findings indicate that patients moved more after r-TMS treatment and this may reinforce the treatment effect. LPA contributes significant health benefits independent of those provided by MVPA (Füzéki, Engeroff, & Banzer, 2017; LaMonte et al., 2007). It is speculated that MVPA did not increase for the responders as no PA intervention was applied during this trial. Direct intervention may be required to increase MVPA (e.g., aerobic exercise; playing sports) in comparison to LPA (i.e., walking, housework, gardening). It is speculated, that upon responding to r-TMS or iTBS, an MVPA intervention may be suitable as responders are beginning to move more albeit at a lower intensity. Finally, the neurophysiological profile changes that typically occur during both brain stimulation and exercise treatment (i.e., increases in brain-derived neurotrophic factor, norepinephrine and decreases in cortisol; Noda et al., 2015; Szuhany, Bugatti, & Otto, 2015; Wegner et al., 2014) may lay the foundation for cumulative effects.

These findings highlight the value in assessing PA during the treatment of MDD as an increase in PA may reflect a positive treatment response. It is important to highlight that as a secondary analysis it is likely the analysis was underpowered while the long-term effect of treatment on PA was not assessed. Future work should systematically examine the role of PA before, during and after depression treatments as important synergistic mechanisms may be at play in the treatment of MDD.

Declaration of interest

MF has no interests to declare. GF reports research grants from the Canadian Institutes of Health Research and also receives support through a Canadian Institutes of Health Research-Public Health Agency of Canada (CIHR-PHAC) Chair in Applied Public Health. LY is supported by a MITACS Accelerate award. MD is supported by a CIHR Doctoral Award. DB reports research grants from the Canadian Institutes of Health Research, US National Institutes of Health, Weston Brain Institute, Brain Canada, the Temerty Family Foundation (through the Centre for Addiction and Mental Health Foundation and the Campbell Research Institute), and Brainsway; reports receiving in-kind equipment support for investigator-initiated studies (including this study) MagVenture; is the site principal investigator for three sponsor-initiated studies for Brainsway; and has been on an advisory board for Janssen Pharmaceutical. FV-R reports research grants from CIHR, Brain Canada, Michael Smith Foundation for Health Research, and Vancouver Coastal Health Research Institute; reports receiving in-kind equipment support for this investigator-initiated trial from MagVenture; and has been on an advisory board for Janssen. ZJD reports research grants and equipment in-kind support for an investigator-initiated study from Brainsway and Magventure. JD reports research grants from CIHR, the National Institute of Mental Health, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Weston Foundation, the Klarman Family Foundation, the Arrell Family Foundation, and the Buchan Family Foundation, travel stipends from Lundbeck and ANT Neuro, in-kind equipment support for investigator-initiated trials from MagVenture, and is an advisor for BrainCheck, TMS Neuro Solutions, and Restorative Brain Clinics.

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