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Sleep-wake, cognitive and clinical correlates of treatment outcome with repetitive transcranial magnetic stimulation for young adults with depression

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A B S T R A C T

The utility of key phenotypes of depression in predicting response to repetitive transcranial magnetic stimulation (rTMS), namely sleep-wake behaviour, cognition and illness chronicity, has been understudied and not been extended to young samples. This study aimed to determine whether sleep-wake disturbance, cognition or depression chronicity are associated with rTMS outcome in young depressed adults. Sixteen depressed young adults diagnosed with mood disorders (aged 18–29 years) completed this open-label study. Neuronavigationally targeted high-frequency rTMS was administered at 110% of motor threshold on the left dorsolateral prefrontal cortex for 20 sessions over 4 weeks. Clinical, sleep-wake and cognitive assessments were undertaken pre- and post-treatment. Repeated-measures and correlational analyses determined pre- and post-treatment changes and predictors of treatment outcome. rTMS significantly reduced depression and anxiety. Better cognitive flexibility, verbal learning, later age of onset and greater number of depressive episodes were associated with better treatment outcome. There were no other significant/trend-level associations. rTMS had no effect on sleep-wake or cognitive measures. We provide the first evidence for the utility of cognitive flexibility and verbal learning in predicting rTMS outcome in depressed young adults. This research provides preliminary support for rTMS as an early intervention for depression and supports the need for sham-controlled trials.

1. Introduction

An earlier age of illness onset (Allen et al., 2007) and a greater number of depressive episodes (Berwian et al., 2017; Bockting et al., 2015) are robust predictors of recurrence and relapse of depression. The delivery of treatments early in the course of illness results in better response outcomes and can prevent onset of chronic illness (Lee et al., 2012; McGorry et al., 2006). To this end, developing and evaluating optimal early intervention strategies for depression is imperative. High-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) is efficacious for refractory depression (Kedzior and Reitz, 2014) and preliminary research is now emerging to show that rTMS may be effective as an early intervention for youth depression (Bloch et al., 2008; Huang et al., 2012; Wall et al., 2011). Response rates in clinical trials of rTMS for treatment-resistant depression range from 30% (Berlim et al., 2013) to 50% (Ren et al., 2014) and identifying predictors of response is critical to reduce the burden (in terms of time and expense) of non-response on individuals and services. Efforts towards understanding this variability in chronic depression have been growing and have largely focused on using neurophysiology and imaging to identify predictors of response (Arns et al., 2012; Fox and Pascual-Leone, 2012; Weigand et al., 2018). However, there is a paucity of investigations into the utility of clinical (e.g., illness chronicity, sleep-wake/circadian changes) and cognitive features (e.g., episodic memory) in predicting rTMS treatment outcome for depression. Furthermore, this type of research has not yet been extended to adolescent or young adult depression populations, an important step towards evaluating rTMS as an early intervention approach.

Sleep-wake disturbance is among the most common symptoms of depression (Benca et al., 1992). In mood disorders, sleep disturbance corresponds with poorer pharmacological and psychosocial treatment

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outcomes (Manglick et al., 2013) and, often persists even when mood symptoms have remitted (Geoffroy et al., 2014; van Mill et al., 2010). Whether sleep-wake disturbance can be normalised by rTMS treatment or has utility in informing rTMS treatment outcomes for depression is unclear. Effects of rTMS treatment in this regard remains equivocal, with rTMS being linked to improved sleep (Brakemeier et al., 2007; Nishida et al., 2017; Pellicciari et al., 2013) as well as having no effect on sleep (Antczak et al., 2017; Brakemeier et al., 2008; Lowe et al., 2013; Rosenquist et al., 2013). Notably, most of these investigations are limited by the use of symptomatic sleep data rather than objective measures of sleep-wake behaviour. Three studies have, however, utilised polysomnography (Pellicciari et al., 2013) or actigraphy (Antczak et al., 2017; Nishida et al., 2017) to investigate the effect of rTMS treatment for depression on sleep-wake behaviour. No change in sleep-wake variables were noted in these studies (Antczak et al., 2017; Nishida et al., 2017), except for one finding of a trend-level improvement with rTMS in wakefulness after sleep onset (Pellicciari et al., 2013). These studies included older cohorts with mean ages of 45 years or older, a potential reason for the null findings given that sleep-wake disruption is age related in mood disorders. Specifically, younger people with mood disorders present with delayed sleep-wake patterns, more sleep disturbance and poorer consolidation of sleep compared with older people, suggestive of different aberrations in underlying circadian processes across depressive age groups (Robillard et al., 2013, 2014). As such, further evaluation of objective sleep-wake measures as potential predictors of rTMS treatment response for depression is required.

Similarly, the utility of cognition in informing outcomes of rTMS treatment for depression has not been comprehensively investigated. However, rTMS-associated improvements in cognition reportedly occur prior to any improvements in mood and are predictive of favourable rTMS outcome for chronic depression (Hoy et al., 2012). Typically, cognitive deficits are apparent before or at the time of illness onset (Lee et al., 2012) and we have previously shown that neuropsychological functioning is a robust predictor of longitudinal functioning, over and above symptomatology, in young psychiatric patients (Lee et al., 2013). Given this, evaluating the association between cognitive functioning and improvements in depression following rTMS in young people may be important, in terms of predictive utility. Of note, improvements in cognition with rTMS treatment for depression have been frequently demonstrated in chronic patients (Hoy and Fitzgerald, 2010) and more recently, in adolescents (Huang et al., 2012; Wall et al., 2013). Commensurate with cognitive deficits, impaired psychosocial functioning in depression (which is subserved by cognitive, emotional and social cognitive elements) can often persist despite symptomatic recovery and is associated with long term prognosis (Knight and Baune, 2017; Tohen et al., 2000). Despite that recovery of psychosocial functioning has been understudied in the rTMS depression literature, small to moderate improvements in quality of life have been noted with rTMS (Dumas et al., 2012). Evaluating psychosocial functioning change in addition to symptom change with rTMS would provide a more global assessment of recovery of depression and is of particular significance in adolescents or young adults people given the importance of educational and occupational performance in this patient group.

There are some data suggesting that rTMS treatment may be more effective at early illness stages of depression rather than at chronic stages. A series of studies have reported that younger age is associated with better response in people with depression (Aguirre et al., 2011; Figiel et al., 1998; Fregni et al., 2006; Pallanti et al., 2012; Rostami et al., 2017). Some of these studies were on older (i.e. 50 years or older) cohorts (Fregni et al., 2006; Pallanti et al., 2012) and for those that compared younger and older groups, the age groups were defined as younger or older than 45 (Aguirre et al., 2011) and, younger or older than 60 (Pallanti et al., 2012) years old. Given that about 50% of people with depression will experience their first episode before 30 years of age (Kessler et al., 2005), the extant literature is limited in informing whether rTMS may be better targeted to those at early stages of depression. Other work supporting rTMS as an early intervention approach analysed clinical measures of chronicity and severity of illness revealing that better response with rTMS was achieved by those with a later age of onset, shorter duration of illness, lower baseline score of depression (Fitzgerald et al., 2016) and who are less medication refractory (Fregni et al., 2006). Nevertheless, these studies included chronic depression samples with broad age ranges and it is unclear whether a similar pattern of associations would be observed in younger, early stage depression patients to whom early interventions would typically be provided for.

The primary objective of the present study was to determine whether sleep-wake and cognitive measures are associated with outcome of rTMS treatment for depression in young adults. In addition, in a young adult sample, we explored the relationship between measures of illness chronicity (i.e. age of onset, duration of illness and number of depressive episodes) and improvements in depression with rTMS. Lastly, we sought to determine if there are improvements in sleep-wake disturbance, cognition and psychosocial functioning with rTMS in addition to improvements in depressive symptoms in a young adult cohort.

2. Methods

2.1. Participants

Participants aged 18–30 years old were recruited from a specialised inpatient and outpatient early intervention for mental health problems facility, the Young Adult Mental Health Service at St Vincent's Private Hospital, Sydney, Australia. All participants had a primary diagnosis of a mood (i.e. depressive or bipolar) disorder as determined by their treating psychiatrist, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria. All patients were receiving clinician-based case management. Participants underwent clinical interviews, actigraphy monitoring, neuropsychological assessments and MRI scanning within 2 weeks pre-treatment (mean days before treatment $= 5.1 \pm 3.8$). Participants underwent clinical interviews, actigraphy monitoring and neuropsychological assessments within 4 weeks post-treatment (mean days after treatment $= 10.1 \pm 6.2$). Participants visited the Brain and Mind Centre, University of Sydney for all pre- and post-treatment research assessments. rTMS treatment was conducted at the Young Adult Mental Health Service, St Vincent's Private Hospital. Written informed consent was obtained from all participants and the study was approved by the St Vincent's Hospital (Sydney) and University of Sydney Human Research Ethics Committees.

Inclusion criteria were: (i) diagnoses of a mood disorder with a current moderate to severe depressive episode according to The Quick Inventory of Depressive Symptomatology (score of 10 or more) (Rush et al., 2003) that was stable over a 2-week period (as determined by weekly QIDS assessments), (ii) failure to respond to a minimum of two adequate trials of antidepressant medication (i.e. at least four weeks of treatment at a therapeutic dose as determined by the study psychiatrist, ES) and, (iii) that medications were stabilised for at least 2 weeks before treatment and throughout the treatment course. Participants were excluded if they were pregnant or lactating, had current psychosis or mania, severe restrictive eating disorders, substance use disorders, a major developmental disorder (e.g. autism), a diagnosis of epilepsy or history of seizure in the last 5 years, any other neurological illness or medical illness impacting brain function, intellectual disability or inability to provide informed consent, a history of a sustained head injury (loss of consciousness for more than 30 min), insufficient English for assessment or, a contraindication to MRI scanning and/or TMS including but not limited to the presence of implanted metallic components in the cranium, a pacemaker, cochlear implant, medication pump or other electronic device. No medication changes were permitted during the rTMS treatment course and participants were

Table 1
Diagnoses and current medications for each participant. *Note*: 1 = primary; MDD = major depressive disorder; BP = bipolar disorder; GAD = generalised anxiety disorder; SAD = social anxiety disorder; OCD = obsessive compulsive disorder; BPD = borderline personality disorder, and; ADHD = attention deficit hyperactivity disorder.

	1° Diagnosis	Other diagnoses	Antidepressants	Mood stabilizers/anticonvulsants	Antipsychotics	Other medications
1	MDD	Nil	Phenelzine, Agomelatine	Nil	Quetiapine	Nil
2	MDD	GAD, Asperger's Syndrome	Nortriptyline	Lamotrigine	Quetiapine	Nil
3	MDD	Nil	Duloxetine	Nil	Nil	Nil
4	MDD	OCD	Duloxetine	Nil	Quetiapine	Nil
5	MDD	Nil	Duloxetine, Agomelatine	Nil	Nil	Nil
6	MDD	Nil	Venlafaxine, Agomelatine	Lamotrigine	Nil	Nil
7	MDD	GAD	Nil	Nil	Nil	Nil
8	MDD	Nil	Nortriptyline	Nil	Olanzapine	Nil
9	MDD	GAD	Venlafaxine	Pregabalin	Quetiapine	Nil
10	MDD	SAD	Nil	Nil	Nil	Nil
11	MDD	GAD	Agomelatine	Nil	Nil	Nil
12	MDD	Nil	Nortriptyline	Lamotrigine	Nil	Nil
13	BP II	BPD, GAD	Duloxetine	Lamotrigine	Nil	Modafinil
14	BP II	Nil	Nil	Nil	Nil	Modafinil
15	BP II	GAD	Nil	Pregabalin	Nil	Nil
16	BP II psychosis	BPD, ADHD	Nil	Nil	Asenapine	Methylphenidate

withdrawn from the trial if their treating psychiatrist determined a medication change was necessary. There were no exclusion criteria relating to type of psychotropic medications used.

Out of the twenty-one participants that were recruited into the study, sixteen participants (mean age = 22 ± 3.9; age range = 18–29; 15 females; 12 inpatients) completed the minimum of pre-treatment clinical assessment, rTMS treatment and post-treatment clinical assessment. Six participants dropped out of the trial ($n = 2$ became too unwell and required other treatment, $n = 2$ changed their mind, $n = 1$ was unable to sustain inpatient status and, $n = 1$ did not return for post-treatment clinical assessment). One of the participants who dropped out because they were too unwell, re-entered the trial at a later date. All 16 participants completed pre- and post-treatment neuropsychological assessment. Fourteen completed/had valid pre-treatment actigraphy data, however, only 9 participants completed/had valid post-treatment actigraphy data. Primary diagnosis, comorbid diagnoses and medication list for each participant is shown in Table 1.

2.2. Magnetic resonance imaging and neuronavigation for site of stimulation localisation

Participants underwent MRI scanning on a 3-Tesla GE MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) with five fiducial markers which were placed on the left and right pre-auricular points, nasion, inion and vertex. To enable neuroanatomical analysis at high resolution (0.9 mm isotropic resolution), a customised MP-RAGE 3D T1-weighted sequence with the following parameters was acquired: repetition time (TR) = 7264 ms; echo time (TE) = 2784 ms; flip angle = 15°; coronal orientation; field of view (FOV) = 230 mm; acquisition matrix = 256 × 256; total slices = 196.

Standard procedure using the Acsension TrakSTAR (Acsension Technology Corporation, VT, USA) was used for site of stimulation localisation together with the MRIcro/MRIreg package in order to import individual MRI scans to co-register with corresponding individuals head geometry, as previously published (Fitzgerald et al., 2009). Once co-registration of the chosen points was completed, MRIcro/MRIreg tracker mode was enabled to identify the location on the scalp that was most proximal to a cortical brain site on the 3D scan identified as the target site for stimulation. The left middle frontal gyrus (the corresponding region of the junction of Brodman areas 9 and 46) was chosen as the stimulation site, in line with previous literature (Fitzgerald et al., 2009; Paus and Barrett, 2004). The left middle frontal gyrus was identified on each MRI scan by a trained research psychologist (MK) supervised by a neuroimaging specialist (JL). The matching site on the scalp was then marked with a surgical pen and was used as the site of rTMS treatment.

2.3. Repetitive transcranial magnetic stimulation treatment

Stimulation was delivered using a MagVenture MagPro R30 (MagVenture, Denmark) with 70 mm figure of 8 coil secured in place by the super flexible arm. The TMS coil was positioned with the centre of the coil in contact with the head and at a 45° angle from the midline, with the coil handle facing backwards and away from the midline. The standard method for visual determination of resting motor threshold was employed (Fitzgerald et al., 2009; Pridmore et al., 1998). For rTMS treatment, 50 trains of 5 s duration with an inter-train interval of 25 s was administered at 10 Hz and 110% of resting motor threshold to the left DLPFC. Participants received 20 rTMS sessions over 4 weeks following 5-day on and 2-day off schedule.

2.4. Clinical and neuropsychological assessment

Trained research psychologists conducted clinical interviews and neuropsychological assessments (MK, RSCL). Clinical information was collected (i.e. age of onset, duration of illness and number of depressive episodes) and symptom scales were administered during pre-treatment assessment, Symptom scales were, the Hamilton Depression Rating Scale (HDRS, 17-item) (Hamilton, 1967) to quantify depressive symptoms, the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) to quantify overall psychiatric symptoms and the Social and Occupational Functioning Assessment Scale (SOFAS) to assess psychosocial functioning. The BPRS depression sub-score was empirically derived as a secondary measure of depressive symptoms. Specific cognitive domains assessed in this study were verbal learning and memory (Wall et al., 2013) and, cognitive flexibility (Huang et al., 2012) in keeping with previous reports of cognitive improvements with rTMS in depressed youth. Cognitive flexibility was assessed via the Trail-Making Test, part B (TMT-B) (Franzen et al., 1990) and, verbal learning and memory were assessed by the Rey Auditory Verbal Learning Test (RAVLT) sum of trial 1–5 (RAVLT sum) and 20 min delayed recall (RAVLT A7), respectively (Taylor, 1959). Neuropsychological variables were converted to demographically corrected z-scores using established norms (Rickert and Senior, 1998; Tombaugh et al., 1998). Each participant was tested using standard and alternate forms of TMT and RAVLT to limit practice effects and the order of form versions were counterbalanced across participants.

2.5. Sleep-wake assessment

All participants wore an actigraphy device on their non-dominant wrist for approximately 10 days (GENEActiv, Activinsights, Kimbolton, UK; 50 Hz sample rate) and completed a concurrent sleep diary. The number of days with valid data ranged from 5 to 14 days (mean 10.0 ± 2.6 days) for pre-treatment assessment and ranged from 6 to 12 days (mean 9.0 ± 2.3 days) for post-treatment assessment. Due to equipment error and data loss, actigraphy data was not able to be analysed for three participants at pre-treatment and six participants at post-treatment. Estimates of sleep onset and offset times were manually scored by trained technicians (JC) using visual inspection and the sleep diaries. This method provides an indirect estimate of sleep, however the terms 'sleep' and 'wake' are used here for descriptive purposes. Estimates of wake during the sleep episode were generated using a previously validated MATLAB program (te Lindert and Van Someren, 2013). The following sleep-wake parameters were generated: average sleep onset and offset times (timing of the onset and offset of the rest episode) and average wake after sleep onset (WASO: the duration of awakenings during the rest period).

2.6. Statistical analyses

SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) for Windows was used to perform statistical analyses. All data were analysed for normality with the Kolmogorov–Smirnov test. To evaluate group difference in pre- to post-treatment clinical, sleep-wake and neuropsychological characteristics, paired samples *t*-tests (95% CI) were employed for normality distributed variables and Wilcoxon signed-rank test was used for non-normally distributed variables. Cohen's *d* effect sizes were calculated to determine the magnitude of the effect of rTMS for significant pair-wise comparisons. To examine whether pre-treatment sleep-wake, neuropsychological and clinical characteristics were associated with improvement in depression with rTMS, first raw change scores for BPRS and HDRS variables were calculated whereby positive changes scores represented improvements in symptoms with treatment. Subsequently, Pearson's correlations (or Spearman's Rho for non-normal data) were performed between pre-treatment sleep-wake, neuropsychological and clinical characteristic variables and, change scores for symptoms scales.

3. Results

3.1. Change in clinical, sleep-wake and neuropsychological measures with rTMS treatment

The pre-treatment and post-treatment mean and standard deviations for clinical, sleep-wake and neuropsychological variables and pair-wise comparison statistics are shown in Table 2. Overall, with rTMS treatment, significant improvements in depression and anxiety were found but there were no differences in psychosocial functioning, sleep-wake parameters or cognition. Specifically, significant decreases from pre-treatment to post-treatment assessment were observed for HDRS total score [t (15) = 2.7, p = 0.02, d = 0.5] and HDRS anxiety subscore [t (15) = 2.5, p = 0.02, d = 0.6]. There was, however, no significant change in BPRS depression subscore [t (14) = 1.4, p = 0.18] or psychosocial functioning [t (15) = −0.04, p = 0.96]. No significant changes in sleep onset (z = −0.1, p = 0.95), sleep offset [t (8) = 0.86, p = 0.42] or WASO [t (8) = 0.80, p = 0.45] were observed. Similarly, there were no significant changes in neuropsychological performance on TMT B [t (14) = −0.4, p = 0.67], RAVLT sum (z = −0.4, p = 0.72) or RAVLT A7 (z = −0.1, p = 0.92). Table 3 shows the percentage change in HDRS depression scores from pre- to post-treatment. Five participants showed a reduction of 20% or more in HDRS scores and two participants met response criteria (i.e. a reduction of 50% or more in HDRS scores).

Table 2
Sample descriptives for pre- and post-treatment time points and, paired-sample t statistics or Kruskal-Wallis z statistics for clinical and neuropsychological measures. *Note:* M = mean; SD = standard deviation; HDRS = Hamilton Depression Rating Scale; BPRS = Brief Psychiatric Rating Scale; WASO = wake after sleep onset; SOFAS = social and occupational functioning scale; TMT = Trail-Making Test; RAVLT = Rey Auditory Verbal and Learning Test; * denotes significance at $p < 0.05$.

	Pre-treatment		Post-treatment		Test Statistic
	M	SD	*M*	SD	
HDRS Total	18.9	6.9	15.4	6.9	t = 2.7*
HDRS Anxiety	4.4	2.1	3.2	2.1	t = 2.5*
BPRS Dep	17.6	4.6	16.3	4.4	t = 1.4
SOFAS	54.4	14.3	54.6	16.4	t = < −0.0
Sleep Onset	24:06	1:29	24:09	1:15	z = −0.1
Sleep Offset	09:53	1:43	09:32	1:40	t = 0.9
WASO	64.1	29.8	59.1	30.4	t = 0.8
TMT B	−0.4	1.8	−0.2	1.0	t = −0.4
RAVLT Sum	0.3	1.3	0.2	1.2	z = −0.4
RAVLT A7	0.2	1.0	0.2	1.2	z = −0.1

Table 3
Percentage change in HDRS scores with rTMS treatment for each participant. *Note*: HDRS = Hamilton Depression Rating Scale.

Participant	% HDRS change
1	−67%
2	−22%
3	+31%
4	−3%
5	−15%
6	−5%
7	−69%
8	−7%
9	−13%
10	−44%
11	0%
12	0%
13	−26%
14	−18%
15	0%
16	−23%

3.2. Associations between sleep-wake, neuropsychological and clinical patient characteristics and, improvements in psychiatric symptoms

The correlation matrix of associations between pre-treatment sleep-wake, neuropsychological and clinical measures and, change in symptom score variables is provided in Table 4. For the sleep-wake variables, pre-treatment sleep-onset, pre-treatment sleep-offset and pre-

Table 4
Pearson's bivariate correlational analyses for clinical and neuropsychological measures. *Note*: HDRS = Hamilton Depression Rating Scale; BPRS = Brief Psychiatric Rating Scale; TMT = Trail-Making Test; RAVLT = Rey Auditory Verbal and Learning Test; † denotes Spearman's Rho correlation; # denotes trend-level significance (all p = 0.07); * denotes significance at $p < .05$; ** denotes significance at $p < .01$.

	HDRS Total Change	BPRS Dep Change
Sleep Onset	0.28	0.22
Sleep Offset	0.19	0.18
WASO	0.17	0.03
TMT B	0.36	0.53*
RAVLT Sum	0.07	0.49#
RAVLT A7	0.08	0.44
Age of Onset	0.07	0.48#
Duration of Illness†	0.33	−0.12
Number of Dep. Episodes†	0.34	0.55*

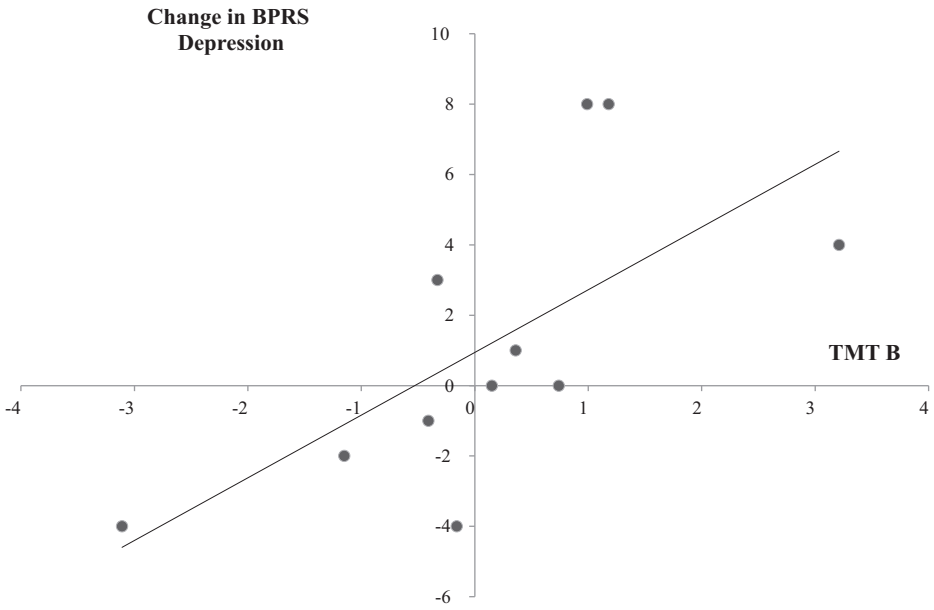

Fig. 1. Scatter plot showing the association between change in BPRS depression scores (before and after treatment) with TMT B. Better cognitive flexibility performance is reflected by greater TMT B *z* scores and greater improvements in depression with rTMS is reflected by greater change in BPRS depression values. *Note*: BPRS = Brief Psychiatric Rating Scale; TMT = Trail Making Test.

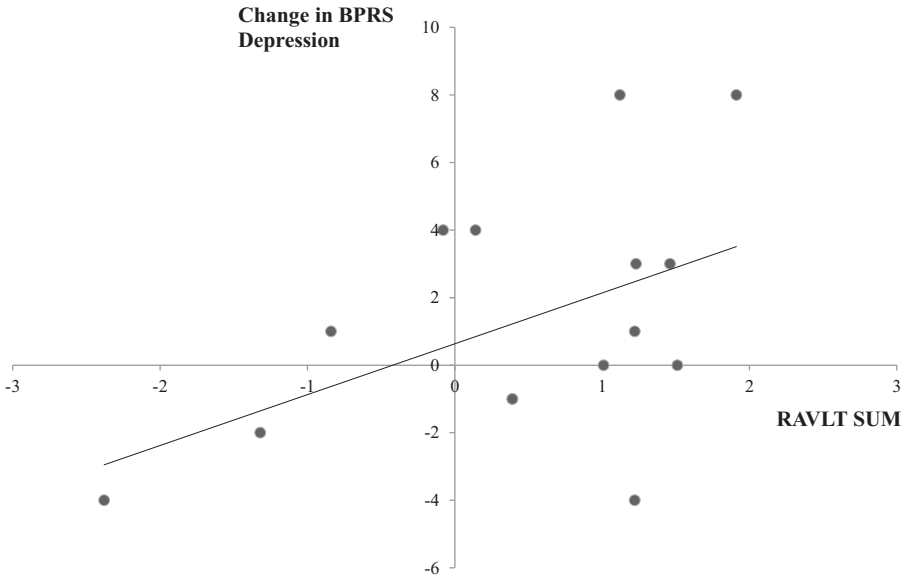

Fig. 2. Scatter plot showing the association between change in BPRS depression scores (before and after treatment) with RAVLT sum. Better verbal learning performance is reflected by greater RAVLT sum *z* scores and greater improvements in depression with rTMS is reflected by greater change in BPRS depression values. *Note*: BPRS = Brief Psychiatric Rating Scale; RAVLT = Rey Auditory Verbal and Learning Test.

treatment WASO were not significantly associated with change in HDRS total (all $p > 0.05$) or change in BPRS depression subscore (all $p > 0.05$). A significant positive relationship was observed between pre-treatment neuropsychological variables TMT B ($p = 0.04$; see Fig. 1) and, at the trend-level, RAVLT sum ($p = 0.07$; see Fig. 2) and change in BPRS depression subscore. There was no significant relationship between RAVLT A7 and BPRS depression subscore ($p > 0.05$). None of the pre-treatment neuropsychological variables were associated with change in HDRS (all $p < 0.05$). Number of depressive episodes ($p = 0.03$) and age of onset of psychiatric disorder (at the trend-level; $p = .07$) but not duration of illness ($p > 0.05$) was positively associated with change in BPRS depression subscore (see Fig. 3). There were no significant correlations between age of onset, duration of illness or number of depressive episodes and change in HDRS scores (all $p > 0.05$).

4. Discussion

This study was the first to examine the utility of key phenotypic features of depression (i.e., sleep-wake, cognitive and clinical characteristics) for predicting rTMS treatment outcome in young adults. Depressive symptoms were significantly reduced with rTMS treatment as expected and, for the first time in a youth sample, we provide evidence of a concomitant reduction in anxiety. While rTMS treatment outcome was not related to pre-treatment sleep-wake parameters, it was associated with initial cognitive and clinical features. Specifically, better cognitive flexibility and verbal learning (but not verbal memory) were associated with greater improvements in depression with rTMS. With regards to clinical measures, a later age of onset and greater number of depressive episodes (but not duration of illness) corresponded with better rTMS outcomes. There was no significant effect of rTMS treatment on sleep-wake, cognitive or psychosocial features in the current study.

The lack of significant correlations between pre-treatment sleep-wake variables and improvement in depression with rTMS is in keeping with previous studies (Brakemeier et al., 2008; Lowe et al., 2013). Our data suggests that sleep-wake characteristics may not have utility in predicting rTMS treatment response, however, further investigations

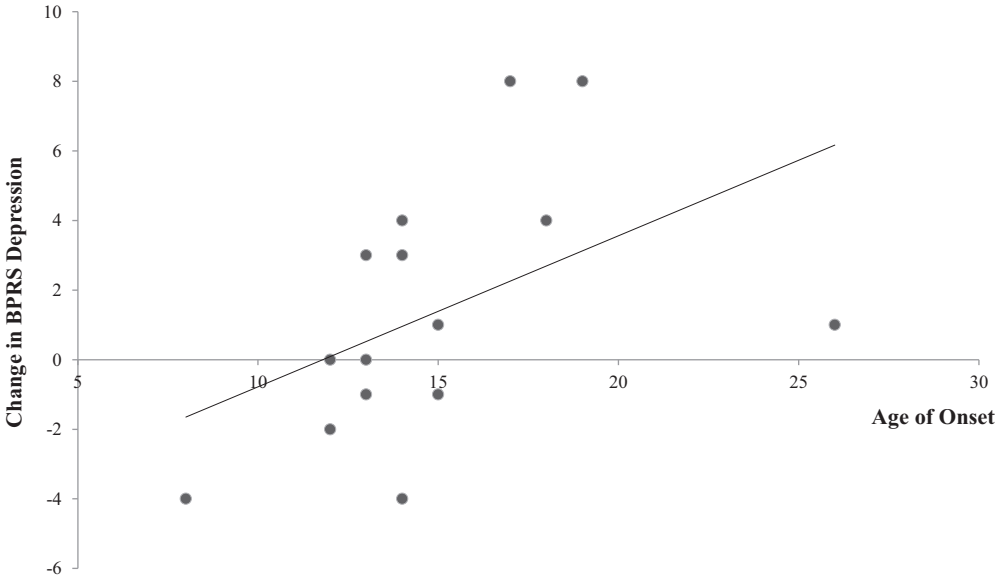

Fig. 3. Scatter plot showing the association between change in BPRS depression scores (before and after treatment) with age of onset. Greater improvements in depression with rTMS is reflected by greater change in BPRS depression values. *Note*: BPRS = Brief Psychiatric Rating Scale.

with larger samples of young depressed adults are needed before any definitive conclusions can be drawn. For a more comprehensive evaluation, it may be useful to specifically recruit samples with atypical depression features characterised by sleep-wake dysregulation. Sleep-wake measures, sleep efficiency, total sleep time and circadian rhythmicity, have previously shown to inform longitudinal clinical outcomes in young people with depression (Robillard et al., 2016) and as such, these measures may be more suited to assessing predictive utility of treatment response and should be considered in future studies. Additionally, the result of no effect of rTMS on objective sleep-wake measures in the current study corroborates previous research (Antczak et al., 2017; Nishida et al., 2017). It is noteworthy, however, that trend-level improvements in WASO with rTMS have been reported in chronically depressed patients (Pellicciari et al., 2013) and therefore, it is possible that in young depressed samples where aberrant sleep-wake behaviour may be less pronounced, larger samples may be necessary to detect main effects.

We provide the first evidence of a relationship between pre-treatment cognition and improvements in depression with rTMS. These data critically suggest that cognitive functioning may have value in predicting favourable outcome of rTMS treatment for depression and, are consistent with Hoy and colleagues' (2012) observation that initial improvement in cognition with rTMS treatment for depression is associated with response. The cognitive domains we found to be associated with rTMS outcome, cognitive flexibility and verbal learning, have also been shown to improve with rTMS in youth/adolescent depression (Huang et al., 2012; Wall et al., 2013). This suggests that cognitive flexibility and verbal learning may have particular relevance to rTMS treatment for younger populations. The therapeutic benefit of rTMS for depression is thought to result from neurochemical and blood flow changes within the DLPFC as well as extending to functionally connected regions (Noda et al., 2015). Given the pivotal role of the DLPFC in executive functions and verbal learning, we could speculate that the degree to which the DLPFC and functionally inter-connected regions are amenable to neuromodulation may depend on the functional integrity of these regions, providing a potential explanation for the correlation between pre-treatment cognitive measures and rTMS outcome for depression. Nevertheless, we acknowledge that the cognitive impairment in depression is intrinsically and complexly linked to depressive symptoms and the mediating effect of one on the other can often be unclear. However, there was no significant change in cognition with rTMS observed suggesting that the changes in depression with rTMS in this study may be independent of changes in cognition and therefore, may not have influenced the significant relationships between pre-treatment cognition and improvements in depression. Lastly, determining if this relationship is bidirectional and whether targeting cognitive impairment (e.g., using cognitive remediation) could improve response to rTMS to depression would be a valuable next step.

These data showing that a later age of onset and greater number of depressive episodes were associated with greater improvements in depression with rTMS extends previous findings by Fitzgerald and colleagues (2016) from a large, chronic depression sample (n = 1132; mean age = 46 years). However, we did not find a relationship between duration of illness and change in depression with rTMS unlike the previous study where a shorter duration of illness corresponded with the greatest improvements in depression. The modest sample size and narrow age range in our sample may account for this discrepancy. Our finding that a later age of onset (i.e. less chronic illness) corresponds with greater improvements in depression is somewhat in contrast to the finding that a greater number of episodes (i.e. more chronic illness) corresponds with greater improvements in depression. The age of onset data presented here supports the general consensus that less refractory depression corresponds with better response (Fitzgerald et al., 2016; Fregni et al., 2006; Pallanti et al., 2012). It is vital to highlight that while clinical measures such as age of onset and number of depressive episodes are easily obtained, clinically useful measures of chronicity, they do not necessarily reflect the neuropathological stage of illness. Thus, the capacity to make inferences on the relationship between illness chronicity and improvements in depression with rTMS using these measures is limited and further research aiming to elucidate neuropathological changes as disease progresses relative to response to rTMS would be highly valuable as a next step. Moreover, patient-level meta-analyses are likely to provide important insights into the contribution of measures of illness chronicity to response to rTMS for depression, however, there are too few clinical trials on younger, early stage cohorts to allow for this.

The reduction in depression with rTMS treatment in this study is the first to be reported in a young adult cohort and is in keeping with the adolescent (Bloch et al., 2008; Wall et al., 2011) and adult (Kedzior and Reitz, 2014) literature. While it has not been commonly investigated in studies of rTMS for depression, the improvement in anxiety symptoms reported in this research is consistent with previous reports in adults

(Fitzgerald et al., 2013; White and Tavakoli, 2015) and adolescents (Bloch et al., 2008). Critically, our result of no change on measures of verbal learning, verbal memory or cognitive flexibility buttress other evidence that rTMS does not have adverse effects on cognition. Despite reports of improvements in cognition with rTMS (Huang et al., 2012; Wall et al., 2013), our findings corroborate several clinical trials demonstrating no effect (for review see Serafini et al., 2015). It is possible that a more sensitive cognitive battery may have been necessary to detect subtler changes that may be present in early stage depression samples. Similarly, no significant change in measures of psychosocial functioning following rTMS treatment was noted, in contrast with previous studies (Dumas et al., 2012; Janicak et al., 2013). This difference may be explained by the measure used; due to restrictions on multiple comparisons, we utilised an overall measure of psychosocial functioning whereas the two previous studies more assessed psychosocial functioning by using scales with sub-domains and calculated subdomain composite scores (i.e. Medical Outcome Study Short-Form Health Survey and/or EuroQoL 5 Dimension Questionnaire).

The current study is exploratory in nature and as such, limited by issues pertaining to sample characteristics, including a modest sample size. Moreover, due to the modest sample size, it was not possible to covary for inpatient or outpatient status and inpatients are likely to have received the added benefit of residing in an inpatient unit, such as, potentially greater face to face contact and daily schedule regulation. Additionally, cognitive and clinical measures were only associated with change in one measure of depression, the BPRS depression subscore, indicating that the associations may be relevant to specific symptoms of depression better captured in the BPRS subscore than a more comprehensive overall measure of depression. While depression symptoms were reduced with rTMS for several participants (see Table 3), a low proportion of approximately 13% met response criteria. Within 11 days of rTMS, 75% of participants had undergone post-treatment assessment and it is possible that we did not capture reduced depressive symptoms of delayed responders. There are reports of reduced response in bipolar patients (Fitzgerald et al., 2016) as well as no difference in response between unipolar and mixed (unipolar and bipolar) samples (Berlim et al., 2014). Further, there is some indication that patients with comorbidities may show reduced response (Fitzgerald et al., 2016). As such, it is possible the inclusion of bipolar disorder and patients with comorbidities may have influenced the current findings. Similarly, sixteen participants were on psychotropics and any potential effect of psychotropic use cannot be accounted for in the current study. Notably, the literature on response differences between rTMS as a monotherapy and as an adjunctive therapy is inconsistent (Berlim et al., 2014; Fitzgerald et al., 2016; Slotema et al., 2010). Lastly, most of our samples were female. It is unclear, however, whether gender is associated with response to rTMS given mixed reports (Huang et al., 2008; Kedzior and Reitz, 2014; Rostami et al., 2017). Given the aforementioned caveats, the current findings should be interpreted with caution and replication in larger samples is necessary.

In conclusion, by showing reduced depressive and anxiety symptoms and, no cognitive deterioration, this preliminary investigation provides some promising results for rTMS as an early intervention strategy for young adults with depression, warranting sham controlled clinical trials. Critically, this study has identified cognitive flexibility and verbal learning as potential predictors of favourable treatment response in young adults with depression.

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Conflicts of interest

In the last 3 years, PBF has received equipment for research from Magventure A/S, Medtronic Ltd, Neurosoft and Brainsway Ltd. He has served on a scientific advisory board for Bionomics Ltd and LivaNova and is a founder and board member of TMS Australia. We have no other conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.002.

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