Journal of Anxiety Disorders 49 (2017) 31–39

Contents lists available at ScienceDirect

Journal of Anxiety Disorders

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

Sleep disturbances in obsessive-compulsive disorder: Association with non-response to repetitive transcranial magnetic stimulation (rTMS)

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ARTICLE INFO

Keywords:
Obsessive-compulsive disorder (OCD)
Treatment non-response
Biomarker
Sleep
Circadian rhythm
Repetitive transcranial magnetic stimulation (rTMS)

ABSTRACT

Background Repetitive transcranial magnetic stimulation (rTMS) is a promising augmentation strategy for treatment-refractory OCD. However, a substantial group still fails to respond. Sleep disorders, e.g. circadian rhythm sleep disorders (CRSD), are highly prevalent in OCD and might mediate treatment response. The aims of the current study were to compare sleep disturbances between OCD patients and healthy subjects as well as between rTMS responders and non-responders, and most importantly to determine sleep-related predictors of rTMS non-response.

Methods 22 OCD patients received at least 10 sessions rTMS combined with psychotherapy. Sleep disturbances were measured using questionnaires and actigraphy. Sleep in patients was compared to healthy subjects. Treatment response was defined as > 35% reduction on YBOCS. Treatment response prediction models were based on measures of CRSD and insomnia.

Results Sleep disturbances were more prevalent in OCD patients than healthy subjects. The OCD group consisted of 12 responders and 10 non-responders. The CRSD model could accurately predict non-response with 83% sensitivity and 63% specificity, whereas the insomnia model could not.

Conclusions CRSD is more prevalent in OCD patients than healthy subjects, specifically in rTMS non-responders. Therefore, CRSD may serve as a biomarker for different subtypes of OCD corresponding with response to specific treatment approaches.

1. Introduction

Obsessive-compulsive disorder (OCD) is a debilitating disorder that is often chronic in its course, causing significant impairment in social and occupational functioning (Ruscio, Stein, Chiu, & Kessler, 2010). Furthermore, a substantial portion of patients does not benefit sufficiently from first-line treatment strategies including cognitive-behavioural treatment (CBT) and selective serotonin reuptake inhibitors (SSRIs) (Eisen et al., 2010; Pallanti & Quercioli, 2006). Therefore, alternative treatment approaches have been proposed for treatment-refractory OCD patients. Recent insights into underlying neural processes have given rise to brain stimulation techniques as potential treatment approaches. One of these approaches is repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique that directly affects brain physiology through the application of short magnetic pulses over the scalp. Importantly, rTMS results in lasting changes in metabolic activity not only at the site of stimulation, but also at distant, connected sites (Ridding & Rothwell, 2007). Targeting superficial sites accessible to rTMS may thereby modulate neural networks implicated in OCD. Accumulating evidence consistently indicates that cortico-striato-thalamo-cortical (CSTC) circuits are associated with pathophysiology in OCD (Ahmari and Dougherty, 2015; Lapidus, Stern, Berlin, & Goodman, 2014). These include the affective circuit, the dorsal cognitive circuit, the ventral cognitive circuit and the sensorimotor circuit. Communication within and between these networks is implicated in functions such as habit and reward learning as well as compulsivity (Van den Heuvel et al., 2016). Normalizing the activity within these networks through rTMS may therefore result in OCD symptom relief. Recent meta-analyses indicate that approximately 35% of treatment-resistant OCD patients benefit from rTMS, particu-

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http://dx.doi.org/10.1016/j.janxdis.2017.03.006
Received 12 July 2016; Received in revised form 14 March 2017; Accepted 29 March 2017
Available online 31 March 2017
0887-6185/

larly when applied over the supplementary motor area (SMA) or orbitofrontal cortex (OFC) (Berlim, Neufeld, & Van den Eynde, 2013; Saba, Moukheiber, & Pelissolo, 2015). However, the majority of patients receiving rTMS still fails to respond. Therefore, identifying predictors of treatment non-response may enhance treatment efficacy.

One potential predictor of non-response is the presence of sleep disturbances. In depression, a higher level of sleep disturbances has been postulated to affect response to rTMS (Brakemeier, Luborzewski, Danker-Hopfe, Kathmann, & Bajbouj, 2007). A similar process may apply to rTMS response in OCD. Although sleep has not extensively been investigated in OCD, emerging evidence indicates that OCD is associated with a number of specific sleep disturbances (Nota, Sharkey, & Coles, 2015; Paterson, Reynolds, Ferguson, & Dawson, 2013). Most importantly, circadian rhythm sleep disorder (CRSD) is present in a relatively large proportion of OCD patients. Specifically, delayed sleep phase disorder (DSPD) is highly prevalent among these patients, with prevalence rates of 17–42% as compared to 0.17–0.72% in the general adult population (Drummond et al., 2012; Mukhopadhyay et al., 2008; Turner et al., 2007). DSPD is characterized by a persistent inability to fall asleep and awaken at a desired or conventional time, with patients typically reporting bedtimes later than 02:00 AM(Chang, Reid, Gourineni, & Zee, 2009; Sack et al., 2007). In addition to the notable high prevalence of DSPD, OCD patients exhibit hormonal dysregulation in circadian cortisol, nocturnal growth hormone, and melatonin (Lange, Lange, Hauser, Tucha, & Tucha, 2012), which provides further support of abnormal circadian rhythms.

Secondly, a body of research suggests diminished sleep quality and altered sleep architecture in OCD, although the small amount of studies has yielded divergent results. Polysomnographic studies have repeatedly shown a longer sleep onset latency and reduced sleep duration, awakenings after sleep onset and sleep efficiency in OCD (Hohagen et al., 1994; Insel et al., 1982; Voderholzer et al., 2007), whereas others failed to demonstrate differences between OCD patients and controls in these parameters (Kluge, Sch & ssler, Dresler, Yassouridis, & Steiger, 2007; Robinson, Walsleben, Pollack, & Lerner, 1998). With respect to sleep architecture, abnormalities have been found in rapid eye movement (REM) latency and efficiency (Insel et al., 1982; Voderholzer et al., 2007) and occasionally sleep onset REM periods have been found (Kluge et al., 2007). However, no abnormalities in REM sleep were found in other controlled studies among medication-free OCD patients (Hohagen et al., 1994; Robinson et al., 1998). Since many of the sleep disturbances are similar to those observed in depression, it is often suggested that comorbid depression mediates the relationship between sleep disturbances and OCD. However, most studies that take depressive symptoms into account indicate that at least some differences are independent of depression (Insel, Mueller, Gillin, Siever, & Murphy, 1984; Timpano, Carbonella, Bernert, & Schmidt, 2014; Voderholzer et al., 2007) and meta-analyses indicate that comorbid depression cannot fully explain the sleep disturbances observed in OCD (Cox & Olatunji, 2016; Díaz-Román, Perestelo-Pérez, & Buela-Casal, 2015; Nota et al., 2015). Most notably, in a study in which patients with OCD only, OCD with comorbid depression, and depression only were compared, DSPD was uniquely associated with OCD (Bobdey, Fineberg, Gale, Patel, & Davies, 2002). In summary, the strongest evidence exists for a higher prevalence of DSPD, whereas less consistent findings have been reported on sleep quality and REM sleep.

Hence, the existing literature suggests that sleep disturbances, CRSD in particular, play a role in OCD. It may therefore be hypothesized that CRSD could affect treatment efficacy. A few previous studies have investigated the effect of sleep difficulties on OCD treatment. For example, a pharmacological approach was reported in two cases in which aripiprazole at bedtime was effective in decreasing both OCD symptoms and sleep disturbance (Takaki, 2014). Furthermore, two case studies have used psychotherapeutic approaches for sleep disturbance in OCD. One patient received psychological monitoring and sleep hygiene education, and as a result recovered from his subjective insomnia (Abe, Nishimura, & Endo, 2012). Another OCD patient with severely delayed bedtime was treated with CBT and chronotherapy simultaneously, which resulted in substantial improvements in both circadian rhythm and OCD symptoms (Coles & Sharkey, 2011). These studies suggest that sleep disturbance might play a role in treatment response, but the mechanism by which the effect operates is not yet fully understood.

With respect to treatment response, Ivarsson and Skarphedinsson (2015) found that non-responding children and adolescents with OCD had more severe or more frequent sleep problems than responders to CBT. Furthermore, a reduction in sleep problems could predict treatment response. It is important to note that sleep mechanisms and circadian rhythms change across the lifespan (Crowley, 2016; Skeldon, Derks, & Dijk, 2015), impeding the generalizability of the findings to adults. One study in adult patients showed that REM latency could predict OCD treatment response to both CBT and SSRIs (Voderholzer et al., 2007). Apart from these two studies, no studies to date have focused on the predictive value of sleep in the treatment of OCD and none have focused on the potential role of CRSD specifically.

The aim of the current study was three-fold: to compare sleep disturbances between OCD patients and healthy subjects, to compare sleep disturbances between OCD patients classified as rTMS responders and non-responders, and to determine whether specific sleep measures could predict rTMS non-response in treatment-resistant OCD patients. Based on previous findings, the expectation was that OCD patients would have a delayed sleep phase, decreased sleep duration and lower sleep efficiency compared to healthy individuals. It was expected that these sleep disturbances would be more severe in rTMS non-responders than in responders. Furthermore, it was hypothesized that CRSD, the most prevalent sleep disturbance in OCD, would predict treatment non-response to rTMS, more so than other sleep disturbances.

2. Methods and materials

2.1. Participants

All patients with OCD registered between 1 July 2013 and 30 November 2015 for treatment at neuroCare Group (Nijmegen, The Netherlands) were treated with rTMS in an open-label design. Patients were not eligible for rTMS if they had previously been treated with electroconvulsive therapy (ECT), a history of psychosis or epilepsy, had a pacemaker or metal parts in the head, and in case of current pregnancy. Data were screened for inclusion in the study post-hoc. Patients were included if they had a primary DSM-IV diagnosis of OCD based on the MINI International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), had failed at least two previous treatment approaches, signed informed consent, and completed at least 10 sessions of rTMS. A comparison group of healthy participants was recruited that completed the same measurements as the patients. The comparison group was matched based on age and gender. Participants from the comparison group were excluded if they met criteria of any psychiatric disorder based on MINI or if their scores on screening questionnaires as listed in the section below exceeded clinical cut-off scores.

2.2. Outcome measures

2.2.1. Questionnaires

OCD patients (not healthy subjects) completed the Yale-Brown Obsessive-Compulsive Screening (Y-BOCS), which is a reliable and valid scale for the assessment of OCD symptom severity (Goodman, Fleischmann et al., 1989; Goodman, Delgado et al., 1989), in order to monitor obsessive-compulsive symptoms. A cut-off criterion of 16 was used for diagnosis; a reduction of at least 35% from pre- to post-treatment was used as criterion for clinically relevant treatment response (Farris, McLean, Van Meter, Simpson, & Foa, 2013). In addi-

tion, all participants completed questionnaires on depression and sleep. The Beck Depression Inventory (BDI-II-NL; Van der Does, 2002) was used to determine severity of depressive symptoms.

2.2.1.1. Holland sleep disorders questionnaire (HSDQ). The HSDQ was used to determine severity of sleep disorders. It is a self-report questionnaire for sleep disorders based on the International Classification of Sleep Disorders-2. It consists of 32 items rated from 0 to 5. The total score is the mean of all item scores. In addition, the items are divided into six scales: insomnia, parasomnia, CRSD, hypersomnia, restless legs syndrome/periodical limb movement disorder (RLS/PLMD), and sleep-related breathing disorder (SBD). Cut-off scores are defined for each scale separately based on Youden's criterion for an optimum balance between sensitivity and specificity; furthermore, the HSDQ has been validated against polysomnography (Kerkhof et al., 2012).

2.2.1.2. Pittsburgh sleep quality index (PSQI). The PSQI was used for monitoring the course of subjective sleep disturbances during treatment. It is a self-report questionnaire for the assessment of sleep quality during the previous month. It is composed of 19 self-rated questions and five questions rated by a close relative. The total score ranges from 0 to 21. A global score higher than 5 suggests significant sleep disturbance. In addition, seven component scores can be calculated: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score ranges from 0 to 3. The PSQI has acceptable values of internal consistency, test-retest reliability and concurrent validity for use in clinical practice as well as research (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

2.2.2. Actigraphy

Objective sleep-wake and activity measures were obtained using an Actiwatch Spectrum Plus or Actiwatch 2 (Respironics), which is a valid method for the assessment of sleep disturbances and the circadian rhythm (Ancoli-Israel et al., 2003; Marino et al., 2013). All participants were asked to wear the Actiwatch for one week. Recordings were performed with 1-miute epoch length and 32 Hz sampling rate. From the raw recordings, several standard measures were calculated with Actiware 5 software (Respironics): bedtime, total sleep time (TST), total time in bed (TIB), sleep onset latency (SOL), sleep efficiency (SE), wake after sleep onset (WASO), and number of awakenings. Activity levels were calculated with a time above threshold algorithm; the threshold was automatically determined based on the activity data. Bedtime was converted from a 24-h cycle with midnight as reference point to a cycle with noon as a reference point for the statistical analysis. In addition to wearing the Actiwatch, participants were asked to keep sleep logs, in which they specified bedtimes, get-up times, physical activity, use of computer/smartphone/tablet, and use of caffeine/alcohol/medication. These sleep logs were used to verify the recordings of the Actiwatch.

2.3. Procedure

All participants completed an intake procedure prior to treatment, including a clinical interview, the questionnaires listed above, and actigraphy. In addition, an EEG assessment was conducted in order to rule out contraindications for rTMS. OCD patients received standardized rTMS treatment for at least 10 sessions over the SMA and/or psychotherapy. rTMS was administered following the procedure of Mantovani, Simpson, Fallon, Rossi, and Lisanby (2010) using a figure-8 coil with a frequency of 1 Hz, 1000 pulses per session, 110% MT. The SMA was localized using the 10–20 EEG system, measured as 15% of the distance between nasion and inion anterior to the vertex on the sagittal midline. In case of comorbid depression as defined by diagnosis based on the MINI, rTMS was applied sequentially over the bilateral SMA and right dorsolateral prefrontal cortex (DLPFC) (1 Hz, 1200 pulses per session, 120% MT), since rTMS over the DLPFC is an evidence-based method for treatment of depression (Lefaucheur et al., 2014; Schutter, 2010). The moment of the day rTMS sessions took place and the number of sessions per week varied per patient, as treatment was applied in a naturalistic clinical setting. Questionnaires (Y-BOCS, BDI, and PSQI) were completed each fifth session. At the end of treatment, patients completed post-treatment EEG, questionnaires (Y-BOCS, BDI, and PSQI) and actigraphy. Healthy subjects did not receive treatment and therefore completed measurements only at baseline.

2.4. Statistics

Firstly, to evaluate treatment outcome, repeated-measures analyses of variance (ANOVAs) were used to test changes over time in the group of OCD patients in Y-BOCS, BDI and PSQI scores. Factorial repeated-measures ANOVAs (group x time) were used to compare these changes in responders and non-responders. Effect sizes were calculated using η^2.

To address the first research question on differences in sleep between OCD patients and healthy subjects, one-way ANOVAs were used to test differences on clinical questionnaires (BDI and Y-BOCS), sleep questionnaires (HDSQ and PSQI) and actigraphy. Non-parametric tests were computed if the assumption of normality and/or homogeneity of variance was violated. Effect sizes were calculated using Cohen's *d*, in which an effect size of 0.20 is small, 0.50 is medium, and 0.80 is large (Cohen, 1992). In order to answer the second research question on differences between responders and non-responders, similar analyses were carried out.

For the purpose of the third research question, discriminant analysis was performed to test whether measures of CRSD or insomnia could predict treatment non-response, using independent measures from two different instruments. In discriminant analysis, classification of groups is determined by predefined variables. If the model is significant, the predictor variables can accurately discriminate between the groups. Insomnia was selected as best comparison prediction model, as this is the most common sleep disorder in psychiatric patients (Spiegelharder, Regen, Nanovska, Baglioni, & Riemann, 2013). The first model included measures of CRSD: 1) bedtime based on actigraphy, and 2) self-reported CRSD as measured by the HSDQ. The second model included measures of insomnia: 1) sleep duration based on actigraphy, and 2) self-reported insomnia as measured by HSDQ. In both models, the HSDQ items were included as continuous measures in order to be able to detect subtle effects. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were computed for both models.

3. Results

3.1. Demographics

A total of 25 OCD patients was included in the current study. Their mean age was 39.3 years (SD = 13.5). In the patient group, 9 were female and 16 were male. The control group consisted of 26 healthy subjects with a mean age of 34.2 years (SD = 9.9), in which 14 were female and 12 male. No difference in age existed between patients and healthy subjects, $F(1, 45) = 2.37$, $p = 0.13$. Levene's test was not significant, confirming that variance was equal in both groups. No differences were found in gender either, $\chi^2(1) = 1.64$, $p = 0.20$. Thus, the patient and control group were comparable regarding age and gender.

3.2. Treatment outcome

A total of 22 OCD patients completed treatment. The reason for non-completion was a lack of perceived improvement in two patients and is unknown for one patient. The group consisted of 12 responders and 10 non-responders, with response defined as a minimum reduction of 35% on the Y-BOCS from intake to outtake (Farris et al., 2013). The

Table 1
Demographic data and Y-BOCS, BDI, and PSQI scores of responders and non-responders.

	Responder (n = 12)	Non-responder (n = 10)	Total group (n = 22)
Age (years)	40.67 (12.12)	37.60 (17.32)	39.27 (14.42)
Gender (f/m)	5/7	2/8	7/15
Y-BOCS			
Pre-treatment	26.92 (5.71)	26.56 (6.04)	26.76 (5.71)
Post-treatment	9.25 (6.17)	24.33 (7.67)	15.71 (10.14)
Pre-post change	67%	8%	42%
Effect size	d = 2.97	d = 0.32	d = 1.34
BDI			
Pre-treatment	22.50 (13.11)	30.00 (9.85)	26.33 (12.22)
Post-treatment	5.83 (6.81)	26.89 (14.49)	14.86 (14.95)
Pre-post change	77%	17%	51%
Effect size	d = 1.60	d = 0.25	d = 0.84
PSQI			
Pre-treatment	6.55 (3.09)	10.78 (4.02)	8.09 (4.03)
Post-treatment	4.27 (3.26)	8.75 (3.69)	6.10 (4.01)
Pre-post change	37%	23%	31%
Effect size	d = 0.72	d = 0.53	d = 0.49

demographic data and Y-BOCS, BDI, and PSQI scores are specified in Table 1. No differences in age ($F(1, 20) = 0.24$, $p = 0.63$) or gender ($\chi^2(1) = 1.18$, $p = 0.28$) were detected between those groups. Furthermore, no significant differences between responders and non-responders existed at intake in OCD symptom severity, $F(1, 19) = 0.02$, $p = .89$, and depression severity, $F(1, 19) = 3.03$, $p = 0.10$. In contrast, sleep disturbances were more severe in non-responders at baseline, $F(1, 19) = 7.33$, $p < 0.05$ (see also Section 3.3.2).

Factorial repeated-measures ANOVAs (group × time) demonstrated a significant reduction in OCD symptoms as measured by the Y-BOCS from baseline to post-treatment for the total group, $F(1, 19) = 63.14$, $p < 0.001$, $\eta^2 = .77$. A significant difference was found between responders and non-responders, $F(1, 19) = 8.59$, $p < 0.01$, $\eta^2 = .31$. As expected, there was a larger reduction in the group of responders, indicated by a significant interaction effect, $F(1, 19) = 38.07$, $p < 0.001$, $\eta^2 = .67$.

A similar effect applied to depressive symptoms as measured by the BDI, with a significant reduction for the total group from pre- to posttreatment, $F(1, 15) = 24.96$, $p < 0.001$, $\eta^2 = .57$, a significant difference between responders and non-responders, $F(1, 15) = 11.32$, $p < 0.01$, $\eta^2 = .37$, and a significant interaction effect, $F(1, 15) = 8.13$, $p < 0.01$, $\eta^2 = .30$.

For sleep disturbances as measured by the PSQI, significant differences from pre- to posttreatment were revealed for the total group, $F(1, 18) = 38.07$, $p < 0.01$, $\eta^2 = .37$, as well as a difference between responders and non-responders, $F(1, 18) = 7.64$, $p < 0.01$, $\eta^2 = .30$, but no interaction effect was observed.

In conclusion, a reduction of OCD, depression and sleep disturbances was observed in the total group. As expected, responders had a larger reduction in OCD symptoms; in addition, they showed a greater decrease in depressive symptoms. For sleep disturbances, the symptoms remained more severe for non-responders throughout the course of treatment. The patterns of symptom reduction are depicted in Fig. 1.

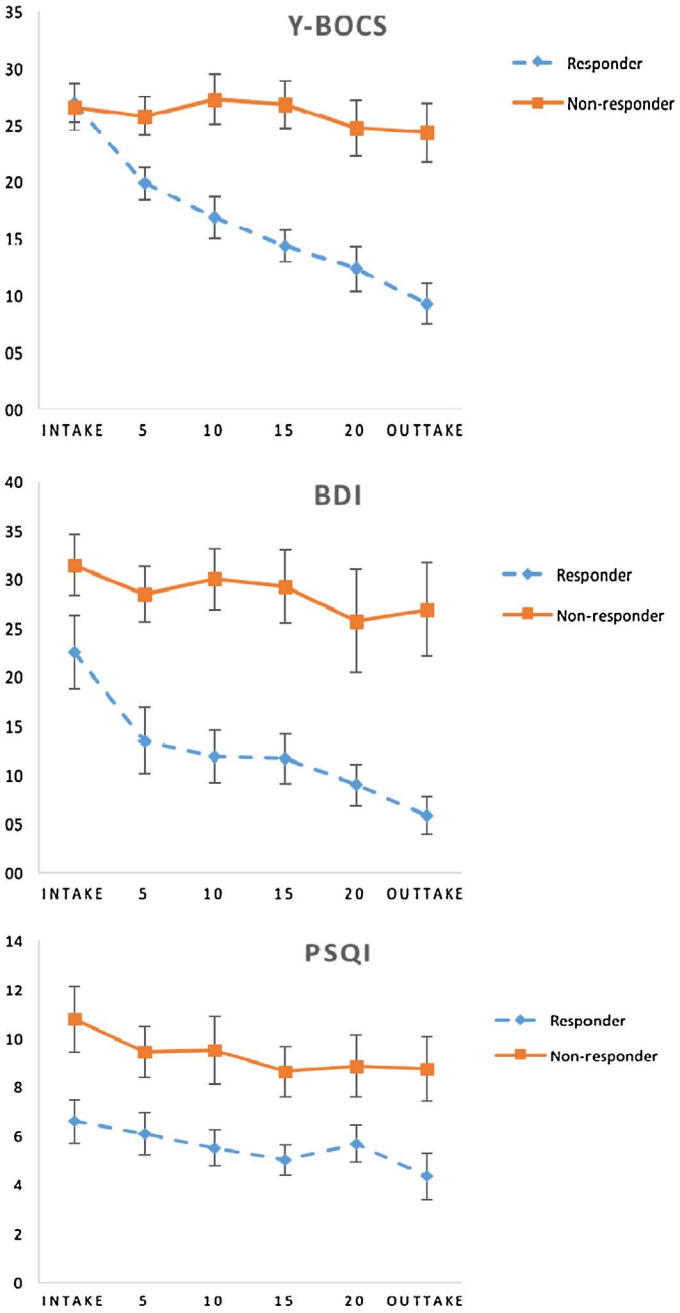

Fig. 1. Differences between responders and non-responders in changes over the course of treatment on Y-BOCS, BDI and PSQI global score. Error bars represent SEM.

3.3. Sleep in OCD

3.3.1. OCD vs. healthy comparison group

To investigate sleep disturbances in OCD, patients were compared to healthy subjects on subjective and objective measures of sleep. All results are specified in Table 2. Firstly, as indicated by the HSDQ, all sleep disturbances occurred significantly more often in the OCD group, with the exception of RLS/PLMD. Effect sizes were medium to large.

Furthermore, the PSQI global score was significantly higher in the OCD group, $U = 44.50$, $p < 0.001$, $d = 1.77$. A few specific components were higher in OCD patients, whereas others were similar to healthy subjects. Significant differences were found for subjective sleep quality, sleep latency, habitual sleep efficiency, and daytime dysfunction. Effect sizes were large. No differences existed in the components sleep duration, sleep disturbances, and use of sleep medication.

Actigraphy revealed significant differences between OCD patients and healthy subjects in total sleep time, onset latency, and sleep efficiency, with medium effect sizes. No differences were found in bedtime, total time in bed, wake after sleep onset and number of awakenings.

3.3.2. Responders vs. non-responders

When responders were compared to non-responders, a few specific differences were found at baseline (see Table 3). With respect to specific sleep disorders, no significant differences were found on the HSDQ, although there was a trend toward more severe CRSD with a large effect

Table 2
Differences in sleep measures between OCD patients and healthy subjects.

	HSDQ					
	Insomnia	Parasomnia	CRSD	Hypersomnia	RLS/PLMD	SBD
OCD	$M = 2.56$	$M = 1.52$	$M = 1.94$	$M = 1.94$	$M = 1.77$	$M = 1.68$
($n = 23$)	$SD = 1.03$	$SD = 0.56$	$SD = 0.79$	$SD = 0.70$	$SD = 0.77$	$SD = 0.70$
Control	$M = 1.52$	$M = 1.13$	$M = 1.29$	$M = 1.25$	$M = 1.36$	$M = 1.36$
($n = 26$)	$SD = 0.33$	$SD = 0.25$	$SD = 0.30$	$SD = 0.30$	$SD = 0.45$	$SD = 0.47$
Mann-Whitney test	$U = 126.00$	$U = 144.50$	$U = 153.00$	$U = 127.50$	$U = 217.00$	$U = 200.50$
	$p < 0.001$*	$p < 0.001$*	$p < 0.01$*	$p < 0.001$*	$p = .09$	$p < 0.05$*
Effect size	$d = 1.36$	$d = 0.89$	$d = 1.09$	$d = 1.28$	$d = 0.65$	$d = 0.54$

	PSQI						
	Subjective sleep quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleep medication	Daytime dysfunction
OCD	$M = 1.63$	$M = 1.63$	$M = 0.68$	$M = 0.68$	$M = 1.26$	$M = 0.58$	$M = 1.68$
($n = 19$)	$SD = 1.10$	$SD = 1.01$	$SD = 0.82$	$SD = 1.10$	$SD = 0.65$	$SD = 1.12$	$SD = 0.82$
Control	$M = 0.54$	$M = 0.58$	$M = 0.31$	$M = 0.04$	$M = 0.92$	$M = 0.08$	$M = 0.42$
($n = 26$)	$SD = 0.51$	$SD = 0.58$	$SD = 0.47$	$SD = 0.20$	$SD = 0.48$	$SD = 0.27$	$SD = 0.50$
Mann-Whitney test	$U = 95.00$	$U = 102.00$	$U = 190.00$	$U = 163.50$	$U = 184.00$	$U = 198.00$	$U = 59.00$
	$p < 0.001$*	$p < 0.001$*	$p = .13$	$p < 0.01$*	$p = .06$	$p = .07$	$p < 0.001$*
Effect size	$d = 1.27$	$d = 1.27$	$d = 0.55$	$d = 0.81$	$d = 0.60$	$d = 0.61$	$d = 1.86$

	Actigraphy						
	Bedtime (time of day)	TIB (hrs)	TST (hrs)	SOL (min.)	SE (%)	WASO	Awakenings
OCD	$M = 23{:}59$	$M = 8{:}23$	$M = 6{:}38$	$M = 12.14$	$M = 77.54$	$M = 70.82$	$M = 27.27$
($n = 22$)	$SD = 0{:}57$	$SD = 1{:}17$	$SD = 1{:}12$	$SD = 7.06$	$SD = 14.28$	$SD = 53.34$	$SD = 10.01$
Control	$M = 00{:}07$	$M = 8{:}07$	$M = 7{:}00$	$M = 7.98$	$M = 86.02$	$M = 47.34$	$M = 27.36$
($n = 26$)	$SD = 1{:}24$	$SD = 0{:}33$	$SD = 0{:}39$	$SD = 5.39$	$SD = 5.41$	$SD = 22.18$	$SD = 7.38$
Mann-Whitney test	$U = 275.00$	$U = 266.00$	$U = 190.00$	$U = 172.50$	$U = 154.00$	$U = 219.00$	$U = 256.00$
	$p = .82$	$p = .68$	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p = .17$	$p = .54$
Effect size	$d = 0.12$	$d = 0.25$	$d = 0.53$	$d = 0.66$	$d = 0.79$	$d = 0.58$	$d = 0.01$

size in the group of non-responders, $U = 25.00$, $p = 0.07$, $d = 0.99$. The PSQI revealed significant differences in the global score, with non-responders reporting more severe sleep disturbances than responders, $U = 22.00$, $p < 0.05$, $d = 1.17$. At the level of component scores, significant differences were found in subjective sleep quality, sleep latency, sleep duration, and daytime dysfunction, which were significantly higher among non-responders.

All responders and nine out of ten non-responders completed the actigraphy before treatment. Contrary to self-reported sleep disturbances, no differences in these objective sleep measures were found.

3.4. rTMS non-response prediction

Two discriminant analyses were performed to test whether responders and non-responders can be classified based on sleep disturbances. The CRSD model, incorporating bedtime as measured by actigraphy and self-reported CRSD, could accurately predict rTMS non-response, $\Lambda = 0.68$, $p < 0.05$. This model had a sensitivity of 83.3% and a specificity of 62.5%. The ROC curve had an AUC of 0.83 (see Fig. 2). The insomnia model, encompassing sleep duration based on actigraphy and self-reported insomnia, could not accurately discriminate between responders and non-responders, $\Lambda = 0.87$, $p = 0.31$. This model had a sensitivity of 58.3% and a specificity of 62.5%, and the ROC curve had an AUC of 0.66. These findings suggest that CRSD is an accurate predictor of rTMS non-response in OCD, whereas insomnia is not.

4. Discussion

The aim of the current study was to investigate the role of sleep disturbances in OCD and its predictive value for rTMS treatment non-response. Firstly, in line with the expectation, OCD patients showed a higher degree of sleep disturbances compared to healthy subjects, with large effect sizes. Secondly, circadian rhythm disorders could accurately predict non-response to rTMS treatment. These findings may have theoretical and clinical implications, which will be discussed here.

Regarding sleep disturbances in OCD, actigraphy showed significantly shorter sleep duration, longer sleep onset latency and lower sleep efficiency in patients compared to healthy subjects. These findings are similar to those reported in the literature (Nota et al., 2015; Paterson et al., 2013). Previous studies strongly suggest a higher prevalence of DSPD in OCD (Drummond et al., 2012; Mukhopadhyay et al., 2008; Turner et al., 2007). Although bedtime was not significantly delayed at the level of actigraphy, patients subjectively reported more severe symptoms of CRSD, along with all other sleep disorders measured by the HSDQ, with the exception of RLS/PLMD. Patients further reported a higher degree of disturbances in subjective sleep quality, habitual sleep latency, sleep efficiency and daytime functioning. Taken together, the current study presents evidence of circadian rhythm disorders as well as other sleep difficulties in OCD patients.

Furthermore, the current study shows differences between responders and non-responders on several dimensions of subjective, but not objective, sleep. More specifically, non-responders reported more severe disturbances in subjective sleep quality, sleep latency, sleep duration, and daytime dysfunction, as well as a trend toward more complaints of CRSD among non-responders. Interestingly, the differences between responders and non-responders applied to subjective sleep only. It should be noted that this discrepancy between objective and subjective sleep may be due to a difference in power, as the number of patients who completed actigraphy was slightly smaller than the total group; in addition, effect sizes were large for objective measures. Although the role of objective sleep disturbances cannot be ruled out, it can be speculated that a link might exist between subjective sleep quality and treatment non-response.

A possible explanation for the difference between responders and

Table 3
Differences in sleep measures between rTMS responders and non-responders.

	HSDQ					
	Insomnia	Parasomnia	CRSD	Hypersomnia	RLS/PLMD	SBD
Responders (n = 12)	M = 2.38 SD = 1.05	M = 1.62 SD = 0.67	M = 1.66 SD = 0.65	M = 1.97 SD = 0.65	M = 1.57 SD = 0.61	M = 1.79 SD = 0.88
Non-responders (n = 8)	M = 3.06 SD = 0.92	M = 1.35 SD = 0.37	M = 2.42 SD = 0.87	M = 1.83 SD = 0.74	M = 1.93 SD = 0.89	M = 1.56 SD = 0.50
ANOVA/Mann-Whitney test	F = 2.23 p = .15	U = 39.50 p = .51	U = 25.00 p = .07	F = 0.20 p = .66	U = 36.00 p = .34	U = 44.50 p = .78
Effect size	d = 0.65	d = 0.50	d = 0.99	d = 0.20	d = 0.47	d = 0.32

	PSQI						
	Subjective sleep quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleep medication	Daytime dysfunction
Responders (n = 10)	M = 1.00 SD = 0.82	M = 1.20 SD = 0.92	M = 0.30 SD = 0.68	M = 0.40 SD = 0.70	M = 1.20 SD = 0.42	M = 0.40 SD = 0.97	M = 1.30 SD = 0.82
Non-responders (n = 9)	M = 2.33 SD = 0.87	M = 2.11 SD = 0.93	M = 1.11 SD = 0.78	M = 1.00 SD = 1.32	M = 1.33 SD = 0.87	M = 0.78 SD = 1.30	M = 2.11 SD = 0.60
Mann-Whitney test	U = 12.50 p < 0.01*	U = 22.50 p < 0.05*	U = 19.50 p < 0.05*	U = 35.00 p = .34	U = 42.00 p = .77	U = 38.50 p = .49	U = 21.50 p < 0.05*
Effect size	d = 1.58	d = 0.99	d = 1.12	d = 0.57	d = 0.19	d = 0.33	d = 1.12

	Actigraphy						
	Bedtime (time of day)	TIB (hrs)	TST (hrs)	SOL (min.)	SE (%)	WASO	Awakenings
Responders (n = 12)	M = 23:44 SD = 0:42	M = 8:17 SD = 0:58	M = 6:23 SD = 0:47	M = 13.45 SD = 7.80	M = 77.71 SD = 10.52	M = 78.06 SD = 67.64	M = 26.89 SD = 7.86
Non-responders (n = 9)	M = 00:39 SD = 2:00	M = 8:37 SD = 1:43	M = 6:59 SD = 1:39	M = 10.82 SD = 6.56	M = 76.27 SD = 19.25	M = 64.79 SD = 30.46	M = 27.90 SD = 13.26
ANOVA/Mann-Whitney test	U = 49.00 p = .72	F = 0.32 p = .58	F = 1.20 p = .29	F = 0.68 p = .42	U = 52.00 p = .89	U = 48.00 p = .67	F = 0.05 p = .83
Effect size	d = 0.57	d = 0.25	d = 0.47	d = 0.37	d = 0.09	d = 0.25	d = 0.09

non-responders in subjective sleep specifically might be that non-responders have a higher degree of negative cognitive bias, reflected in reporting more severe symptoms than measured objectively. It is well known that OCD patients have a tendency to interpret ambiguous information in a negative manner (Williams & Grisham, 2013). This may not only apply to the OCD symptoms, but also to the sleep disturbances these patients experience. In accordance with this view, a recent report demonstrated that the tendency to experience cognitive concerns is related to subjectively reported insomnia in OCD (Raines et al., 2015). Reducing these subjective symptoms may therefore increase treatment response. For example, subjective symptoms may be responsive to modification by relatively simple interventions such as psychoeducation and sleep hygiene monitoring, as has been demonstrated in a case report on treatment of subjective insomnia in an OCD patient (Abe et al., 2012). Another possibility could be CBT, since a recent meta-analysis reported that CBT for comorbid insomnia can improve both insomnia and comorbid symptoms in several psychiatric and medical conditions (Wu, Appleman, Salazar, & Ong, 2015). These findings are promising, but future studies directly targeting subjective sleep disturbance before OCD treatment are necessary to test these hypotheses.

With respect to predicting rTMS non-response, the model based on CRSD could accurately discriminate between responders and non-responders, whereas the model based on insomnia could not. Sensitivity and specificity of the CRSD model were exceptionally high. These findings suggest that assessment of circadian rhythms may be

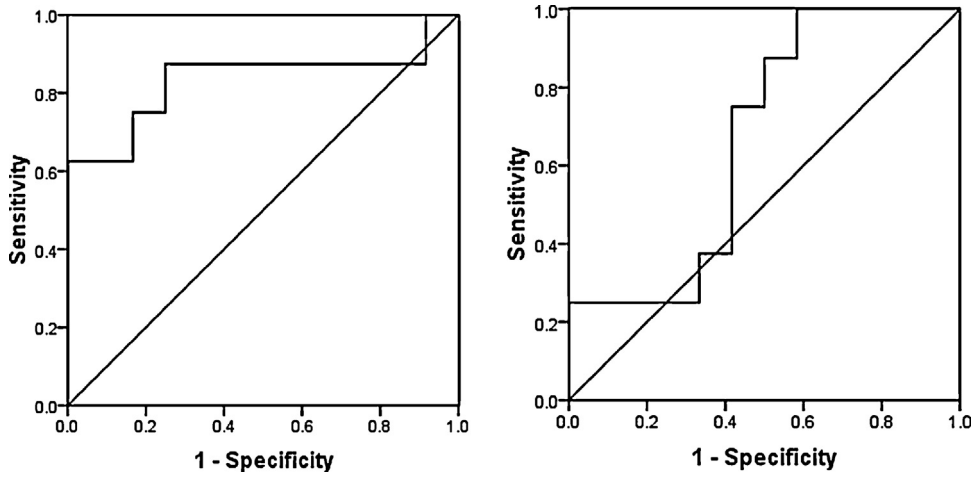

Fig. 2. ROC curves of the CRSD model (left) and the insomnia model (right).

highly useful in rTMS treatment response prediction. Furthermore, this implies that interventions focused on normalizing circadian rhythm, for example through melatonin or bright light therapy (Dodson & Zee, 2010), prior to rTMS treatment could enhance treatment efficacy. Taking this idea further, a healthy circadian rhythm may be a prerequisite for treatment response in general. This hypothesis is in line with the notion that circadian rhythm dysregulation is associated with physical and mental disease (Roenneberg & Merrow, 2016). Whether normalizing the circadian rhythm can turn non-responders into responders, and whether this is specific to rTMS for OCD or can be generalized to other treatment strategies and patient groups are interesting questions for future work.

Alternatively, these findings may indicate that CRSD could be related to different subtypes of OCD, with an overlap in clinical symptoms but differences in underlying neurobiological mechanisms, requiring different treatment approaches. Such a conceptualization is in accordance with the Research Domain Criteria (RDoC), a new approach to psychopathology with a focus on underlying biological markers rather than discrete clinical entities (Insel et al., 2010 Lilienfeld & Treadway, 2016). This approach may give rise to a shift in theory as well as clinical practice, focusing on the treatment of underlying mechanisms instead of overt symptom categories. Studying the variables associated with response and non-response can provide insight in possible subgroups that may be suggestive of biomarkers for these groups. This approach could be helpful in future studies addressing the RDoC perspective. Whether CRSD may be a biomarker for a subgroup of OCD remains a matter of speculation at this point, as the current study mainly revealed differences at the subjective level. Future studies directly comparing OCD patients without comorbid sleep disorders to patients with both OCD and clinical CRSD may provide more insight into the mechanism, using several physiological measures of the circadian rhythm.

Such an approach has previously been applied in other psychiatric populations. For example, CRSD-like symptoms, especially delayed sleep onset, are present in a majority of patients with ADHD, and through chronic sleep restriction result in impaired vigilance regulation and drowsiness as measured in the EEG (e.g. excess delta and theta) as well as inattention (see Arns, Feddema, and Kenemans (2014) for overview). Prior studies have found that such EEG measures reflective of impaired vigilance regulation were associated with non-response to SSRIs in OCD (Prichep et al., 1993), non-response to antidepressants in MDD (Arns et al., 2015), and non-response to neurofeedback in OCD (Kopřivová et al., 2013). Abnormalities in vigilance regulation have also been demonstrated in OCD (Olbrich, Olbrich, Jahn, Sander, & Adamaszek, 2013). Therefore, a direct link between CRSD, impaired vigilance regulation and treatment non-response may exist in a subgroup of OCD patients, similar to what has been reported for ADHD where clinical response to neurofeedback was mediated by normalized sleep onset insomnia (Arns and Olbrich, 2014). It may be hypothesized that this subgroup of OCD patients with higher levels of CRSD could benefit more from interventions specifically aimed at normalizing CRSD complaints, such as light therapy, melatonin or sensorimotor rhythm-neurofeedback. Intervention studies aimed at normalizing the circadian rhythm could evaluate whether this approach is effective in patients diagnosed with OCD and comorbid CRSD. Furthermore, future studies incorporating physiological measures such as EEG and objective (as opposed to subjective) sleep assessment could provide insight into the association between sleep and related biomarkers of OCD treatment response.

In addition, future work is needed to clarify the nature of the relationship between OCD and sleep, since this is not yet fully understood. One possible explanation is that OCD symptoms may lead to CRSD as they interfere with falling asleep (Boland & Ross, 2015). Some observations suggest that compulsions prevent the patient from sleeping (Coles & Sharkey, 2011), whereas others suggest that obsessions are related to insomnia (Timpano et al., 2014). On the other hand, sleep disturbances may directly or indirectly affect OCD symptoms. In this respect, the relationship may be mediated by cognitive functioning. Sleep deprivation and sleep restriction are strongly associated with cognitive impairment (Durmer & Dinges, 2005). Therefore, cognitive dysfunctions in OCD patients may be exacerbated by sleep disturbance (Nota et al., 2015). Executive functions associated with frontostriatal networks in particular have repeatedly been shown to be impaired in OCD (Menzies et al., 2008; Kuelz, Hohagen, & Voderholzer, 2004). Further decline of these cognitive functions due to sleep difficulties may therefore be related to increased symptom severity. Alternatively, the association between OCD and sleep disturbances may be explained by a third variable or a shared underlying mechanism, in some cases resulting in OCD symptoms, in other cases in sleep disturbances, or both. To investigate whether sleep disturbance plays a causal or mediating role in OCD pathology, future studies could use interventions focused on improving sleep prior to treatment of OCD symptoms.

A limitation of the current study is that it was not possible to control for comorbid depression. Only three patients in our sample did not have depressive symptoms, which was an insufficient number for covarying or comparing groups with and without comorbid depression. As noted above, most sleep disturbances in OCD patients are considerably similar to those observed in depression, but on the other hand, at least some of the sleep difficulties are independent of depressive symptoms (Cox and Olatunji, 2016Cox & Olatunji, 2016; Díaz-Román et al., 2015; Nota et al., 2015). Moreover, although some patterns in OCD may be similar to those seen in affective disorders, these should not necessarily be attributed to depressive symptoms, because a considerable amount of the symptoms of OCD and depression overlap (Baer et al., 2015; Goodwin, 2015). To provide insight into the specific effects of OCD, future studies should either exclude patients with comorbid depression or attempt to match the level of depressive symptoms in the OCD and control group.

Another limitation of this study is the lack of a treatment control condition. OCD patients were treated with rTMS and compared to healthy subjects with respect to sleep, but not to an OCD group receiving placebo rTMS or treatment as usual. Therefore, it may be argued that responders could be placebo responders. However, it can also be argued that placebo effects are irrelevant in the current prediction model, as the sleep disturbances predict non-response instead of response. Nevertheless, in order to rule out placebo effects, future studies could incorporate a treatment control condition.

A few other directions for future research are important to acknowledge. Firstly, it should be noted that rTMS is not a first-line treatment approach for OCD but an augmentation strategy that has mainly been applied in chronic and treatment-resistant patients (Berlim et al., 2013). Therefore, findings of the present study cannot be generalized to other treatment strategies, although it would be interesting to investigate whether the same prediction models apply to OCD treatment in general. Secondly, incorporating more extensive measures of circadian rhythm may be helpful for a more solid understanding of the link between OCD and CRSD. Recommendations to assess CRSD include up to two weeks actigraphy recording, measurements of endogenous melatonin onset, and questionnaires on chronotype (Zucconi & Ferri, 2014). Finally, it might be useful to standardize or monitor the moment of the day rTMS is administered, as this might interact with its effect. Earlier reports suggest that factors related to the circadian rhythm, such as variability in hormonal release and arousal, may affect neuroplasticity induced by TMS (Sale, Ridding, & Nordstrom, 2008). Especially in light of the current findings, circadian variability in neuroplasticity may then also depend on the circadian rhythm of the individual patient. Including a measure of chronotype may be helpful in future studies to test this hypothesis.

In summary, the current study confirms that some sleep disturbances are more prevalent in OCD patients than healthy subjects. The strongest evidence was found for circadian rhythm disorders, a reduced sleep duration and efficiency, and a longer sleep onset latency. Most

importantly, the findings suggest that CRSD variables can predict treatment non-response to rTMS in a sample of treatment-resistant OCD patients. This may suggest that normalizing the circadian rhythm prior to rTMS treatment for OCD symptoms can enhance treatment response. Furthermore, the findings are possibly suggestive of a subgroup of OCD patients with a different etiology, in line with the RDoC approach. These findings are promising, but as they are derived from a small sample, replication and cross-validation of this prediction model is crucial. In addition, several hypotheses can be generated for future work. The most important questions that should be addressed are whether sleep interventions prior to further treatment of OCD can turn non-responders into responders, whether the present findings can be generalized to rTMS treatment in other patient groups or other treatment approaches for OCD, and whether CRSD is related to biomarkers reflecting different forms of underlying pathology of the disorder.

Disclosures

PBF is supported by a NHMRC Practitioner Fellowship [1078567]. PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech and Brainsway Ltd and funding for research from Neuronetics and Cervel Neurotech. He is on the scientific advisory board for Bionomics Ltd. MA reports research grants, options/shares from Brain Resource Ltd. (Sydney, Australia) and neuroCare group and he is also a co-inventor on 4 patent applications [A61B5/0402; US2007/0299323, A1; WO2010/139361 A1] related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents.

Acknowledgements

We would like to thank Vera Kruiver, Rosalinde van Ruth, Irene Giesbers, Marleen Stam, Myrthe van Eerdt and Nicole van Merode for support and collecting the data used in this study.

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