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An open label pilot trial of sequential bifrontal low frequency r-TMS in the treatment of primary insomnia

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ABSTRACT

This pilot study examines the therapeutic effects of bifrontal low frequency (LF) TMS on primary insomnia. In this prospective, open-label study 20 patients with primary insomnia and without major depressive disorder received 15 sequential bifrontal LF rTMS stimulation sessions. By week 3, PSQI scores declined from baseline score of 12.57(*sd* 2.74) to 9.50 (*sd* 4.27), a large effects size (0.80 (CI 0.29, 1.36)), and CGI-I scores improved for 52.6% of participants. Results of this pilot indicate that the novel bifrontal LF rTMS benefitted this group of patients suffering from primary insomnia, with absence of sham control a significant study limitation.

1. Introduction

Insomnia affects 10–30% of the population, and primary insomnia not secondary to co-morbid psychiatric, medical, or substance use, is present in 1-2% of the general population (Doghramji, 2006). Insomnia is strongly correlated to numerous health conditions and reduces quality of life (Morin and Benca, 2012). Treatment options for chronic insomnia include non-pharmacologic and pharmacologic options, frequently requiring both (Morin and Benca, 2012). Despite multiple treatment options, approximately 40% of affected patients remain treatment-resistant (Qaseem et al., 2016). Transcranial Magnetic Stimulation (TMS) treatment studies and general neurophysiological studies have shown presence of a diffuse cortical hyper-arousal in patients with chronic insomnia (Bonnet and Arand, 2010), with frontal cortices the most implicated in hyperarousal (Nofzinger et al., 2006). The meta-analytic findings on studies exploring repetitive TMS (rTMS) benefits in sleep disorders indicate that low frequency (LF) rTMS outperforms control conditions in regards to sleep improvement measured by the Pittsburgh Sleep Quality index (PSQI) (Jiang et al., 2019; Sun et al., 2021), albeit with notable sham stimulation placebo effect (Jiang et al., 2019). To date, such studies not only fail to offer specific guidance on rTMS insomnia protocols, current insomnia treatment guidelines do not even reference rTMS (Qaseem et al., 2016).

In this brief report we present findings from a pilot study evaluating a novel rTMS protocol in the treatment of primary insomnia. Considering findings from prior neurophysiologic, intervention studies, we opted for neuroinhibition through utilization of bilateral LF rTMS to the dorsolateral prefrontal cortex (DLPFC). We hypothesized that such neuroinhibitory effects would dampen the diffuse cortical hyperarousal as seen in chronic insomnia patients, thus improving symptoms of primary insomnia.

2. Material and methods

2.1. Participants

This study used a prospective, open label design to examine the therapeutic effects of 15 sequential bilateral LF TMS in 20 patients ages 21 to 65 years meeting DSM-IV criteria for primary insomnia. Exclusion criteria included: current diagnosis of major depressive disorder; substance abuse in the two weeks prior to baseline; and current or past history of a major medical or psychiatric disorder potentially contributing to insomnia. Psychotropic medications were permitted, with medication change prohibited within 2 weeks prior to TMS treatment and during the 3-week treatment period. The study was approved by the University of Florida Institutional Review Board and all participants provided written consent prior to initiation of study procedures. The baseline visit included a clinical diagnostic assessment, physical exam, and clinician and patient ratings. Subjects were treated 5 days per week for 3 weeks. Primary and secondary outcomes were obtained weekly.

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2.2. Assessments

Primary Outcomes: The study used two primary outcomes to determine treatment efficacy, the Pittsburgh Sleep Quality index (PSQI) and the Clinical Global Impression Scale - improvement (CGI-I) (Berk et al., 2008; Mollayeva et al., 2016). The PSQI is a widely used 19-item self-report that evaluates a patient's insomnia over the past month (Mollayeva et al., 2016). Seven component scores are combined to a PSQI Global Score ranging from 0 to 21. The CGI is clinician-rated measure with established validity and sensitivity to change and is commonly used in clinical trials, providing ratings for severity of illness (CGI-S) and global improvement (CGI-I) (Berk et al., 2008).

Secondary Outcomes: Secondary measures included the Insomnia Severity Index (ISI) (Bastien et al., 2001), the Epworth Sleepiness Scale (ESS) (Kendzerska et al., 2014), the Pittsburgh Insomnia Rating Scale (PIRS) (Vernon et al., 2010) and the CGI-S. Three component scores of the PSQI, sleep latency, sleep duration and habitual sleep efficiency, were also examined. Furthermore, Montgomery Asberg Depression Rating Scale (MADRS) ratings were used to document any concurrent depression symptomatology (Svanborg and Asberg, 1994).

2.3. Treatment

Treatment was provided with the NeuroStar system targeting the DLPFC. Subjects received 15 sessions of daily, sequential bifrontal LF rTMS stimulation over three weeks. Stimulation parameters were 1 Hz at 80–120% motor threshold (MT). Forty minutes of treatment each was provided over the left, then right, prefrontal cortex. During week 1, subjects were treated at 80% MT, 100% during week 2 and 120% for week 3.

2.4. Statistical analysis

Changes from the baseline measure were summarized, and simultaneous 95% confidence limits presented. For continuous measures, we used Dunnett's t-test to compare the changes at each visit from the baseline measure, and calculated effect sizes for changes from baseline to week 3 using Hedges' g and its 95% Confidence Interval. We interpreted effect size magnitudes as small (0.20), medium (0.50), and large (0.080). For the evaluation of CGI-I changes we reported percentages of patient with significant improvement (scores of 1 or 2) and used the Cochran-Mantel-Haenszel Statistic to test whether CGI-I estimates were equal at weeks 1, 2 and 3. Statistical analysis was performed using SAS 9.4 (NC, Cary).

3. Results

3.1. Primary outcomes

PSQI scores steadily declined over the course of treatment from 12.50 (*sd* 2.74) to 9.50 (*sd* 4.27) and improvement reached statistical significance by week 3 with a large effect size (0.80 (CI 0.29, 1.36)). Significant CGI-I improvements occurred for 52.6% of participants by week 3 (df 2/13.2255, $p = 0.0013$). Further detail is provided in Table 1.

Table
Summary of means and standard deviations, test of change from baseline, and effect sizes (Hedges' g).

Instrument	Visit	N	Mean	Standard Deviation	Difference to Baseline	Simultaneous 95% CI		Significant comparisons at 0.05 level	Hedges' g (95% CI)
						Lower	Upper		
PSQI Global	Baseline	20	12.50	2.74					
	EOW1	20	11.70	3.73	−0.8000	−2.9534	1.3534		
	EOW2	19	10.37	4.04	−2.1053	−4.2868	0.0762		
	EOW3	19	9.50	4.27	−3.0000	−5.2124	−0.7876	*	0.80 (0.29, 1.36)
PSQI Latency	Baseline	20	2.20	0.89					
	EOW1	20	2.05	1.19	−0.1500	−0.7197	0.4197		
	EOW2	19	2.00	1.15	−0.1579	−0.7351	0.4193		
	EOW3	19	1.58	1.26	−0.5789	−1.1561	−0.0018	*	0.54 (0.10, 1.02)
PSQI Duration	Baseline	20	2.25	0.85					
	EOW1	20	2.10	1.02	−0.1500	−0.5794	0.2794		
	EOW2	19	1.95	0.85	−0.2632	−0.6982	0.1719		
	EOW3	19	1.39	1.14	−0.7778	−1.2190	−0.3366	*	0.82 (0.41, 1.29)
PSQI Efficiency	Baseline	20	1.30	1.22					
	EOW1	20	1.55	1.00	0.2500	−0.6715	1.1715		
	EOW2	19	1.26	1.05	0.0526	−0.8810	0.9862		
	EOW3	19	0.84	1.07	−0.3684	−1.3020	0.5652		0.38 (−0.24, 1.04)
ISI	Baseline	19	20.05	5.14					
	EOW1	19	18.37	5.49	−1.684	−5.064	1.696		
	EOW2	18	13.94	7.10	−6.056	−9.482	−2.629	*	
	EOW3	18	10.29	7.74	−9.412	−12.890	−5.934	*	1.41 (0.79, 2.16)
ESS	Baseline	17	6.29	6.71					
	EOW1	16	5.56	5.49	−0.625	−4.868	3.618		
	EOW2	16	4.50	3.88	−2.188	−6.430	2.055		
	EOW3	16	4.06	4.40	−2.625	−6.868	1.618		0.37 (−0.24, 1.01)
PIRS	Baseline	17	93.59	30.47					
	EOW1	17	87.24	36.31	−6.35	−30.91	18.20		
	EOW2	16	69.31	43.19	−25.00	−49.94	−0.06	*	
	EOW3	16	56.50	43.91	−37.81	−62.75	−12.87	*	0.62 (0.08, 1.20)
CGI-S	Baseline	20	4.10	0.72					
	EOW1	20	4.00	0.82	−0.1053	−0.5590	0.3485		
	EOW2	19	3.67	0.84	−0.3889	−0.8490	0.0713		
	EOW3	19	3.11	1.05	−0.9474	−1.4011	−0.4936	*	1.05 (0.51, 1.67)
MADRS	Baseline	20	7.30	2.49					
	EOW1	20	6.85	3.12	−0.450	−3.514	2.614		
	EOW2	19	6.21	3.21	−1.053	−4.157	2.052		
	EOW3	19	5.84	4.96	−1.421	−4.525	1.683		0.34 (−0.32, 1.03)

Note: PSQI - Pittsburgh Sleep Quality index; ISI - Insomnia Severity Index; ESS - Epworth Sleepiness Scale; PIRS - Pittsburgh Insomnia Rating Scale; CGI-S - Clinical Global Impression-severity; MADRS - Montgomery Asberg Depression Rating Scale; EOW - end of week.

3.2. Secondary outcomes

ISI scores steadily declined over the course of treatment from 20.05 (*sd* 5.14) to 10.29 (*sd* 7.74) and week 3 effect size was large (1.41 (95% CI 0.79, 2.16)). ESS scores were in the non-sleepy range at baseline (6.29, *sd* 6.71) and did not change significantly during treatment. PIRS scores steadily declined over the course of treatment from 93.59 (*sd* 30.47) to 56.50 (*sd* 43.91) and week 3 effect size was medium (0.62 (95% CI 0.08, 1.01)). Of the PSQI component scores, efficiency did not improve significantly, but latency and duration improved with medium and large week 3 effect sizes, respectively. MADRS scores at baseline were low (mean 7.30, *sd* 2.49), consistent with the exclusion of patients with major depressive disorder and did not change significantly by week 3 (mean 5.84, *sd* 4.96).

3.3. Safety

The TMS sessions were well tolerated.

4. Discussion

We report significant sleep improvements per PSQI and CGI-I scores after three weeks of treatment in this open label pilot of bilateral LF DLPFC rTMS in the treatment of primary insomnia in patients without depression. Our PSQI findings are similar to Feng et al.'s study utilizing a 10-treatment bilateral LF protocol of 750 pulses applied to the left and right DLPFC cortex daily in 32 patients with primary insomnia and without psychiatric or neurological comorbidities (Feng et al., 2019). The current study showed clinical effectiveness of bilateral LF rTMS in the treatment of primary insomnia using a novel three-week protocol (2400 pulses delivered to both left and right DLPFC daily for 15 sessions); the week-to-week progression of improvements in the current study is consistent with meta-analytic results reported by Jiang et al. who observed effect size increases with lengthening treatment duration within 30 days (Jiang et al., 2019).

Of note, all but one of the nine studies included in the meta-analysis by Jiang et al. and 19/35 studies included by Sun et al. had targeted the right DLPFC (Jiang et al., 2019; Sun et al., 2021). The contribution of frequency and location to the efficacy of rTMS for insomnia is unknown, unlike depression or OCD, where relative efficacy of different stimulation protocols have been formally examined through network metanalysis methods (Brunoni et al., 2017; Fitzsimmons et al., 2022). The initial lower intensity rTMS (80% MT) with weekly increases to 100% MT and 120% MT was selected for tolerability to foster patient retention. In fact, the sequential bilateral rTMS treatment was well tolerated with no participant attrition. Of note, one hypothesized mechanism of action for rTMS is neural plasticity (Liston et al., 2014), such that our weekly intensity increases could theoretically have contributed to some unknown neurobiological effect or beneficial enhancement on neural plasticity. Additionally, during the treatment course there was no significant change in patient mood or MADRS scores.

The study strengths included screen-out of comorbidity and breadth in employed insomnia rating scales. Yet the study was limited in its design given the lack of randomization or control conditions. This is a considerable weakness, given the sizeable placebo effect of sham rTMS previously noted (Jiang et al., 2019). Another potential practical limitation was the lengthy (80-minute) rTMS protocol which may be unacceptable for patients. In summary, although our pilot study used an open-label design, it demonstrates a feasible, well tolerated protocol that was effective for this group of participants with primary insomnia.

5. Conclusion

This pilot study contributes to our knowledge about the potential for clinical effectiveness in primary insomnia using bilateral LF rTMS to DLPFC. Clinically significant benefit was demonstrated in the primary outcome measures (PSQI and CGI-I) as well as secondary measures. Although the results of rTMS in this study are quite encouraging, the absence of a sham control condition significantly limits the interpretation of findings. Given its potential, bilateral LF rTMS to the DLPFC should be further evaluated in double-blind, sham-controlled trials.

CRediT authorship contribution statement

Richard C. Holbert: Conceptualization, Methodology, Project administration, Investigation, Writing – original draft, Writing – review & editing. **Brent R. Carr:** Conceptualization, Writing – original draft, Writing – review & editing. **Regina Bussing:** Conceptualization, Resources, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None of the authors have a conflict of interest to declare in regards to this research. Research reported in this publication was supported through an internal Department of Psychiatry seed funding award and through statistical analysis support provided by the University of Florida Clinical and Translational Science Institute, which is supported in part by the NIH National Center for Advancing Translational Sciences under award number UL1TR001427. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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