Brain Stimulation 12 (2019) 184–186

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Sleep improvements and associations with default mode network functional connectivity following rTMS for generalized anxiety disorder

Keywords:
Neuromodulation
Neuroimaging
Anxiety
Clinical trial

Dear editor:

Sleep disturbance is endorsed by over two-thirds of patients diagnosed with generalized anxiety disorder (GAD; [1]). Neuromodulation has the potential to improve sleep in patients with GAD either directly (by altering neurocircuitry) or indirectly (by improving anxiety symptoms). A recent randomized-controlled trial (RCT) reported that low-frequency repetitive transcranial magnetic stimulation (rTMS) of the parietal cortex improved sleep in patients diagnosed with GAD and comorbid insomnia [2]. However, no neuroimaging data were reported. Sleep disturbance is associated with altered functional connectivity (FC) of the default mode network (DMN; [3]) – a circuit of brain regions which systematically demonstrates synchronous increased activation during passive resting state and can be reliably measured by resting-state functional magnetic resonance imaging (rsfMRI). Altered DMN-FC is also implicated in excessive worry [4] – a core feature of GAD. Here we report a secondary analysis on sleep outcomes from a RCT comparing active versus sham low-frequency rTMS of the right dorsolateral prefrontal cortex (rDLPFC) for GAD [5] and identify neural correlates. We hypothesized that patients receiving active versus sham would report more post-rTMS sleep improvements, and improvements would be associated with posttreatment changes in DMN-FC during rsfMRI.

Study procedures were approved by the Hartford Hospital Institutional Review Board and all patients gave written informed consent. The study was listed on clinicaltrials.gov (Registration Number: NCT01659736). Detailed information regarding recruitment and participant flow were presented elsewhere [5]. Briefly, we randomized adult patients with GAD to either active ($n = 13$; age $M = 44.00$, $SD = 11.95$; 85% Women; 92% White) or sham ($n = 12$; age $M = 44.58$, $SD = 14.75$; 67% Women; 100% White). Groups were matched on age [$t\,(23) = 0.11$, $p = .91$], gender [$\chi^2\,(1, N = 25) = 1.10$, $p = .29$], and race [$\chi^2\,(1, N = 25) = 1.10$, $p = .31$]. Treatment entailed 30 sessions (5 days/week) rDLPFC-targeted low-frequency (1 Hz, 90% resting motor threshold, 900 pulses/session) rTMS using the FDA-Cleared NeuroStar TMS Therapy System. Sham was administered using a sham coil (Neuronetics XPLOR). Neuronavigation was used to locate rDLPFC according to the Montreal Neurological Institute (MNI) coordinates ($x = 42$, $y = 36$, $z = 32$) based upon previous research [6].

Sleep disruption was assessed at pre, post, and 3-month follow-up using the Insomnia Severity Index (ISI, [7]). ISI scores were analyzed using the intent-to-treat sample with a linear mixed effects model with treatment (active vs. sham) as a between-subject factor, time (pretreatment, posttreatment, follow-up) as a within-subject factor and the interaction between treatment and time. Least square means (LSM) and standard errors (SE) were plotted (See Fig. 1 Panel A) and post-hoc tests were performed to explain significant effects. As predicted, there was a significant group by time interaction [$F\,(2, 33.3) = 3.81$, $p = .03$], with only the active group demonstrating statistically significant improvement over time [$F\,(2, 33.8) = 11.27$, $p = .0002$]. In active, ISI scores were clinically elevated at pretreatment, subthreshold at posttreatment, and nonclinical at 3-month follow-up. Sham ISI scores were subthreshold at all timepoints. Group ISI scores differed significantly only at baseline [$F\,(1, 35.3) = 5.36$, $p = .03$].

rsFMRI was collected for 5.25 minutes at pre and posttreatment. Blood oxygenation level dependent (BOLD) signal was obtained with T2*-weighted echo planar imaging (EPI) sequence (TR/TE = 1500/27 msec, 29 contiguous slices, $3.4 \times 3.4 \times 5$ mm^3 voxels, 210 timepoints; first 6 excluded from analysis). The final imaging sample was 16 (active $n = 9$; sham $n = 7$) due to attrition from the clinical trial ($n = 6$), patient refusal to complete posttreatment MRI ($n = 2$), or exclusion of MRI data due to incidental findings without clinical manifestations ($n = 1$). Data were preprocessed using SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London), using realignment, slice timing correction spatial normalization to MNI space, and smoothing with 9 mm^3 Gaussian kernel.

Independent components analysis (ICA) was used to identify temporally distinct resting-state components. Group spatial ICA was conducted using the Infomax algorithm [8] within the GIFT software (http://icatb.sourceforge.net/, version2.0a). Seventy-five components were modeled and DMN components of interest were identified based on the Stanford functional ROI atlas (http://findlab.stanford.edu/functional_ROIs.html), resulting in seven components (See Fig. 1 Panel B). Functional network connectivity (FNC) toolbox version 2.3a (http://mialab.mrn.org/software/fnc/) was used to estimate correlations between these components. We computed within-DMN FC strength by calculating the sum of correlation values (Fisher Z value) of all 21 component-pairs within

https://doi.org/10.1016/j.brs.2018.09.004

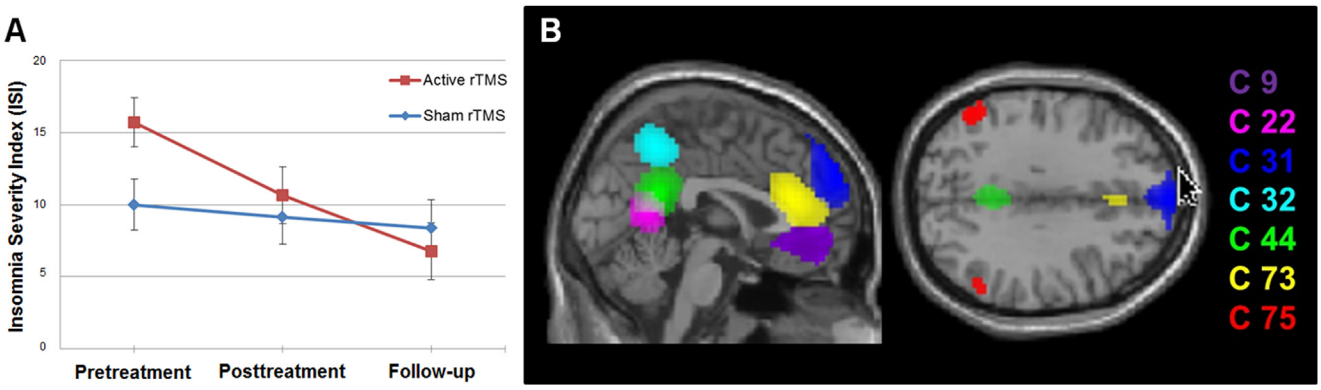

Fig. 1. Panel A. Insomnia Severity Index least square means and standard errors for pretreatment, posttreatment, and 3-month follow-up by group. Panel B. Maps of the seven ICA components (C) identified as part of the default mode network during the resting state fMRI scan. Frontal lobe midline clusters including medial prefrontal cortex and anterior cingulate cortex = components 31, 73 and 9, posterior cingulate cortex/precuneus clusters = components 22, 32 and 44, and bilateral inferior parietal lobe = component 75.

the DMN. This was calculated for each participant at each timepoint (pre- and post-treatment).

In patients receiving active rTMS, pre-to-post percentage improvement (i.e., decrease) in ISI correlated significantly with decreased within-DMN FC [$r = 0.73$, $p = .025$]. This association remained statistically significant when controlling for changes in anxiety (Hamilton Anxiety Rating Scale), worry (Penn State Worry Questionnaire), and depression (Hamilton Rating Scale for Depression) [*partial* $r = 0.90$, $p = .014$]. In the sham group the association between DMN-FC and ISI percent change was moderately positive ($r = 0.55$), but not statistically significant ($p = .196$), and became moderately negative ($r = -0.41$, $p = .416$) after excluding one outlier. Partial correlations were not performed for the sham group due to the analysis having only one degree of freedom.

Results suggest that rTMS may improve sleep in patients with GAD and these improvements correlate with changes in DMN-FC. However, sample sizes were small and replication with larger samples is needed. In addition, sleep problems were assessed using self-report and groups were not equated on the ISI at pretreatment. Nevertheless, only the active group demonstrated clinically meaningful improvement that was associated with decreased within DMN-FC, and this pattern argues in favor of a treatment effect. These results are in contrast to previous research in depression where no rTMS effect on sleep was found (e.g., [9]). This could be explained by differences in sleep psychopathology and/or neurobiology by diagnosis [10] or differences in study-specific rTMS parameters. Future GAD research is needed to identify optimal rTMS parameters and determine causal pathways among changes in DMN-FC, worry, and sleep following rTMS.

Declaration of interest

Drs. Diefenbach and Goethe report that they receive material support from Neuronetics. Dr. Goethe reports that he has received speaker fees to discuss rTMS at professional conferences from Neuronetics and grant support from Alkermes, Amerex, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Eisai, Forest, Janssen, Johnson & Johnson, Merck/Schering-Plough, Neuronetics, Neosync, Novartis, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, and Teva. Dr. Tolin receives funding from Palo Alto Health Sciences. Drs. Rabany, Hallion, Gueorguieva, Assaf, and Mr. Zertuche report no potential conflicts of interest.

Acknowledgments

This work was supported by the Hartford HealthCare Research Funding Initiative (#129522). The funding source had no role in the study design; collection, analysis, interpretation of data; writing the report, or in making the decision to submit the article for publication. Material support was provided by Neuronetics. Neuronetics reviewed a draft of this report prior to submission and otherwise had no role in the study design; collection, analysis, interpretation of data; writing the report, or in making the decision to submit the article for publication.

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Gretchen J. Diefenbach*
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA
Yale University School of Medicine, 333 Cedar Street, New Haven, CT, USA

Liron Rabany
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

Lauren S. Hallion[1]
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

David F. Tolin
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

Yale University School of Medicine, 333 Cedar Street, New Haven, CT, USA

John W. Goethe
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

Ralitza Gueorguieva
Yale University School of Medicine, 333 Cedar Street, New Haven, CT, USA

Luis Zertuche
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

Michal Assaf
The Institute of Living, 200 Retreat Avenue, Hartford, CT, USA

Yale University School of Medicine, 333 Cedar Street, New Haven, CT, USA

* Corresponding author. Anxiety Disorders Center, The Institute of Living, 200 Retreat Avenue, Hartford, CT, 06106, USA.
E-mail address: Gretchen.Diefenbach@hhchealth.org (G.J. Diefenbach).

27 August 2018
Available online 12 September 2018

[1] University of Pittsburgh, 4200 Fifth Avenue, Pittsburgh, PA, USA.