Psychiatry Research 186 (2011) 138–140

Contents lists available at ScienceDirect

Psychiatry Research

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

Brief report

Temporo-parietal junction stimulation in the treatment of depersonalization disorder

Antonio Mantovani [a,b,*], Daphne Simeon [c], Nina Urban [d], Peter Bulow [a], Anouk Allart [a], Sarah Lisanby [a]

[a] Division of Brain Stimulation and Therapeutic Modulation, Department of Psychiatry, Columbia University/New York State Psychiatric Institute, New York, USA
[b] Division of Psychiatry, Department of Neuroscience, Siena University, Siena, Italy
[c] Department of Psychiatry, Albert Einstein School of Medicine/Beth Israel Medical Center, New York, USA
[d] Division of Clinical Psychobiology, Department of Psychiatry, Columbia University/New York State Psychiatric Institute, New York, USA

ARTICLE INFO

Article history:
Received 31 May 2010
Received in revised form 14 July 2010
Accepted 18 August 2010

Keywords:
Depersonalization disorder
Repetitive Transcranial Magnetic Stimulation
Temporo-parietal junction

ABSTRACT

This is the first clinical trial of repetitive Transcranial Magnetic Stimulation (rTMS) in depersonalization disorder (DPD). After 3 weeks of right temporo-parietal junction (TPJ) rTMS, 6/12 patients responded. Five responders received 3 more weeks of right TPJ rTMS showing 68% DPD symptoms improvement. Right TPJ rTMS was safe and effective.

1. Introduction

Neither medications nor psychotherapy have been shown to be effective for DPD (Sierra, 2008), prompting exploration of other treatment modalities.

In one case high-frequency repetitive Transcranial Magnetic Stimulation (rTMS) to left dorsolateral prefrontal cortex (DLPFC) improved DPD symptoms (Jiménez-Genchi, 2004). However, excitatory rTMS to DLPFC may not be optimal given reports of increased activity in prefrontal cortex (Phillips and Sierra, 2003), and evidence for involvement of other brain regions in DPD (Simeon et al., 2000). Importantly, DPD patients showed increased glucose metabolism in temporal, parietal, and occipital areas, suggesting abnormalities along auditory, somatosensory, and visual processing pathways, as well as in areas responsible for an integrated body schema.

Using evoked potential mapping, Blanke et al. (2005) demonstrated bilateral temporo-parietal junction (TPJ) activation when healthy volunteers imagined themselves in position and visual perspective that generally are reported by people experiencing spontaneous "out of body experiences (OBEs)." Applications of single-pulse TMS to TPJ impaired mental transformation of one's own body and had no effect for imagined spatial transformations of external objects. This suggests that TPJ has a crucial role in the conscious experience of the normal self, and mediates spatial unity of self and body, process impaired in dissociative conditions.

We present results of the first trial testing the effects of inhibitory low-frequency rTMS administered to TPJ in DPD patients. We hypothesized that right-side stimulation would be more effective because excitation of this site by electrical stimulation induced OBEs (Blanke et al., 2002). At the same time, since bilateral involvement has been reported, we allowed partial responders and nonresponders to right-side stimulation to cross over to left TPJ stimulation. Subjects were informed that either right or left-sided stimulation might be effective.

2. Methods

This open-label cross-over study consisted of two phases: (1) 3 weeks of right TPJ rTMS, (2) 3 more weeks of right TPJ rTMS for full responders, who showed 50% improvement on the Cambridge Depersonalization Scale (CDS), our primary outcome measure, by the end of phase 1, or 3 more weeks of right or left TPJ rTMS for partial responders, who showed at least 25% decrease on the CDS, or 3 more weeks of left TPJ rTMS for non-responders to phase 1.

Twelve right-handed outpatients (9 male; age 33.6 ± 12.9 years) who met DSM-IV-TR criteria for DPD entered the study. DPD age of onset was 33.6 ± 12.9 years and illness duration was 9.8 ± 12 years. Participants were recruited from the Brain Behavior Clinic of Columbia Psychiatry and the Depersonalization and Dissociation Program of Mount Sinai and Beth Israel Medical Centers in New York. Two patients were unmedicated and 10 had their concomitant medications (e.g. Serotonin Reuptake Inhibitors, Anticonvulsants, Atypical Antispychotics, and Benzodiazepines) at stable doses for at least 2 months prior to rTMS and throughout the trial. Two patients met criteria for Major Depressive Disorder, 3 for Generalized Anxiety Disorder, and 1 for Panic Disorder. Nobody else met criteria for any other axis I and/or II disorders by using the Structured Clinical Interview (SCID-I and II) for the DSM-IV. Individuals with a history of seizure or head trauma were excluded. All patients gave written informed consent, and the

* Corresponding author. Division of Brain Stimulation and Therapeutic Modulation, Department of Psychiatry, Columbia University/New York State Psychiatric Institute, 1051 Riverside Drive, Unit 21, New York, NY 10032, USA. Tel.: +1 212 543 6081; fax: +1 212 543 4284.
E-mail address: am2518@columbia.edu (A. Mantovani).

0165-1781/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psychres.2010.08.022

protocol was approved by the New York State Psychiatric Institute/Columbia University IRB.

rTMS was administered with the MAGSTIM super-rapid stimulator (Magstim Company, Ltd., Whitland, U.K.) using a vacuum cooled 70-mm figure-8 coil. Stimulation parameters were 1-Hz, 30 min train (1800 pulses/day) at 100% of resting motor threshold (EMG-determined, and repeated weekly). The coil was positioned over the right and left TPJ, between T4/P4 and T3/P3 respectively, according to the 10–20 International EEG System.

Symptoms were rated at baseline and after each week by observer- and self-reported scales. Clinician-Administered Dissociative States Scale (CADSS), Hamilton Depression and Anxiety Rating Scales (HDRS and HARS), and Clinical Global Impression-Severity (CGI-S) were administered by a psychiatrist not involved in the treatment, while CDS, Dissociation Evaluation Scale (DES), Beck Depression Inventory (BDI–II), Zung Self-rating Anxiety Scale (Zung-SAS), and Patient Global Impression (PGI) were filled in by patients. The primary efficacy measure was the CDS, a comprehensive 29-item scale inquiring about subjective experiences associated with depersonalization symptoms (Sierra and Berrios, 2000).

Statistical analyses were performed using SPSS library, 13.0 version. Chi-Square and Student *t*-test were applied to compare demographic and clinical data. Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, was applied to evaluate time-dependent effects of rTMS on depersonalization (CDS, CADSS and DES), depression (HDRS-24, BDI), anxiety (HARS, Zung-SAS), and clinical global impression severity scores (CGI-S, PGI), followed by LSD post-hoc tests. Pearson's correlations were applied to examine the relationship between depression/anxiety and DPD symptoms.

3. Results

All 12 patients completed phase 1, with no adverse events. Four patients dropped out after phase 1 because subjectively they did not feel any benefit from rTMS.

At 3 weeks (end of phase 1) the entire sample response rate was 50% (6 out of 12). Specifically 4 patients were classified as full responders and 2 as partial responders. All responders, except for 1, who experienced a partial response and wanted to be crossed over to the left TPJ rTMS, entered phase 2 to test whether additional right TPJ stimulation would improve further their symptoms. After 6 weeks (end of phase 2), response rate was still 50%, with the same responders as at the end of phase 1. Of the 3 who were switched to left TPJ rTMS, 1 remained a partial responder and 2 were classified as nonresponders.

Responders did not significantly differ from nonresponders in demographics, number of concurrent axis I disorders, baseline clinical ratings, or with regard to their daily dose of Benzodiazepines. Specifically, 2 of the 6 responders were on lorazepam equivalent dose of 4 mg/d, and 3 of the 6 non-responders were on lorazepam equivalent

Table 1
Clinical measures across 3 and 6 weeks of TPJ rTMS in DPD patients.

Phase 1 – entire sample				Phase 1 responders crossed to Phase 2			Phase 1 non-responders crossed to Phase 2				
Right TPJ rTMS ($n=12$)				Phase 1 right TPJ rTMS ($n=6$)		Phase 2 right TPJ rTMS ($n=5$)	Phase 1 right TPJ rTMS ($n=6$)		Phase 2 left TPJ rTMS ($n=3$)		
Dependent measures	Baseline	Week 3	ANOVA[a]	Baseline	Week 3	Week 6	Baseline	Week 3	Week 6	ANOVA[b]	ANOVA[c]
CDS[d]	113.9 ± 41.1	86.7 ± 46.9	$F=4.5$, $df=3$, $p=0.009$	105.7 ± 49.9	52.3 ± 31.6	35.8 ± 29.9	122.2 ± 32.8	121.2 ± 31.9	106.3 ± 55.7	$F=7.4$, $df=6$, $p=0.000$	$F=2.6$, $df=6$, $p=0.033$
CADSS[d]	22.7 ± 12.3	12.2 ± 8.2	$F=6.3$, $df=3$, $p=0.002$	27.7 ± 14.6	12 ± 10.4	3.6 ± 3.3	17.7 ± 7.9	12.5 ± 6.1	15.5 ± 9.5	$F=6.2$, $df=6$, $p=0.000$	ns
DES[d]	55.7 ± 37.2	35.5 ± 17.1	$F=3.1$, $df=3$, $p=0.041$	66.2 ± 49.9	29 ± 16.3	14 ± 10.3	45.3 ± 17.3	42 ± 16.5	43.8 ± 18.5	$F=3.8$, $df=6$, $p=0.004$	ns
HDRS-24[d]	17.8 ± 6.1	14 ± 5.3	$F=3.5$, $df=3$, $p=0.025$	15 ± 5.9	11.5 ± 5.9	4.2 ± 4	20.7 ± 5.2	16.5 ± 3.4	17.7 ± 2.6	$F=4.3$, $df=6$, $p=0.002$	ns
BDI–II[d]	15.7 ± 8	13.1 ± 8.1	ns	14.7 ± 9	8.2 ± 7.3	5.4 ± 6.8	16.8 ± 7.5	18 ± 5.8	17 ± 4	$F=3.9$, $df=6$, $p=0.003$	ns
HARS[d]	14.7 ± 6.2	9.7 ± 5.7	$F=6.3$, $df=3$, $p=0.002$	11.7 ± 6.2	6.7 ± 4.9	2.8 ± 3.6	17.8 ± 4.8	13.3 ± 4.2	13.3 ± 7.5	$F=3.9$, $df=6$, $p=0.003$	ns
ZUNG-SAS[d]	34.2 ± 6.4	34 ± 6.3	ns	35.2 ± 7.3	31.8 ± 4	29.4 ± 6.3	34.6 ± 7.5	37.6 ± 7.3	34.9 ± 7.8	$F=2.8$, $df=6$, $p=0.023$	ns
CGI-S[d]	4.7 ± 0.6	4 ± 0.8	$F=4.3$, $df=3$, $p=0.012$	5 ± 0.6	3.5 ± 0.8	2.6 ± 1.1	4.5 ± 0.5	4.5 ± 0.5	4.3 ± 0.6	$F=8.5$, $df=6$, $p=0.000$	$F=7.4$, $df=6$, $p=0.001$
PGI[d]	4.7 ± 1.2	4.6 ± 1.2	ns	4.3 ± 1.4	4 ± 1.1	3.2 ± 1.3	5.2 ± 0.9	5.2 ± 0.9	5 ± 0.6	$F=3.6$, $df=6$, $p=0.006$	ns

TPJ = Temporo-Parietal Junction.
rTMS = repetitive Transcranial Magnetic Stimulation.
DPD = Depersonalization Disorder.
CDS = Cambridge Depersonalization Scale Hamilton Depression Rating Scale.
CADSS = Clinician-Administered Dissociative States Scale.
HDRS-24 = Hamilton Depression Rating Scale.
BDI–II = Beck Depression Inventory.
DES = Dissociation Evaluation Scale.
HARS = Hamilton Anxiety Rating Scale.
ZUNG-SAS = Zung-Self Administered Scale.
CGI-S = Clinical Global Impression-Severity.
PGI = Patient Global Impression.
[a] Repeated-measures analysis of variance (ANOVA), main effect of time after 3 weeks of rTMS ($n=12$).
[b] Repeated-measures analysis of variance (ANOVA), main effect of time after 6 weeks of rTMS ($n=8$).
[c] Repeated-measures analysis of variance (ANOVA), time by group (right TPJ versus right + left TPJ rTMS) interaction after 6 weeks.
[d] Rating scales were administered every week; in the table we report the mean scores obtained every 3 weeks.

dose of 3 mg/d. Responders significantly differ from nonresponders in DPD symptoms age of onset (29.8 ± 9 versus 17.7 ± 3 years) which was significantly younger in nonresponders ($t = -3.13$, $df = 6.01$, $p = 0.020$).

Clinical measures from baseline to week 6 are presented in Table 1. Repeated-measures ANOVA revealed a significant main effect of time on depersonalization and dissociation (CDS, CADSS and DES), depression (HDRS-24), anxiety (HARS), and global impression (CGI-S) at the end of phase 1. On average, the entire sample showed a 24% reduction in CDS total scores after 3 weeks of right TPJ rTMS.

After 6 weeks of rTMS repeated-measures ANOVA revealed a significant main effect of time on depersonalization and dissociation (CDS, CADSS and DES), depression (HDRS-24 and BDI–II), anxiety (HARS and Zung-SAS), and global impression (CGI-S and PGI). Time by group interactions were examined to determine which of these improvements were related to 6 weeks of right TPJ stimulation versus 3 weeks of right TPJ plus 3 weeks of left TPJ rTMS. The only significant time by group interactions were seen with CDS and CGI-S (Table 1).

The group that received 6 weeks of right TPJ rTMS ($n = 5$) demonstrated a significant decrease ($F = 7.87$, $df = 6$, $p = 0.000$) in symptom severity (CGI-S changed from severe to mild-borderline) with a significant ($F = 8.81$, $df = 6$, $p = 0.000$) 68% reduction in CDS scores from the beginning to the end of the treatment. Post-hoc analyses revealed that from week 3 to week 6 there was a significant improvement in CDS total scores by an additional 35% ($p = 0.021$). The group ($n = 3$) that received 3 weeks of left TPJ rTMS after right TPJ rTMS showed no change in symptoms severity ($F = 2.69$, $df = 6$, $p = 0.068$) and only 7% improvement in CDS scores ($F = 0.94$, $df = 6$, $p = 0.501$).

In responders, depression (HDRS and BDI-II) and anxiety (HARS and Zung-SAS) changes from baseline were not correlated with CDS changes after treatment. CDS and CADSS changes from baseline to treatment completion were highly intercorrelated ($r = 0.961$, $p = 0.009$).

4. Discussion

This first open-label cross-over study suggests that low-frequency rTMS to the right TPJ may show therapeutic promise in DPD, if substantiated by future sham-controlled trials. Likely, rTMS produced a clinically significant improvement of DPD symptoms by dampening down TPJ hyperactivity.

Improvements in depression and anxiety were also seen. While it is possible that improvements in DPD symptoms could be secondary to non-specific antidepressant or anxiolytic effects, CDS changes were not correlated with changes in depression and anxiety. Although rTMS to the right parietal cortex (precisely to P4 according to the international 10–20 EEG system) has been shown to have a partial antidepressant and anxiolytic effect in patients with Major Depression (Schutter et al., 2009), there is no evidence from the literature that stimulating over right TPJ can produce an antidepressant or anxiolytic effect. Moreover TPJ is not a region typically implicated in depression circuitry (Mayberg, 2003). For this reason, we believe that changes in HDRS and HARS might be secondary to DPD symptoms improvement, but our sample may have been underpowered to see this association.

Limitations of this study are the open-label design and the small sample size. Arguing against this bias is that nonresponders and 1 partial responder to right TPJ rTMS, once crossed over to left TPJ rTMS, did not show any significant improvement in DPD symptoms. But without a sham condition we cannot rule out a placebo response. Making placebo response less likely is that DPD patients are recognized to have a low placebo response (Simeon et al., 2004), and that our patients had been ill for long periods of time (the illness duration was 9.8 ± 12 years) and had tried many treatments previously (6.6 ± 4.1), without success. In addition, while placebo responses are usually transitory, the clinical improvement we found was gradually progressive, continuing until the sixth week of treatment. A naturalistic follow-up after the end of rTMS will be necessary to establish the long-term clinical stability.

Another limitation is the allowance of concomitant medications. Concomitant medications were held at stable doses for 2 months prior to study entry, and throughout rTMS, so it would be difficult to explain improvements as resulting from medications alone. However, rTMS and medications might have a synergistic effect.

Acknowledgements

The authors thank the staff of the Columbia Brain Behavior Clinic, including Lis Bernhardt, Linda Fitzsimmons, Austin Harrison, and Nancy Turret. Funding support for the study has been provided by the Frontier Fund of the Department of Psychiatry at Columbia University, and the Columbia Division of Brain Stimulation and Therapeutic Modulation.

References

Blanke, O., Ortigue, S., Landis, T., Seeck, M., 2002. Inducing illusory own-body perceptions. Nature 419, 269–270.

Blanke, O., Mohr, C., Michel, C.M., Pascual-Leone, A., Brugger, P., Seeck, M., Landis, T., Thut, G., 2005. Linking out-of-body experience and self processing to mental own-body imagery at the temporoparietal junction. The Journal of Neuroscience 25, 550–557.

Jiménez-Genchi, A.M., 2004. Repetitive transcranial magnetic stimulation improves depersonalization: a case report. CNS Spectrums 9, 375–376.

Mayberg, H.S., 2003. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clinics of North America 13, 805–815.

Phillips, M.L., Sierra, M., 2003. Depersonalization disorder: a functional neuroanatomical perspective. Stress 6, 157–165.

Schutter, D.J., Laman, D.M., van Honk, J., Vergouwen, A.C., Koerselman, G.F., 2009. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. The International Journal of Neuropsychopharmacology 12, 643–650.

Sierra, M., 2008. Depersonalization disorder: pharmacological approaches. Expert Review of Neurotherapeutics 8, 19–26.

Sierra, M., Berrios, G.E., 2000. The Cambridge Depersonalisation Scale: a new instrument for the measurement of depersonalisation. Psychiatry Research 93, 163–164.

Simeon, D., Guralnik, O., Hazlett, E.A., Spiegel-Cohen, J., Hollander, E., Buchsbaum, M.S., 2000. Feeling unreal: a PET study of depersonalization disorder. The American Journal of Psychiatry 157, 1782–1788.

Simeon, D., Guralnik, O., Schmeidler, J., Knutelska, M., 2004. Fluoxetine therapy in depersonalisation disorder: randomised controlled trial. The British Journal of Psychiatry 185, 31–36.