CASE REPORT

Repetitive transcranial magnetic stimulation induced hypomanic symptoms in a woman with a history of electroconvulsive therapy induced mania: a case report [version 1; peer review: 2 approved]

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Abstract
Repetitive transcranial magnetic stimulation (rTMS) is a comparatively novel option for the treatment of major depressive disorder (MDD) and other psychiatric illnesses. Previous research has shown rTMS to be safe and without significant side effects compared to pharmacologic options. However, rare cases of rTMS-induced mania have been reported. This case report describes such an affective switch in a 52 year old female veteran with treatment-resistant MDD and a history of electroconvulsive therapy (ECT)-induced mania. Six treatments of rTMS were administered at 5 Hz for a total of 3000 pulses per day, when the patient began to display multiple hypomanic symptoms. These symptoms decreased after the termination of treatment and abated within a couple of days. In conclusion, caution should be used when administering rTMS to patients with a history of ECT-induced mania.

Keywords
rTMS induced hypomanic symptoms, hypomania, rTMS, case report

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a US FDA-cleared neuromodulatory treatment for major depressive disorder (MDD). rTMS targets the dorsolateral prefrontal cortex, a brain region associated with atypical activation patterns in mood disorders'. Both high (≥10 Hz, considered more excitatory) and lower (5 Hz) frequency rTMS has been shown to be efficacious in reducing depressive symptoms and is generally safe to use in MDD and other populations^2-5. However, rare cases of rTMS-induced mania and hypomania have been reported in bipolar subjects^6,7. The following case report documents 5 Hz rTMS-induced hypomanic symptoms in a patient with MDD but without a definitive history of bipolar disorder. Written informed consent for publication of their clinical details was obtained from the patient.

Case report

Ms. A, a 52 year-old Caucasian veteran with MDD and post-traumatic stress disorder (PTSD), was referred to the rTMS clinic at her local Veterans Affairs hospital, due to continued depressive symptoms despite multiple unsuccessful prior pharmacologic interventions, in October of 2013. In her current major depressive episode, Ms. A had been treated with citalopram (40mg daily) and diazepam (10mg daily), with limited efficacy. On evaluation, Ms. A endorsed active depressive symptoms, including hypersomnia, intense feelings of sadness, weight loss, difficulty with decision-making, anhedonia, psychomotor retardation, anergia, and passive thoughts of death, without outright suicidal ideation. On measures of symptom severity, Ms. A reported scores consistent with a severe symptom burden on the Quick Inventory of Depressive symptoms, self-report (QIDS-SR = 19)^8, the Patient Health Questionnaire 9 (PHQ9 = 16)^9, and PTSD Checklist (PCL = 62)^10.

Regarding her past psychiatric history, Ms. A’s depressive and PTSD symptoms began during her childhood, when she experienced an extended period of reported sexual abuse from close family members and friends during the ages of 3–17. Her MDD and PTSD symptoms were exacerbated when she was sexually assaulted during military service at the age of 22. She still experiences active PTSD symptoms, including avoidance, hypervigilance, and reduced sleep to 3–4 hours. She denied psychotic symptoms and risk-taking behaviors. She reported her “thoughts were racing” and she felt like “this could get worse and [she] would be in trouble.” A diagnosis of rTMS-induced hypomanic symptoms was made. Treatment was suspended and symptoms were monitored. Hypomanic symptoms began decreasing in severity over the following 24 hours and continued to normalize over the next couple of days. A week post-termination of treatment, she reported stable mood and regular sleep of 6–8 hours per night for the previous 5 days, which was maintained at 2-weeks. Her scores on rating scales at one and two-weeks post-treatment reflected relatively retained improvements in mood and PTSD symptoms (QIDS-SR = 10; PHQ9 = 10; PCL = 50, and QIDS-SR = 10; PHQ9 = 11; PCL = 52 for one and two weeks, respectively). At one month post-treatment, there had been no evidence of hypomania since cessation of rTMS.

Discussion

The strong temporal relationship between the presentation of symptoms and the course of treatment, as well as the patient’s history of ECT-induced mania, suggest that rTMS triggered Ms. A’s hypomanic symptoms. However, compared to previously reported cases^6, the patient demonstrated no consistent symptoms of bipolar disorder prior to rTMS therapy.

After signing informed consent, rTMS was administered at 5 Hz for 4 sec, with an inter-train interval of 12 sec, over the left dorsolateral prefrontal cortex at 120% of the motor threshold for a total of 3000 pulses per session, delivered five days a week. This parameter choice reflected the current literature in addition to our previous clinical experience in which patients with significant anxiety often are unable to tolerate 10 Hz. After her fifth treatment Ms. A reported improved MDD and PTSD symptoms, with scores decreasing to 9, 11 and 43 for the QIDS, PHQ9 and PCL, respectively. After the sixth treatment, Ms. A arrived at the clinic displaying multiple hypomanic symptoms, including inflated self-esteem/grandiosity, hypermotoric behavior, pressured speech, and distractibility. She reported an increase in goal-directed behavior, notably shopping, and reduced sleep to 3–4 hours. She denied psychotic symptoms and risk-taking behaviors. She reported her “thoughts were racing” and she felt like “this could get worse and [she] would be in trouble.” A diagnosis of rTMS-induced hypomanic symptoms was made. Treatment was suspended and symptoms were monitored. Hypomanic symptoms began decreasing in severity over the following 24 hours and continued to normalize over the next couple of days. A week post-termination of treatment, she reported stable mood and regular sleep of 6–8 hours per night for the previous 5 days, which was maintained at 2-weeks. Her scores on rating scales at one and two-weeks post-treatment reflected relatively retained improvements in mood and PTSD symptoms (QIDS-SR = 10; PHQ9 = 10; PCL = 50, and QIDS-SR = 10; PHQ9 = 11; PCL = 52 for one and two weeks, respectively). At one month post-treatment, there had been no evidence of hypomania since cessation of rTMS.
with an accelerated antidepressant effect as an add-on treatment to medication in MDD subjects compared to sham\(^7\). Nonetheless, singular cases of rTMS-induced hypomania in bipolar patients have been reported for both 5 and 10 Hz parameters\(^5,7\).

We hypothesize that the increased treatment parameters (3000 pulses per day versus 1600 pulses per day in past 5 Hz literature)\(^2,5,7\) and the aforementioned accelerating effect of rTMS treatment on antidepressants might have triggered the patient’s affective switch. Her history of ECT-induced mania, but not antidepressant-induced switching, suggests a mood regulatory system prone to severe shifts during neuromodulatory intervention. Unlike subjects in previous studies, Ms. A was not taking mood stabilizers that may act as a protective factor\(^5,7\). The presented case report therefore indicates that caution should be used when treating patients with rTMS who have a history of ECT-induced manic symptoms. Further study of patients with a history of affective switch with multiple neuromodulatory interventions is warranted, to better characterize a potentially at-risk population.

### Consent

Written informed consent for publication of their clinical details was obtained from the patient.

### Author contributions

NSP was the clinician overseeing the patient’s treatment. He revised the manuscript for editorial, medical, and intellectual content. SLC was the TMS technician and wrote the first draft of the manuscript.

### Competing interests

The authors have no conflicts of interest to disclose; NSP has received research support from Neuronetics, Inc., and NeoSync, Inc. through contracts with Butler Hospital.

### Grant information

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### References

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The authors describe an interesting case study of rTMS-induced hypomanic symptoms. It is important that such cases and information be published and made public, since it might also provide us more information about the working mechanism of rTMS, and in this case suggests some overlap between ECT and rTMS. The case is well written and clearly presented.

Competing Interests: No competing interests were disclosed.

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The authors present an interesting case of rTMS-induced hypomanic symptoms in a 52 year old woman with treatment-resistant MDD and PTSD. Importantly, the patient had a history of a manic episode induced by a course of ECT 10 years ago. No hypomanic or manic symptoms have been reported after ECT termination and the patient had not been taking mood stabilizers since 2003.

To date, rare cases of affective switches triggered by rTMS have been reported in bipolar subjects. This
important case report indicates that further caution is needed when treating patients with rTMS who have a history of ECT-induced mania.

**Competing Interests:** No competing interests were disclosed.

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