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Effect of Repetitive Transcranial Magnetic Stimulation on Psychomotor Retardation in Major Depression: A Pilot Feasibility Study

Véronique Thomas-Ollivier, Ph.D., Thibault Deschamps, Ph.D., Samuel Bulteau, M.D., Flora Le Gall, Anne Pichot, Pierre Valriviere, Hugo Vachon, Anne Sauvaget, M.D.

This pilot study investigated the feasibility of a comprehensive battery of tests assessing psychomotor retardation after a 3-week protocol of repetitive transcranial magnetic stimulation for depression. In addition to the beneficial effect of this treatment on depression, the results showed positive changes in psychomotor retardation.

Psychomotor retardation is an important symptom of major depression and is characterized by an adverse reduction in many behavioral components, such as speech, facial expression, ideation, and fine and gross motor skills.[1,2] Although clinical rating scales are often included in the diagnostic process, they do not provide information about psychomotor functioning. Moreover, psychomotor retardation has been associated with alterations in the dorsolateral prefrontal cortex and abnormalities in the basal ganglia and dopaminergic pathways.[2–7] Modulating dorsolateral prefrontal cortex activity with noninvasive brain stimulation may improve psychomotor retardation in depression.

Repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex has been proposed as an alternative, effective, and safe therapeutic strategy for major depression.[8,9] Although its positive neurostimulation-related effects on changes in depressive symptomatology are well documented,[10] currently very few studies have investigated whether rTMS changed psychomotor retardation in major depression. Some studies have suggested that rTMS significantly decreased psychomotor retardation,[11–13] whereas others have found that rTMS did not influence this symptom.[14] In these studies, psychomotor retardation was assessed either with one specific scale or with only one item of a specific depression scale, but no detailed information about psychomotor functioning was provided. Accordingly, we hypothesized that an objective detailed assessment of psychomotor retardation was necessary to examine the effects of rTMS, applied to the dorsolateral prefrontal cortex, on this key symptom. Thus, we investigated the feasibility and acceptability of a comprehensive battery of tests for psychomotor retardation (i.e., assessing its main motor and cognitive components) in naturalistic conditions before and after a 3-week rTMS protocol for major depression.

METHODS

Participants

Seven patients with major depression participated in this open, unblinded study at Nantes University Hospital. Inclusion criteria were ages 18–75 years, diagnosis of major depression according to *DSM-IV*, partial medication resistance or low tolerance, a Montgomery-Åsberg Depression Rating Scale score ≥20, and no neurological, psychotic, or addictive disorders. Exclusion criteria included contraindication to rTMS and any change in psychoactive drugs during rTMS therapy. Patients were stimulated to the left or right add-on to continued psychopharmacological treatment in a naturalistic clinical setting. All eligible patients provided a signed form for participation. Table 1 summarizes patients' characteristics.

Study Design

A pre–post study design was adopted in which the participants underwent a battery of psychomotor tests before and after 15 sessions of active rTMS, which were conducted within a 3-week period. For rTMS, the intensity was 110% of the individual's motor threshold, which was the minimum stimulus required to induce contraction of the right thumb at least five of 10 times. Five patients underwent high-frequency rTMS on the left dorsolateral prefrontal cortex (10 Hz, 40 trains of 4 seconds with 28-second intertrain intervals,

TABLE 1. Baseline Characteristics of Seven Patients With Major Depressive Disorder and Main Results Before and After 15 Sessions of Active rTMS Within a 3-Week Period[a]

Characteristic	Baseline Value	Before rTMS Treatment	After rTMS Treatment	% Evolution	p Value
Age	54 (9.2);(45–71)				
Gender					
Men	2				
Women	5				
Tests assessing psychomotor retardation					
MADRS	32.28 (20–41)	32.28 (20–41)	18.14 (2–34)	−43.8	0.02[b]
3-Meter Timed Up and Go test (seconds)		8.18 (5.7–13.3)	7.7 (5.7–10.1)	−3.2	0.40
Balance (COP mean velocity in millimeters per second)					
Simple task					
Eyes open		12.48 (5.83)	10.68 (5.11)	−16.86	0.07
Eyes closed		16.61 (6.43)	14.80 (5.70)	−12.17	0.07
Dual task					
Eyes open		14.75 (7.50)	12.62 (6.07)	−20.74	0.04[b]
Eyes closed		18.49 (5.46)	14.91 (3.11)	−24.04	0.04[b]
Finger-tapping test (no. of taps)					
Left		51.14 (2–62)	54.42 (44–67)	+3.86	0.09
Right		54.85 (45–71)	57 (38–73)	+6.97	0.03[b]
Handgrip test (kg)					
Left		22.27 (16.66–35.03)	22.73 (11.03–37.3)	+8.09	0.23
Right		22.38 (14.16–36.44)	23.3 (16.51–36.37)	+4.62	0.73
Letter fluency task		16.60 (4.32–31)	16.57 (8–22)	−0.19	0.86
Category fluency task		19.7 (7.8–27.75)	22.14 (8–36)	+12.37	0.61
Subtest WAIS-IV symbol search		24.57 (9–36)	24.42 (8–42)	−0.61	0.90
DP-15		1.28 (0–3)	2.28 (0–5)	+10.0	0.17
RPE		4.57 (2–8)	3.42 (0–7)	−7.61	0.39

[a] Data are presented as means with standard deviations or minimum to maximum values. Maximum scores were 60, for the MADRS and WAIS-IV symbol search test, 15 for the DP-15, and 10 for the RPE. COP, center of pressure; DP-15, perceived difficulty 15-point category scale; MADRS, Montgomery-Åsberg Depression Rating Scale; RPE, ratings of perceived exertion; rTMS, repetitive transcranial magnetic stimulation.
[b] Significant evolutions (p values from paired-sample Wilcoxon tests).

providing a total of 1,600 pulses over 20 minutes). Two patients underwent low-frequency rTMS on the right dorsolateral prefrontal cortex (1 Hz, 12 trains of 60 seconds with 30-second intertrain intervals, providing a total of 720 pulses over 17 minutes). Both sessions (before and after rTMS) lasted 45 minutes and included seven psychomotor tests.

Assessments

To examine gait speed and balance, the patients performed the Timed Up and Go test. Balance was measured using a force platform to record the center-of-pressure–based parameters such as the mean velocity (in millimeters per second). Four conditions were tested (random order): two trials of standing balance with eyes open or eyes closed and two trials (eyes open versus eyes closed) of counting backward (dual task; the enumerated figures were recorded with a tape recorder). The trial duration was 60 seconds, followed by a short rest period. A finger-tapping test examined motor speed. Participants were asked to tap their right and left index finger on a lever as quickly as possible within a 10-second time interval. Finally, manual strength was measured with a handheld dynamometer and repeated with both hands three times with 30 seconds of recovery between each effort. Verbal fluency tasks were proposed to test clustering and shifting ability. Participants were required to say as many words as possible within 1 minute, which began with a given letter (R or P) and belonged to a specified semantic category (fruit or clothes). The symbol subtest of the WAIS symbol search was performed as a processing speed index. The order of the tests was randomly counterbalanced within sessions. The perceived difficulty 15-point category scale[15] assessing the perceived difficulty of performing the tasks and the 10-point Borg scale of perceived exertion[16] provided feedback regarding the feasibility and acceptability of psychomotor assessments.

RESULTS

All participants complied with the protocol. None of the participants withdrew from the study. Participants reported no adverse effects of the intervention associated with completion of the battery. The low 15-point categorical scale scores and ratings of perceived exertion suggest that psychomotor assessments are highly acceptable. Notably, the Montgomery-Åsberg Depression Rating Scale scores showed a significant decrease after the rTMS intervention (paired-sample Wilcoxon test: $p=0.02$, large Cohen's $d=1.42$). Moreover, t tests revealed positive effects of the rTMS intervention

on postural control, with a significant decrease in center-of-pressure mean velocity at post-rTMS evaluation compared with baseline assessment in a dual-task condition (eyes open condition: −20.74%, p=0.04, medium Cohen's d=0.42; eyes closed condition: −24.04%, p=0.04, large Cohen's d=1.04). Note that no change in the number of enumerated figures or errors while counting backward aloud was found. A positive effect was also found for the dominant right finger–tapping performance (+6.97%, p=0.03, small Cohen's d=0.21). All results are summarized in Table 1.

DISCUSSION

Our study showed that administering a comprehensive psychomotor battery of tests during rTMS is feasible, free of adverse effects, and well tolerated by the patients in naturalistic conditions before or after the treatment. Moreover, this pilot study—despite the limited sample—showed a significant effect of rTMS treatment on depression, which is consistent with the previous literature.[17] In addition, after the intervention, participants showed positive changes in psychomotor impairment, and they were able to perform more functional motor activities (e.g., more efficient postural control) associated with probable improvement in cognitive efficiency (e.g., improved dual postural performance). Accordingly, a better reweighting of velocity information, as indicated by lower mean velocity values after rTMS treatment, appears to be a meaningful objective index of an effective adaptive process, given the baseline characteristics related to psychomotor retardation (Mignardot et al.[18] arrived at similar conclusions in patients with Alzheimer's disease). This point is also of special interest for clinical balance assessment and the risk for falls in major depression.[19] Overall, our findings are in line with previous studies that reported improvements in the Depressive Retardation Rating Scale scores, a subjective scale validated to assess the severity of psychomotor retardation.[11] In support of our expectations, these present objective and motoric markers are likely sensitive to improvement of psychomotor retardation in depressed patients after 3 weeks of rTMS intervention.[13] However, two studies reported that psychomotor retardation significantly improved only after 10 sessions of rTMS,[11,12] yet another study with 15 sessions did not report any improvements.[14] The features of the assessment tools for psychomotor retardation may thus influence the results of the studies, regardless of rTMS duration or other parameters, such as frequency and laterality of stimulation site.[12] Concerning the underlying neurophysiological mechanisms, two different but not exclusive processes may have induced improvement of psychomotor retardation. First, such improvement is probably attributable to an effect of rTMS on dopamine release in the caudate nucleus and mesolimbic and mesostriatal systems.[20] Second, rTMS, when applied to the dorsolateral prefrontal cortex, is known to have remote effects on other dorsal regions, such as the anterior cingulate cortex, which is implicated in attentional and cognitive control. Thus, the rTMS probably reduced the attentional and cognitive deficits related to psychomotor retardation in patients with major depression.[21]

In summary, our study shows that our comprehensive battery of tests assessing psychomotor retardation is feasible, safe, and well accepted in rTMS routine practice for patients with major depression, and it allows us to identify motor and cognitive dimensions of the RPM. However, this clinical study has a number of limitations. First, a psychomotor retardation scale was not included in this feasibility study to link to the current objective tests with respect to a validated scale. We nevertheless assume that the comprehensive battery of tests we used constitutes a reliable tool for the assessment of psychomotor retardation. In addition, it might be more sensitive to positive effects of rTMS intervention compared with the psychomotor retardation scale. Second, the pilot study reported here involved a small group of participants. Nevertheless, if the reported effects are large (see the Cohen's d values as measures of effect size), supporting the consistency of the significant findings, they need to be confirmed in a larger population. These positive results would then help guide the feasible development of a large, double-blind, sham-controlled trial protocol for administering rTMS treatment in appropriate sample sizes[22] of patients with depression and for testing its predictive efficiency while accounting for the objective RPM baseline assessment.

AUTHOR AND ARTICLE INFORMATION

From the Motricité, Interactions, and Performance Laboratory (UPRES-E.A.4334), University of Nantes, Nantes, France (VT-O, TD, FLG, HV); and the Addictology and Liaison Psychiatry Dept. and the BALANCED (Behavioral Addictions and Complex Affective Disorders) Clinical Investigation Unit (UIC 18), University Hospital, Nantes, France (SB, AP, PV, AS).

Send correspondence to Dr. Thomas-Ollivier; e-mail: veronique.thomas-ollivier@univ-nantes.fr

Drs. Thomas-Ollivier and Deschamps are co-first authors.

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