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SHORT COMMUNICATION

A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer disease

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Alzheimer's disease (AD) is the most common type of dementia. Current medication treatment is based on two main groups: anticholinesterases (IAChE) and NMDA receptor antagonists. These medications have demonstrated a symptomatic effect on certain cognitive and noncognitive symptoms of AD in the short term (6 months in most studies), although these effects are only limited.[1,2] With diagnostic tools for AD becoming increasingly sophisticated, the pathology is identified at earlier stages than before,[3] so suitable therapies must follow to limit the progression of the illness and the cognitive loss associated with it. We report the use of a noninvasive procedure, repetitive transcranial magnetic stimulation (rTMS), on cognitive symptoms of an AD patient.

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Materials and methods

Case study

The patient was a 75-year-old right-handed man with a high educational level, selected from the Memory Center of Research and Resources of Besançon. He was diagnosed 2 years ago with probable AD according to NINCDS-ADRDA criteria[4] and treated with memantine (20 mg/d up to 36 months), donepezil (10 mg/d up to 36 months), and venlafaxine (75 mg/d up to 12 months) because of the emergence of depressive symptoms in reaction to the diagnosis and resolved last year. His wife had noticed progressive difficulty in remembering recent events and spatiotemporal disorientation for about 2 years associated with word finding problems and poor decision-making capacity that interfere with daily living activities. A T2-weighted magnetic resonance image (MRI) demonstrated mild hippocampal atrophy and marked biparietal atrophy with no vascular leukoencephalopathy (Figure supplementary material).

The ethics committee of Besançon University Hospital gave its official approval to conduct the protocol and the

patient gave informed consent. The patient was administrated a complete neuropsychologic battery of tests as described previously[5,6] 4 months before the rTMS treatment (baseline time 0) and 1 month after the last stimulation session (time 1). The patient was reassessed 5 months after rTMS treatment (time 2) for a follow-up evaluation. The patient was maintained on his psychotropic medications for all the trial duration. There was no concurrent major depressive episode from time 1 to time 2. Before rTMS treatment, the Beck Depression Inventory (BDI) score was 7 and the Hamilton Depression Rating Scale (HDRS) was 6.

Application of rTMS

The patient was treated by rTMS for ten stimulation sessions of 20 minutes each spread over 2 weeks. A Magstim Super rapid[2] (Magstim Company Ltd, Whitland, Wales, UK) with an air cooling figure-of-eight coil was used. The rTMS was administered at 10 Hz during 5 seconds, 25 seconds between train, and 100% (because of the risk of seizure in AD)[7] of the motor threshold (MT) over the left dorsolateral prefrontal cortex (DLPFC) per 20 minutes session (2000 stimuli per day) with the coil angled tangentially to the head. The left prefrontal cortex rTMS stimulation site was determined by measuring 5 cm anterior and parasagittal line from the hand motor area.

Results

At time 0 (Table), the neuropsychologic evaluation revealed episodic memory deficits (Memory Impairment Screen, Free, and Cued Recall Test) and executive dysfunction (Isaacs Set Test, Trail-Making Test B), a slowing of information processing (Trail-Making Test A), a visuospatial disorganization (copying geometric figure), a slight anomia on picture naming and a MMSE score below the normal range. At time 1, there were improvements in cognitive performance on 8 of the 10 tests used. These improvements occurred especially in tests of episodic memory and in test of speed processing. Clinically, the patient's wife reported an improvement for initiating activities such as walking, having a meal, writing, or using the telephone. There were no adverse events and the treatment was well tolerated (no pain at the site of coil placement or headache and no seizure).

Discussion

This case study reported possible improved cognitive skills after application of rTMS treatment in an AD patient, who had previously been treated for depression but was not depressed at the time of the treatment. It is possible that the improvements seen were due to practice effects (PE) because the patient was reassessed with the same test materials.[8] A long interval between testing slightly reduced this potential. In addition, several studies have demonstrated that PE are largely absent in patients with dementia[9-11] even for those with mild AD for short test-retest intervals,[12,13] suggesting that the score improvements at time 1 were due to rTMS treatment. In addition, comparison of time 2 scores with time 0 scores showed that the patient tended to maintain his level of memory performance from baseline to follow-up suggesting possible slowing in memory decline rate at 9 months. Finally, we used the standard method of localization (5 cm method) for which lack of precision is reported.[14]

A few studies have dealt specifically with rTMS effects on the cognitive capacity of AD patients and highlighted

Table Cognitive performances for the patient at baseline (time 0), 1 month (time 1), and 5 months (time 2) after the rTMS treatment

				Change scores	
	Time 0	Time 1	Time 2	Difference T1-T0[a]	% of improvement from baseline[b]
Neuropsychologic tests					
Mini-Mental State Examination (range 0-30)	20	22	19	2	10
Memory Impairment Screen (range 0-8)	3	7	4	4	133
Free and Cued Recall Test					
Immediate recall (range 0-16)	10	12	9	2	20
Free recall (range 0-48)	5	13	6	8	160
Total recall (range 0-48)	32	43	37	11	34
Recognition (range 0-16)	14	16	15	2	14
Isaacs Set Test	15	17	21	2	13
Trail-Making Test					
Part A (range 0-150)	220	135	316	−85	39
Part B (range 0-300)	Failed	Failed	Failed	-	-
Picture naming (range 0-30)	29	29	26	0	0
Copy (range 0-6)	4	1	1	−3	−75

[a] Changes in cognition were calculated by subtracting scores at time 1 from scores at time 0 for each test (eg, time 1 Free recall-time 0 Free recall).
[b] Percentages of improvement from baseline (time 0) were calculating by dividing the difference score (T1-T0) by the score at time 0 (eg, [T1 − T0]/T0 × 100). A positive percentage score means that performance increased at time 1 and a negative percentage score indicates that performance decreased.

a positive effect of high frequency rTMS applied on the right or left DLPFC of patients with probable AD during a naming task of an image representing an action or an object.[15-17] In these studies, stimulation to both left and right DLPFC by rTMS improved action performance in the moderate-to-severe group but object naming improved only in the moderately demented group (MMSE <17). Furthermore, Cotelli et al.[17] demonstrated a slight improvement of language performance. Recently, Bentwich et al.[18] treated eight AD patients combining 10 Hz rTMS to six brain regions, including DLPFC (90% MT) with cognitive training during 6 weeks. Their results showed significant improvement for the ADAS-Cog scores. The DLPFC is particularly involved in episodic memory[19] and executive functions.[20] The use of additional neural resources in the DLPFC by rTMS might temper the degeneration caused by AD. rTMS might facilitate cognitive processes that depend partly on DLPFC, particularly cortico-subcortical activation.[21] rTMS effects on cognitive functions as working memory, differ according to the target: right or left DLPFC that would be explained by function lateralisation.[22,23] For example, using rTMS over the right DLPFC in a sham-controlled design, Aleman and van't Wout[24] observed a significant disruption of digit span performance in healthy subjects in the real rTMS condition. As such, we chose the left DLPFC as the target because of a performance improvement during high-frequency stimulation and some adverse effects observed on cognitive functions in healthy subjects during right DLPFC stimulation.[24]

This initial case study provides research opportunities for rTMS therapeutic use in the early AD. Our results showed possible effects just 1 month after stimulation. In this context, future studies may be needed to evaluate the impact of adjunctive rTMS with concurrent medication treatment on the cognitive capacities in a large cohort of patients having mild-to-moderate AD.

Supplementary data

Supplementary data related to this article can be found online at doi: 10.1016/j.brs.2011.03.003.

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