REVIEW ARTICLE

An overview of repetitive transcranial magnetic stimulation (rTMS) in Alzheimer's disease

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ABSTRACT

Background. Alzheimer's disease (AD) is the most frequent neurocognitive disorder. It affects 50% to 75% of the cases of dementia, and is characterized by a progressive cognitive decline that hinders behavior and functionality. Its etiology is still uncertain, and the efficiency of treatments is limited. Repetitive transcranial magnetic stimulation (rTMS) has been used as an alternative therapeutic strategy, but the clinical impact on Alzheimer's disease has hardly been studied. **Objective.** To describe the effects of rTMS on cognition, the behavioral and psychological symptoms of dementia (BPSD), and functionality, considering the various modes of application. **Method.** The PubMed, ScienceDirect, and PsycInfo databases were consulted using key words relating to the topic of study. Articles published between 2006 and 2016 were selected. **Results.** The studies that have assessed the clinical effect of rTMS have used various parameters to stimulate and compare the different cortical areas, principally the dorsolateral prefrontal cortex. A variety of benefits have been proposed for patients with Alzheimer's disease in cognitive domains such as language and episodic memory, as well as behavior and functionality in everyday activities. **Discussion and conclusion.** rTMS has been suggested as a possible treatment for AD, and the results indicate the need for further studies with different methodological designs and more participants, in addition to cognitive rehabilitation techniques. The objective is to identify the most efficient parameters for stimulation and to explore new cortical targets.

Keywords: Alzheimer's disease, repetitive transcranial magnetic stimulation, cognition.

RESUMEN

Antecedentes. La enfermedad de Alzheimer (EA) es el trastorno neurocognitivo más frecuente. Afecta de 50 a 75% de los casos de demencia y se caracteriza por un declive cognitivo progresivo que perjudica la conducta y funcionalidad. Su etiología es aún incierta y la eficacia de los tratamientos limitada. La estimulación magnética transcraneal repetitiva (EMTr) se ha utilizado como una estrategia terapéutica alternativa, pero se ha estudiado poco el impacto clínico que tiene en la EA. **Objetivo.** Describir los efectos de la EMTr sobre la cognición y los síntomas psicológicos y conductuales de la demencia (SPCD), así como en la funcionalidad, considerando las diferentes modalidades de aplicación. **Método.** Se consultaron las bases de datos PubMed, ScienceDirect y PsycInfo utilizando palabras clave relacionadas con el tema de estudio. Se seleccionaron los artículos publicados de 2006 a 2016. **Resultados.** Los estudios que han evaluado el efecto clínico de la EMTr han utilizado diferentes parámetros de estimulación y comparaciones de diferentes áreas corticales, principalmente de la corteza prefrontal dorsolateral. Se postulan diferentes beneficios en pacientes con EA en dominios cognitivos como el lenguaje y la memoria episódica, así como en la conducta y en la funcionalidad de las actividades de la vida diaria. **Discusión y conclusión.** La EMTr se ha sugerido como posible tratamiento para la EA. Los resultados favorecen la necesidad de realizar nuevos estudios con diferentes diseños metodológicos y mayor número de participantes, en combinación con técnicas de rehabilitación cognitiva. La perspectiva es identificar los parámetros de estimulación más eficaces y explorar nuevas dianas corticales.

Palabras clave: Enfermedad de Alzheimer, estimulación magnética transcraneal repetitiva, cognición.

BACKGROUND

Alzheimer's disease is a neurocognitive disorder characterized by chronic, progressive deterioration in cognition and functionality. It also presents significant psychological and behavioral symptoms, and is the most common type of dementia, appearing in 50% to 75% of the cases (WHO & Alzheimer's Disease International [ADI], 2012; Prince et al., 2015). AD is a heterogeneous process that develops in a preclinical period over the course of several decades. It has been theorized that its etiopathology is secondary to the extracellular overproduction and accumulation of beta-amyloid plaques and due to the hyperphosphorylation of tau protein, which causes the formation of neurofibrillary tangles (Dubois et al., 2010; McKhann et al., 2011).

The treatment of Alzheimer's disease is generally pharmacological and based on the use of acetylcholinesterase inhibitors (AChEI): donepezil, rivastigmine, and galantamine, for the treatment of mild to moderate AD. Memantine (the antagonist of the NMDA glutamate receptor) is used for moderate to severe AD. These drugs have demonstrated a positive effect on the manifestation of the disease. However, the treatment is still ineffective in slowing, stopping or reversing the progress of Alzheimer's disease, and many substances under study have been proposed to treat it, yet have failed to produce the expected results (NICE, 2011; Stanzione & Tropepi, 2011).

The challenge of treating AD has been approached with not only pharmacological strategies, but also various neuromodulation techniques as adjuvant, alternative or complementary therapeutic strategies, which seek to inhibit or modify specific neuronal circuits. Among these techniques is repetitive transcranial magnetic stimulation (rTMS), which consists in inducing a pulsating electric current to the cerebral cortex, which allows the non-invasive, focused, safe, and painless stimulation of the brain (Freitas et al., 2011; Rotenberg et al., 2014). In rTMS, several successive pulses are applied rhythmically in the same sequence, and allow the modulation of cortical excitability (Rossi et al., 2009). A frequency is considered to have a low stimulation when it is equal to or above one pulse per second (1 Hz), which fosters inhibitory activity, and to have a high stimulation when it is between 5 Hz and 20 Hz, which causes an increase in cortical excitability (Cotelli, Manenti, Zanetti, & Miniussi, 2012; Higgins, 2008; Hsu, Ku, Zanto & Gazzaley, 2015; Manenti, Cotelli, Robertson & Miniussi, 2012; Nardone et al., 2014).

rTMS has demonstrated its benefit for various neuropsychiatric disorders such as cerebral infarction, depression, and anxiety. It has principally an effect on mood, executive functions, learning, memory, and attention. A study of rTMS conducted among young adults, elderly adults, and persons with memory impairment examined memory processes, and established the role of the right dorsolateral prefrontal cortex (DLPFC), concluding that it is involved in recovering information from the episodic memory. The role of the left DLPFC was determined during the codification of new events, in terms of both precision and reaction times. This finding demonstrated the role of the DLPFC and suggests that it is a fundamental element for memory performance induced by semantic processing (Devi et al., 2014; Innocenti et al., 2010; Manenti et al., 2012).

It has been suggested that the long-term effect of rTMS is due to changes in activity in a network of cortical and subcortical areas, rather than simply the local inhibition or excitement of an individual area. The evidence indicates that the brain operates through networks distributed in a flexible, interactive manner, which have an impact on both cognition and behavior. It has therefore been considered that the modification of one node of a network could affect the entire network, and that the results in one area could have effects on various functions based on the node of activation or on which interconnected networks are activated (Miniussi & Ruzzoli, 2013).

rTMS in Alzheimer's has been shown to induce prolonged functional changes in the cerebral cortex with various studies that have evaluated changes in cortical excitability, but very few studies have addressed the possible clinical impact on cognitive yield, BPSD, and functionality in patients with AD. Accordingly, there is a need to define the parameters for the estimulation to be used, which could be recognized as an indication for the treatment of the disease (Lefaucheur et al., 2014; Miniussi & Ruzzoli, 2013; Nardone et al., 2012).

This review aims to show the most relevant results and provide information on the stimulation applied thus far in various studies. This will make it possible to understand the current situation and propose future studies.

This update aims to describe the effects of rTMS on cognition, the behavioral and psychological symptoms of dementia (BPSD), and functionality in patients with AD, considering the various modes of application.

METHOD

Search strategy

To integrate this revision, a search was conducted in several databases (PubMed, ScienceDirect, and PsycInfo) of articles published between 2006 and 2016. The following route was used: "Alzheimer's disease" AND "transcranial magnetic stimulation" AND "cognition" NOT "motor cortex" NOT "deep brain stimulation". The terms "motor cortex" and "deep brain stimulation" were excluded, as this revision did not consider studies that analyzed motor regions by applying TMS or interventions with deep cerebral stimulation. The articles considered for the revision were clinical

trials, case reports, narrative reviews, systematic reviews, and meta-analyses.

Selection of articles

Articles with the following inclusion criteria were reviewed: 1. measuring the effects of rTMS on cognition using instruments to evaluate cognitive functioning or state and/or; 2. measuring the effects of rTMS on other clinical variables such as functionality (basic, instrumental or advanced activities) and psychological and behavioral symptoms in patients with AD, using clinimetric instruments to evaluate these aspects; 3. articles published in English. Articles that used other techniques of neuromodulation, studies that only addressed changes in cortical excitability, and those with non-human subjects were excluded.

Analysis

A qualitative analysis was undertaken of the type of variables, that is, descriptions of the improvement or increase in cognitive functions, BPSD and/or functionality were considered as indicators of intervention using rTMS. There is also a description of the design and parameters of stimulation used in the various studies conducted thus far on AD (localization, frequency, pulses, number of sessions).

RESULTS

A total of 294 articles were identified, which are disaggregated by search engines for scientific information in Figure 1. Of these, 267 were excluded because they presented repeated records, different neuromodulation techniques to rTMS, non-human subjects of study, book chapters or letters to the editor. Of the remaining 27 articles, the title and abstract were reviewed in a second filter and nine articles were excluded for various reasons mentioned in Figure 1. Finally, 18 articles were included in the narrative review.

Table 1 shows the clinical trials and a case report in which rTMS was applied in patients with AD, and which studied cognition, behavior or functionality.

Modalities and effects of repetitive transcranial magnetic stimulation (rTMS) in Alzheimer's disease

The first studies of rTMS and AD were conducted by Cotelli et al. in 2006 and 2008. The former included 15 patients with moderate AD, and assessed the effect of rTMS applied on the left DLPFC and right DLPFC at high frequencies (20 Hz), compared with a placebo. It observed the effects of applying a session on linguistic designation and performance during the performance of designation tasks as a cognitive measurement. The study showed an improvement in designating the action after the stimulation in comparison with the placebo group. In the second study, this test was only replicated on patients with mild AD; the study included 24 patients with mild and moderate to severe AD. In both studies, since the rTMS was applied in a single session, long-term effects were not evaluated. Moreover, in both cases, rTMS was applied during the task, which affects the modulation of cortical excitation and attempts to change cognitive performance. These studies suggested that rTMS can restore or compensate for damaged function, and proposed this alternative as a tool for cognitive rehabilitation (Cotelli, Manenti, Cappa, Zanetti & Miniussi, 2008; Cotelli et al., 2006).

A trial designed to compare the long-term efficiency of rTMS at high frequencies versus low frequencies, applied on the bilateral DLPFC, studied the cortical excitability and cognitive function of patients with mild to moderate Alzheimer's disease. All the patients received a daily session for five consecutive days. The group that was stimulated at high frequencies (20Hz) improved significantly more than the group stimulated at low frequencies (1 Hz) in the evaluations conducted through the Mini Mental State Examination, Scale for Instrumental Everyday Activities, and Scale for Geriatric Depression, and their effect remained three months after the end of the treatment. Thus, the authors conclude that rTMS applied at high frequencies can be a useful instrument for treating mild to moderate AD (Ahmed, Darwish, Khedr, El serogy & Ali, 2012).

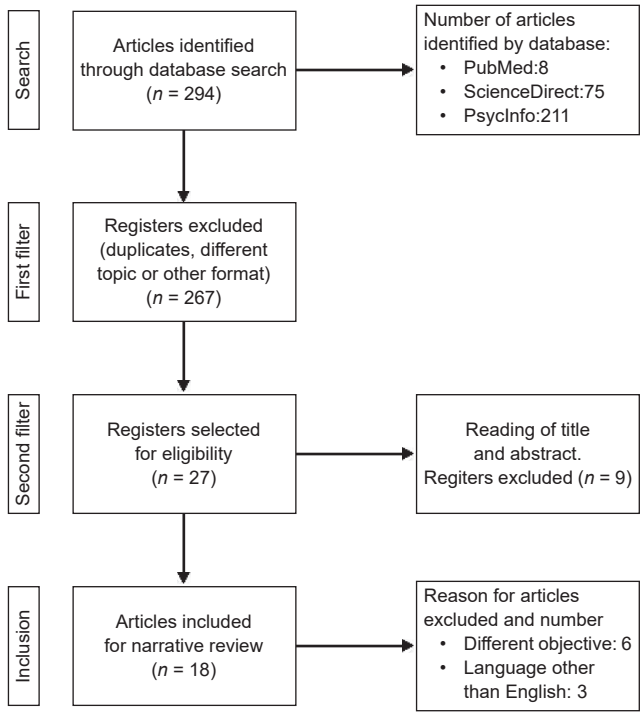

Figure 1. Flow chart of selection process for narrative review.

Table 1
Studies of repetitive transcranial magnetic stimulation conducted on Alzheimer's disease

Study	*n*	Age in years Average (DE) (rTMS/placebo)	MMSE	Localization	rTMS frequency/ total pulses	Number of sessions	Improvement or increase in cognitive functions, BPSD and./or functionality.
Cotelli et. al., 2006[a]	15	76.6 (6.0)	17.8	Left / right FC	20 Hz (600 ms) *On line	1	↑ Designation of action between groups.
Cotelli et. al., 2008[a]	24	76.6 (5.8) / 75.0 (6.2)	Mild AD 19.7 / Moderate AD 14.3	Left DLPFC	20 Hz *On line	1	↑ Designation of action in the mild AD group in comparison with the moderate.
Cotelli et .al., 2011[a]	10	71.2 (6.1) / 74.4 (3.8)	EMTr 16.2 / placebo 16.0	Left DLPFC	20 Hz / 2000	Group 1: 20 Group 2: 10 of rTMS and 10 placebo	↑ Auditory comprehension of phrases after 2 weeks of treatment. ↑ Auditory comprehension of phrases 8 weeks after end of treatment.
Bentwich et al., 2011[a]	8	75.4 (4.4)	18 - 24	Day 1: Right DLPFC Broca Wernicke Day 2: Left DLPFC Bilateral PSAC	10 Hz / 1200	30 (Day 1 and 2 alternating) 6 follow-up sessions every 15 days	ADAS-cog ↑ 4.2 points after 6 weeks and 4 points after 4.5 months of treatment. ADAS-ADL ↑ 4.9 points after 6 weeks and 1.6 points after 4.5 months of treatment. CGIC ↑ 3.4 points after 6 weeks and 2.4 after 4.5 months of treatment. HAM-D and NPI do not present significant differences.
Ahmed et al., 2012[a]	45	20 Hz 65.9 (5.9); 1 Hz 68.6 (6.7) / 68.3 (4.9)	Moderate AD Group 20Hz rTMS 14.7 / placebo 13 Group 10 Hz rTMS 12.7 / placebo 13.9	Bilateral DLPFC	20 Hz 1 Hz / 1200	5	↑ MMSE, Everyday activities and GDS-Y in 20 Hz group in comparison with 1 Hz group.
Haffen et al., 2012[b]	1	75	20	Left DLPFC	10 Hz / 2000	10	↑ MMSE (episodic memory and information processing speed) and other psychological tests. Possible effects one month after treatment.
Rabey et .al., 2013[a]	15	76.6 (8.9) / 75.4 (9.07)	18 - 24	Day 1: Right DLPFC Broca Wernicke Day 2: Left DLPFC Bilateral SP	10 Hz / 1300	30 (Day 1 and 2 alternating) 6 follow-up every 15 days	ADAS-cog ↑ 3.7 points after 6 weeks and 3.52 points after 4.5 months of treatment. CGIC ↑ 3.57 points and 3.6 after 4.5 months of treatment NPI without significant differences.
Lee et al., 2016[a]	26 (18 rTMS + CT)	72.1 (7.6) / 70.3 (4.8)	Mild AD 18-20 / Moderate AD 21-26	Day 1: Right DLPFC Broca Wernicke Day 2: Left DLPFC Bilateral PSAC	10Hz / 1300	30 (Day 1 and 2 alternating)	ADAS-cog ↑ 4.28 points for mild AD compared to moderate AD. Effect maintained for 6 weeks after the rTMS. ↑ Recovery of words, recognizing words, orientation, designating objects, fingers and orders, with rTMS+TC, compared with placebo. MMSE ↑ 1.5 after 6 weeks and 2 after 6 weeks with rTMS+TC. CGIC ↑ 2.4 after 6 weeks and 2.6 later, with rTMS+TC. GDS-Y did not improve significantly.
Wu et al., 2015[a]	54 Group 1: 27 Group 2: 27	71.4 (4.9 / 71.9 (4.8)	rTMS 15.3 / placebo 15.2	Left DLPFC	20 Hz / 1200	20	BEHAVE-AD improved 73.1% versus 42.3 of the placebo group. ADAS-cog ↑ 5.21 Total. ↑ 3.85 Subscale for memory. ↑ 3.19 Subscale for language. ↑ 1.61 Subscale for praxis. ↑ 1.04 Subscale for attention.

Note: *n* = number of subjects; [a]Design = Randomized, double blind and controlled with placebo; [b]Case report; *On line = administering rTMS during performance of task
CT = Cognitive training; DLPFC = dorsolateral prefrontal cortex; PSAC = Parietal Sensory Association Cortex; ADAS-cog = Alzheimer Disease Assessment Scale-cognitive section; ADAS-ADL = Alzheimer Disease Assessment-Activities of Daily Living; MMSE = Mini Mental State Examination; CGIC = Clinical Global Impression of Change; HAM-D = Hamilton Rating Scale for Depression; NPI = Neuropsychiatric Inventory; GDS-Y = Geriatric Depression Scale; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; ↑ = increase/improvement.

A case report was undertaken using rTMS as an adjuvant treatment for mild AD, where the left DLPFC was stimulated. Improvements were observed in cognitive performance, in particular episodic memory, and information processing speed tests. Moreover, the spouse reported improvements in functionality and in beginning activities such as walking, writing or using the telephone, and no adverse effects were reported, as the treatment was well tolerated (Haffen et al., 2012).

In addition to the DLPFC, other targets have been proposed to apply rTMS in patients with AD. The areas included are Wernike and Broca, as well as the cortical regions of somatosensory association in the right and left parietal lobes, in alternating stimulation sessions. In a trial that stimulated these areas, improvements were reported for up to 4.5 months of follow-up in cognition and general functioning measurements. This study researched the combination of rTMS with cognitive training (CT) in patients with Alzheimer's disease and evaluated a possible synergic effect of CT associated with rTMS, comparing it with only CT in a sample of eight patients with mild and moderate AD. It was applied in a combined treatment regimen for five sessions a week for six weeks, followed by maintenance sessions (twice a week) for six months. It was applied in the aforementioned areas and CT tasks adjusted to these areas were developed. Even considering the sample size, improvements were observed in the evaluation scales, but without statistical significance: Alzheimer´s Disease Assessment Scale (ADAS-cog), Clinical Global Impression of Change (CGI), Mini Mental State Examination (MMSE), Evaluation Scale of Daily Activities, and Hamilton Depression Scale. There were no changes in the Cummings neuropsychiatric inventory (NPI) (Bentwich et al., 2011).

Another randomized and double-blind trial included 15 patients and compared the efficiency and safety of rTMS with CT against simulated stimulation. rTMS was applied to the treatment group for an hour, five sessions a week, followed by bimonthly sessions for three months. There were improvements in the average score for ADAS-cog and the average of CGI after six weeks and after 4.5 months of treatment, in comparison with the simulated stimulation group. Again, there were no significant differences when these were evaluated with the NPI (Rabey et al., 2013).

In a study published recently, in which a larger sample of 26 patients was used, CT was combined with rTMS and applied in the same areas as the Bentwich group. The results showed a significant improvement in the domains of memory and language with the combination of both treatments (Lee, Choi, Oh, Sohn & Lee, 2016). In the three trials mentioned, in which various areas of stimulation were proposed, these were localized by a neuronavigator. It is proposed that CT and rTMS localized with a neuronavigator and the system called "NeuroAD" offer a new, safe, and efficient therapy to improve cognitive function, which represents an adjuvant therapy to AChEIs, in particular in the mild phase of AD (Anderkova & Rektorova, 2014; Fonseca, Navatta, Bottino & Miotto, 2015).

As regards the number of sessions administered, the study conducted to evaluate the improvement in language performance in AD after rTMS showed that administering rTMS for four weeks did not produce additional improvement in performance, in comparison with the application of rTMS during two weeks. This suggests that two weeks of rTMS provide sufficient evidence of an improvement in behavior in patients with AD (Cotelli et al., 2011).

A trial examined the effect of rTMS at 20 Hz on BPSD in patients with AD, and also evaluated the cognitive effect. Twenty sessions were applied (five sessions a week for four weeks) on the left DLPFC, and 27 patients, to whom rTMS and 1mg of risperidone was applied, were compared with another 27 patients who had received the simulated maneuver and 1 mg of risperidone. After four weeks, half the total scores on both the Behavioral Pathology in Alzheimer´s Disease Rating Scale (BEHAVE-AD), used to measure behavioral symptoms, and the ADAS-cog in the two groups decreased when compared to the baseline. However, in the group to which rTMS was applied, the difference was 30% higher in BPSD and significantly higher in the ADAS-cog scores (Wu et al., 2015).

Other studies on the treatment of dementia have implemented similar treatment to that for depression, including five sessions per week for two, four, and six weeks, some with maintenance and follow-up evaluations. Since the protocols for the treatment of depression have been effective, similar results are expected for dementia. One example of this is described in a comparative study that applies high-frequency and low-frequency rTMS (20 Hz *vs*. 1Hz) and a group of simulated stimulation applied in the DLPFC bilaterally for patients with AD. All the patients received one session a day for five consecutive days, and displayed significant improvements on the scales of geriatric depression, MMSE, and the evaluation of instrumental everyday activities (Ahmed et al., 2012).

One publication suggested that the optimal specifications for the use of rTMS as treatment for depression are very similar to those employed in studies to treat AD. Indeed, the intensities used to treat dementia are between 90 and 110%, which is a similar range to that used in depression, which is 90 to 120%; the frequencies suggested for depression are between 5 and 20 Hz, and frequencies of 10 and 20 Hz have been used to treat dementia (Fitzgerald & Daskalakis, 2013).

DISCUSSION AND CONCLUSION

Since Alzheimer's disease affects millions of persons and its incidence is increasing, it is crucial for new therapeutic

approaches to be developed as there is currently no treatment that prevents or halts the effects of AD completely. Due to the need for different options to those approved by the FDA (acetylcholine-esterase inhibitors and memantine) and other health regulation agencies across the world, studies were conducted with rTMS to consider it as a therapeutic alternative capable of improving cognition, BPSD, and consequently functionality. This would enable families to be closer to patients and decrease polypharmacy; it has also shown to be a safe technique since few adverse effects have been reported.

Accordingly, there is growing interest in neuromodulation techniques applied to AD, including rTMS, which will require a study of its physiological impact. The evidence suggests that this involves: a) The modification of synaptic plasticity through long-term reinforcement and inhibition mechanisms. The evidence obtained from studies that have addressed changes in cortical excitability suggests that early intervention using rTMS could favor the restoration of partially lost connections. Compensation networks could be restored to recover deteriorated function, and these networks could include perilesional areas or contralateral counterpart cortical regions with a similar anatomic structure, which could thus perform the impaired functions. b) An increase in cerebral blood flow when stimulated at a high frequency. c) The repetitive aspects of TMS could have positive effects on cognitive performance through the modification of cortical oscillatory activity. It has also been postulated that neurotrophic factors could participate as a mechanism induced by rTMS. rTMS could offer a reliable method to characterize important neurophysiological and physiopathological aspects of AD, and a decrease in cortical plasticity and connectivity/reactivity has been identified in comparison with healthy persons and even with other dementias. As a result, rTMS can be proposed as a promising therapy for AD (Bentwich et al., 2011; Brem et al., 2013; Freitas et al., 2011).

In this regard, a decrease in cellular plasticity could be the basis for the motor symptoms of AD, and the result of a deficit of neurotransmission depending on N-methyl-D-aspartate (NMDA) receptors, as these are primary components in cellular plasticity (Freitas et al., 2011).

The dorsolateral prefrontal cortex (DLPFC) has been an area of interest for the application of rTMS, as it is a region localized in the lateral face of the interior frontal gyrus, which makes it accessible to stimulation by the rTMS coil. It is also closely interconnected with structures of the limbic system that have been indicated as important intermediaries in the modulation of feelings and executive functions. Numerous neuroimaging studies have clearly demonstrated the existence of a more widely distributed neuronal network that includes the bilateral dorsolateral prefrontal cortex, medial temporal lobes, and parietal cortexes that maintain the functioning of the memory (Rossi et al., 2009). As a result of its interconnection with other regions of the brain, the DLPFC plays an important role in executive functions. This region coordinates functions with the rest of the brain. The DLPFC also plays a role in working memory, choice, and decision-making, functions that are affected by dementia (Rutherford, Gole & Moussavi, 2013).

rTMS could be used as a potent tool not only for research into the participation of cerebral areas in a specific cognitive task, but also the design of interventionist therapies in persons with a deterioration in cognition and AD (Manenti et al., 2012).

Treatment using rTMS has achieved significant improvement in the scores on the ADAS-cog scale in a comparable manner to the treatments suggested by international guidelines. However, it is not known how long the effect lasts, as there have not been enough studies to determine this in the long term. It is known that the typical annual deterioration in patients without treatment is 2 to 4 points of the MMSE and 7 points of the ADAS-cog scale.

Studies conducted with rTMS thus far have shown an improvement in various stages of the disease, which may have a clinical impact not only for AD but also for its prodromal stages, based on the general hypothesis that the mechanisms of cortical plasticity and altered cerebral networks are the proximal causes of cognitive decline and make a critical contribution to the disease.

The few studies conducted on rTMS in Alzheimer's disease to date display considerable variations in the methodological design. For example, selection criteria vary from one study to another (age of onset of disease, length, and type of treatment previous to the start of the study and all the risk factors associated with AD), which makes it difficult to obtain homogeneous samples. The same occurs with some of the measurement instruments: the selection of neuropsychological tests used to measure cognitive functions, BPSD, and even functional variables are not standardized (Nardone et al., 2014). The lack of multicenter studies may cause another limitation, as one of the advantages of these studies is establishing a better basis for the subsequent generalization of findings. On the other hand, when stimulation is applied, there is a variety in the parameters and pulses used, the frequencies –ranging from low to high frequency (5 Hz, 10 Hz, 20 Hz)–, the areas of application and type of location (10-20 system or by neuronavigation), the moment of application and of evaluation (during or after stimulation), the duration of the effect, and whether there is also a comparison with currently approved drugs or cognitive rehabilitation or stimulation techniques.

Clinical trials conducted with rTMS on patients with Alzheimer's disease, although mainly preliminary, show promising results and require more research to confirm them and identify the most efficient method, comparing results by including various, less studied cortical areas, and assessing how long the results remain in cognitive symp-

toms, BPSD, and functionality (Lefaucheur et al., 2014). Importantly, there are other limitations in the samples studied in the various trials that have examined the use of rTMS, including the heterogeneity of AD and its many comorbidities, in addition to the lack of accurate knowledge on the action mechanism of rTMS.

The overview suggests that future studies with improved experimental designs (larger samples, with an evaluation of various stimulation parameters), using clinical, cognitive, and behavioral instruments and neurophysiological measurements with greater sensitivity and specificity will achieve more solid interventions and make better comparisons in the studies. It is also necessary to determine how long the effect remains for the different modalities of application, and the number of sessions required for treatment, since AD is a chronic, degenerative process, which makes it different from other conditions such as depression, which are resistant to treatment, for which rTMS has already been approved as a method of treatment by the FDA (Brem et al., 2013; Freitas et al., 2011).

The studies presented in this review suggest the therapeutic potential of rTMS in patients with mild to moderate AD by observing the effects that benefit some of the cognitive domains affected by AD, improve the BPSD, and lead to better performance in functionality. The specific benefits of rTMS can translate into benefits for patients in their everyday activities, notably their ability to communicate with the caregiver and the behavior associated with the disease, thus improving their quality of life and even limiting the use of medical services for early conditions and institutionalization. More controlled studies are required with different methodological designs and more participants, principally in conjunction with cognitive rehabilitation techniques, to obtain clearer data, identify the most efficient parameters for stimulation, and compare results with the participation of less studied cortical areas. This will make it possible to describe how long the effect of the treatment lasts and determine the precise mechanism of action in cognitive deterioration processes. These results will be employed to design new research as strategies for treating and rehabilitating patients with AD.

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Conflicts of interest

The authors state that there are no conflicts of interest.

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