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Review article

Cognitive effects of repetitive transcranial magnetic stimulation in patients with neurodegenerative diseases — Clinician's perspective

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) represents a promising tool for studying and influencing cognition in people with neurodegenerative diseases. This procedure is noninvasive and painless, and it does not require the use of anesthesia or pharmacological substances. In this systematic critical review we report outcomes from research focused on behavioral cognitive effects induced by rTMS in patients with Alzheimer's disease (AD), Parkinson's disease (PD), and mild cognitive impairment (MCI) preceding AD. There are still major limitations to rTMS use, such as a poor understanding of its after-effects and inter-individual variability in their magnitude, discrepancies in stimulation protocols and study designs, varied selection of the specific stimulated areas and control procedures, and neuropsychological methods for assessment of after-effects; hence, the results of the present research can only be considered preliminary. The future directions are discussed.

Contents

1. Introduction

A number of studies have investigated repetitive transcranial magnetic stimulation (rTMS) as a potential therapeutic tool. rTMS is a noninvasive method that is able to modulate brain function. Lasting effects on brain plasticity can be observed after application of rTMS [1]. Two common neurodegenerative diseases, Alzheimer's disease and Parkinson's disease, are diagnosed in millions of people worldwide [2]. The diseases share several characteristics: they target predominantly the aging population and show gradual progression, individual disease-specific histopathological brain changes, and molecular mechanisms of pathogenesis. An increasing number of people are diagnosed as a result of population growth and prolonged life expectancies. Alzheimer's disease (AD) and Parkinson's disease (PD) are associated with impaired cognitive functions, reduced independent functioning, and psychological and behavioral problems. The increasing cumulative prevalence of these diseases has a huge economic impact in developed countries throughout the entire world.

Mild Cognitive Impairment (MCI) is a term used for people with impaired memory and/or other cognitive functions beyond the expected

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outcomes for the age and education but not yet within the diagnostic criteria for dementia [3]. MCI patients do not show signs of significant functional impairment but they are at high risk for dementia conversion [2].

The key principle of rTMS is based on regularly repeated stimulation of the focal cortical area by a train of magnetic pulses. Stimulating coils of different shapes induce electric currents in neurons (secondary conducting material). The effect of stimulation decreases with the distance from the stimulating coil. There is an immediate effect on underlying brain tissue to a depth of approx. 2 cm beneath the scalp as well as possible changes in distant interconnected regions. Generally, low-frequency rTMS ($\leq$1Hz) reduces cortical excitability when applied over the motor cortex, and high-frequency rTMS increases it [1,4]. Online stimulation refers to the condition in which a person is executing a task (motor, cognitive, etc.) while receiving rTMS. The offline approach is when stimulation occurs before a task but some rTMS after-effects may interrelate with the final results [5]. There is no universal agreement on the rTMS parameters to be used or on the overall effect of therapeutic rTMS, mainly due to a lack of understanding of the mechanisms responsible for the lasting modifications of cortical excitability induced by stimulation and due to within-subject and between-subject variability of rTMS-induced effects. There is evidence that rTMS induces some after-effects that outlast the period of stimulation and depend on the number of pulses applied, the rate of application, and the intensity of each stimulus [6].

Several neurotransmitter systems can be modulated by rTMS with effects that are measurable for longer periods of time. Application of rTMS to the motor cortex or dorsolateral prefrontal cortex may increase or decrease the release of monoamines (particularly dopamine) in different cortical and subcortical areas of the brain interconnected with the stimulated area [7–9]. In addition, high-frequency rTMS applied over the prefrontal cortex may act via the stimulation of the glutamatergic prefrontal neurons [10] and may increase neurotrophic factors in the brain [11].

Other mechanisms of action have also been proposed, including changes in the effectiveness of synapses between cortical neurons (long-term potentiation and long-term depression). Positive changes can also be measured in behavior [1,5,6].

Since the first introduction in the late 1980s, rTMS has been used as a potential treatment for a variety of neurological and psychiatric disorders [1]. Studies and meta-analyses have included the therapeutic use of rTMS in depression (FDA approved since 2008) [12–14], schizophrenia [15–17], stroke [18,19], tinnitus [20–22], addiction [23,24], obsessive–compulsive disorder [25], Tourette's syndrome [26] and many other diseases.

The fundamental rationale for therapeutic use of rTMS is the fact that the effect of rTMS on cerebral cortex outlasts the duration of stimulation. Moreover, the changes induced by rTMS are not restricted to the stimulated region and possible effect may also occur in the distant functionally connected areas [8,9,27]. Another important issue is the fact that protocols using multiple sessions of stimulation may lead to long-lasting modulation of the brain plasticity [1,5,28]. It is probably not realistic to assume direct neuroprotective effects of rTMS on pathophysiological mechanisms involved in neurodegenerative diseases such as Alzheimer's disease (AD) or Parkinson's disease (PD). However, rTMS may interact with the normal processes of brain plasticity and induce or enhance compensatory mechanism leading to increase of the brain reserve; hence interfere with temporal evolution of clinically relevant cognitive symptoms of neurodegenerative diseases [29]. Postponing the clinical manifestation of fully blown dementia may be the major goal since we still do not have any causal treatment for neurodegenerative diseases.

It has been clearly shown that rTMS induces changes of cortical plasticity of motor cortices [28]. The positive effects of TMS on cognitive P300 event-related potential have also been well documented [27,30]. Although this may provide a rationale for using the rTMS as a therapeutic tool it is still not easy to estimate how and if the altered mechanism of brain plasticity can serve as a model for developing effective protocols [31]. Results of the studies employing functional MRI (fMRI), fluoro-deoxy-glucose PET (FDG PET), and EEG in different patient groups may help in formulating hypotheses to be tested by using rTMS. However, on the whole it is more difficult to induce clear behavioral and clinically relevant benefits of rTMS than to induce changes of cortical plasticity or brain activation/ network connectivity changes [28].

The limited effects of accessible pharmacological treatment for cognitive impairment in AD, PD, and MCI preceding AD has led to an increased interest in research on alternative therapeutic strategies and non-pharmacological interventions [32,33]. This review presents the results of current studies that have used rTMS in people with AD or PD and assessed its effect on cognitive functions. MCI preceding AD is included in the review because of the aim to treat impaired cognitive functions as early as possible.

2. Method

A systematic literature search of articles written in English before June 2013 was conducted in the Web of Science and PubMed databases. A wide range of keywords was used: “rTMS”, “TMS”, “magnetic stimulation”, “cognitive”, “cognition”, “Alzheimer”, “Parkinson”, “MCI”, “mild cognitive impairment”, and “neurodegenerative”. By combining the aforementioned keywords we identified 224 articles retrieved by the Web of Science and 67 papers collected from PubMed databases. We carefully reviewed all titles and abstracts and excluded the meeting abstracts, editorial material and non-english written articles. Then we focused on our predefined selection criteria: application of rTMS, involvement of human subjects, inclusion of patients with MCI, AD or PD, and evaluation of cognitive domains. Articles that did not meet these criteria were excluded. Our aim was to include original studies dealing with the therapeutic application of rTMS and assessing cognitive after-effects as one of the major outcomes. Having said that, we were able to identify 19 articles meeting our focus and field of interest.

Articles were divided into three groups according to the diagnosis (MCI preceding AD, AD, or PD). We found nine studies that included patients with PD, seven articles on patients with AD, and three articles that concern people with MCI. Articles were listed from the most recent to the oldest.

3. Results

We identified 19 studies published before June 2013. The mean clinical population was about 17 people per study (range of 1–45 participants). This review includes 315 people altogether, of which 48 were with MCI, 118 with AD, and 149 with PD. The publications consist of two case studies [34,35], three open studies [36–38] and 14 controlled studies [39–52]. In the text of this review, we focus only on the controlled studies, but information about all 19 studies is displayed in Tables 1–3.

As a sham condition in seven studies [39,40,42,44,45,48,52] active coils were tilted so that no magnetic stimulation reached the brain; in six studies [41,43,46,47,50,51] sham coils were used; and in one study, stimulation of the occipital cortex was used as a control site of stimulation [49].

There was certain uniformity in the selection of the targeted areas. The dorsolateral prefrontal cortex (DLPFC) was stimulated in nearly all of the studies. In 12 controlled studies, researchers stimulated this area either bilaterally [39,41,42,44–46], or unilaterally with a left-sided preponderance [43,48–51]; in one study solely the right DLPFC was stimulated [52]. Other cortical regions were stimulated less frequently, including the inferior frontal gyri [47], dorsal premotor cortex [49], supplementary motor area [52], parietal somatosensory association cortex, and Broca's and Wernicke's areas [41]. The high occurrence

Table 1
rTMS in patients with MCI and its effect on cognition.

Study	Type of study/sham	n	Target area	Number of pulses, sessions	Frequency, intensity	Localization of the area	Test	Results
Turriziani et al. (2012) [34]	Controlled study, sham (TC)	8	Left/Right DLPFC	600/day, 2 sess. separated by 3 weeks (Left DLPFC + sham, 6 h apart; Right DLPFC + sham, 6 h apart)	1 Hz, 90% MT	Template MRI guiding	Verbal and nonverbal recognition memory tasks	↑Memory after R-DLPFC rTMS
Cotelli et al. (2012) [29]	Case study	1	Left IPL	2000/day, 10 sess. over 2 weeks	20 Hz, 100% MT	Template MRI guiding	FNAT, MMSE, RCPM, story recall, AVLT, spatial span, digit span, token test, fluency, ROCF, serial position curve task, De Renzi imitation test, TMT, WCST	↑Memory in FNAT, ↑AVLT delayed recall, ↑Primacy effect of serial position curve task
Solé-Padullés et al. (2006) [35]	Controlled study, sham (TC)	39	PFC	10 trains for 10 s each over 5 min. period, 1 sess.	5 Hz, 80% MT	5 cm anterior method	Associative memory task	↑Associative memory

Legend: n = number of subjects; TC = tilted coil; MT = motor threshold; (DL)PFC = (dorsolateral) prefrontal cortex; IPL = inferior parietal lobules; sess. = session/s; FNAT = face-name association task; MMSE = Mini-Mental State Examination; RCPM = Raven Colored Progressive Matrices; AVLT = Auditory-Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; TMT = Trail Making Test; WCST = Wisconsin Card sorting test; ↑Improvement of.

of DLPFC stimulation might be due to fact that this coil localization has been identified to have antidepressant effects and has therefore been intensively studied in the last years [14,53–58]. The traditional localization of the coil over the DLPFC is quite easy but imprecise (10–20 EEG system, 5 cm anterior to the motor hand area method). These methods are described in more detail below. Stimulation parameters vary from study to study.

Usually offline stimulation is used to measure cognitive effects, but Cotelli also used an online approach [44,45]. The number of pulses ranged from 100 to 2000 per day. In some studies, the effect of single session rTMS was measured [39,40,44,45,52]; other researchers assessed rTMS effects after up to 54 days of stimulation [41], see also Tables 1–3 for the details in stimulation paradigms. In nearly all of the publications high-frequency rTMS (ranged from 5 to 25 Hz) was used. In one controlled study [39] low-frequency rTMS (1Hz) was applied. The intensity of rTMS pulses was between 120% and 80% of the resting motor threshold, which correspond to the lowest intensity capable of inducing motor evoked potentials (MEPs) of the relaxed hand muscle in at least five out of ten trials.

The method of localizing the targeted area is a very important aspect of the protocol. There is no direct evidence in patients with neurodegenerative brain diseases that the neuronavigated coil would result in better cognitive effects. However, there are supporting arguments for the importance of precise coil neuronavigation in depressed patients' studies. Only 7 out of 22 patients showed proper localization of the DLPFC by moving the stimulation coil 5 cm anterior to the hand area hot spot; the rest had the center of the coil located in the premotor cortex [59]. Similar results were replicated by another study [60]. Inaccurate location of the coil was associated with poor antidepressant effects [61]. Some authors prefer "10–20 EEG system" to "5 cm method" in case those neuronavigation methods are not available [62]. But it has again been shown that individualized neuronavigated rTMS has better treatment effects than "10–20 EEG system" localization for the treatment of auditory hallucinations in schizophrenic patients [63]. In the presented review, one controlled study used a 10–20 EEG system [52]; in five controlled studies, researchers moved the stimulating coil 5 cm anterior from the primary motor cortex to localize the DLPFC [40,42,48,50,51]; in four controlled studies, specific brain regions were targeted on the basis of a reconstruction of cerebral cortex in the Talairach coordinate system using the SofTaxic Evolution navigator system and an estimated brain MRI template (www.emsmedical.net) [39,43–45]; and four controlled studies used individual subject's brain MRI data and frameless stereotaxy for the precise coil navigation [41,46,47,49]. Individualized targeting of the coil based on intrinsic functional brain connectivity as assessed by fMRI seems to be an interesting technique which needs further testing in clinical trials in different patient groups [64].

There were no severe adverse effects mentioned in the reviewed literature apart from minor tiredness in one study [36] and mild transient headaches [46–48] in the total of six patients. In four studies [37,39,40,52] the authors did not mention the side effects at all. Safety guidelines [4,65] were followed by ten studies [34,36,37,40–45,51].

The cognitive effects of rTMS are described in the next three sections, divided according to the main diagnosis. On the whole, small sized samples ($n \leq 15$) have been included [39,41,43,45–47,49,52] in most of the controlled studies. The use of improper blinding (e.g. tilted coil) [39,40,42,44,45,48,52] in addition to the use of imprecise coil localization techniques is another major limitation of some studies which will be discussed further in the Discussion section.

4. Mild cognitive impairment

The effects of brain stimulation on cognition were described in two controlled studies and one case study, summarized in Table 1. Turriziani et al. (2012) carried out three experiments that included healthy subjects and one experiment with MCI patients that were characterized mostly by memory impairment and met the diagnostic criteria for MCI

Table 2
rTMS in patients with Alzheimer's disease and its effect on cognition.

Study	Type of study/sham	n	Target area	Number of pulses, sessions	Frequency, intensity	Localization of the area	Test	Results
Rabey et al. (2012) [36]	Controlled study, sham (SC)	15	Left/Right DLPFC, Broca, Wernicke, Left/Right pSAC	1300/day, 54 sess. (5 sess./ weeks for 6 weeks, 2 sess./week for 3 months)	10 Hz, 90/110% MT	Subject MRI guiding	ADAS-cog, CGIC, NPI	↑ADAS-cog, CGIC
Haffen et al. (2012) [30]	Case study	1	Left DLPFC	2000/day, 10 sess. over 2 weeks	10 Hz, 100% MT	5 cm anterior method	MMSE, TMT, MIS, Free and Cued Recall Test, Isaacs Set Test, Picture naming, Copy	↑Episodic memory and speed processing
Ahmed et al. (2012) [37]	Controlled study, sham (TC)	45	Left/Right DLPFC	2000/day, 5 sess. in 5 consecutive days	20 Hz, 90% MT, 1 Hz, 100% MT	5 cm anterior method	MMSE, IADL, GDS	high frequency rTMS improves more than low frequency or sham in MMSE,GDS,IADL
Cotelli et al. (2011) [38]	Controlled study, sham (SC)	10	Left DLPFC	2000/day, 20 sess. over 4 weeks for real–real group, 10 sess. of sham over 2 weeks + 10 sess. of real over 2 weeks for placebo–real group	20 Hz, 100% MT	Template MRI guiding	MMSE, B/IADL, Picture naming, BADA, AAT, Serial position curve task, Cognitive estimation test	↑Auditory sentence comprehension
Bentwich et al. (2011) [31]	Open study	8	Left/Right DLPFC, Broca, Wernicke, Left/Right pSAC	1200/day, 54 sess. (5 sess./ weeks for 6 weeks, 2 sess./week for 3 months)	10 Hz, 90/110% MT	Subject MRI guiding	ADAS-cog, CGIC, NPI, HAMD, MMSE, ADAS-ADL	↑ADAS-cog, MMSE, ADAS-ADL
Cotelli et al. (2008) [39]	Controlled study, sham (TC)	24	Left/Right DLPFC	1-Day sess. divided into 3 blocks (Left DLPFC, Right DLPFC, sham)	20 Hz, 90% MT	Template MRI guiding	Picture naming	↑Object naming only in moderate to severe group, action naming in all patients
Cotelli et al. (2006) [40]	Controlled study, sham (TC)	15	Left/Right DLPFC	1-Day sess. divided into 3 blocks (Left DLPFC, Right DLPFC, sham)	20 Hz, 90% MT	Template MRI guiding	Picture naming	↑Action naming

Legend: n = number of subjects; DLPFC = dorsolateral prefrontal cortex; pSAC = parietal somatosensory association cortex; SC = sham coil; TC = tilted coil; MT = motor threshold; sess. = session/s; MMSE = Mini-Mental State Examination; B/IADL = Basic/Instrumental Activities of Daily Living; BADA = Battery for Analysis of Aphasic Deficits; AAT = Aachener Aphasie Test; ADAS-cog = Alzheimer Disease Assessment Scale-Cognitive ; CGIC = Clinical Global Impression of Change scale; NPI = Neuropsychiatric Inventory; TMT = Trail Making Test; MIS = Memory Impairment Screen; GDS = Geriatric Depression Scale; HAMD = Hamilton Depression Scale; ↑improvement of

Table 3
rTMS in patients with Parkinson's disease and its effect on cognition.

Study	Type of study/sham	n	Target area	Number of pulses, sessions	Frequency, intensity	Localization of the area	Test	Results
Srovnalova et al. (2012) [41]	Controlled study, sham (SC)	10	Left/Right DLPFC	600/day, 4 sess. (real Left/Right DLPFC, sham Left/Right DLPFC)	25 Hz, 80% MT	Subject MRI guiding	TOL	↑Total problem solving time after active Right DLPFC rTMS
Srovnalova et al. (2011) [42]	Controlled study, sham (SC)	10	Left/Right IFG	600/day, 2 sess. (real Left/Right IFG, sham Left/Right IFG)	25 Hz, 80% MT	Subject MRI guiding	Stroop test, FAB	↑All Stroop subsets
Pal et al. (2010) [43]	Controlled study, sham (TC)	22	Left DLPFC	600/day, 10 sess.	5 Hz, 90% MT	5 cm anterior method	MMSE, BDI, MADRS, Stroop test, TMT, UPDRS, HYS, TUG, ADL, VAS, ESS	↑Depression rating scales (MADRS, BDI), ↑accuracy of Stroop test
Sedlackova et al. (2009) [44]	Controlled study, controlled by OCC rTMS	10	Left PMd, Left DLPFC, Left OCC	1350/day, 3 sess.	10 Hz, 100% MT	Subject MRI guiding	VFT, TMT, Digit Span	No significant effect of rTMS
Furukawa et al. (2009) [32]	Open study	6	Frontal region	100/day, 12 sess. over 3 months	0,2 Hz, 120% MT	10–20 EEG system	TMT-B, WCST, WAIS-R, SDS, FIM	↑Scores in TMT-B and WCST
Epstein et al. (2007) [33]	Open study	14	Left DLPFC	2000/day, 10 sess. over 2 weeks	10 Hz, 110% MT	5 cm anterior method	HAMD, BDI, BPRS, HAMA, PDQ-39, RBANS, BTA, DRS, UPDRS	↑ Depression, anxiety, motor and other scales (HAMD, BDI, HAMA, DRS, UPDRS)
Boggio et al. (2005) [45]	Controlled study, sham (SC)	25	Left DLPFC	40 trains/5 s, 10 sess. over 2 weeks	15 Hz, 110% MT	5 cm anterior method	TMT-B, WCST, COWA-FAS, Stroop test, HVOT, digit span, RCPM	↑WCST, Stroop test, HVOT, ↑depression scales (HAMD, BDI)
Fregni et al. (2004) [46]	Controlled study, sham (SC)	42	Left DLPFC	40 trains/5 s, 10 sess. over 2 weeks	15 Hz, 110% MT	5 cm anterior method	MMSE, HAMD, BDI, HY, UPDRS, ADL	↑depression scales (HAMD, BDI), ↑MMSE, ADL
Koch et al. (2004) [47]	Controlled study, sham (TC)	10	Right DLPFC, SMA	250, 1 sess.	5 Hz, 100% MT	10–20 EEG system	Time reproduction task	↑Time perception after Right DLPFC rTMS

Legend: n = number of subjects; DLPFC = dorsolateral prefrontal cortex; IFG = Inferior Frontal Gyri; PMd = dorsal premotor cortex; OCC = occipital cortex; SMA = supplementary motor area; SC = sham coil; TC = tilted coil; MT = motor threshold; sess. = session/s; TOL = Tower of London; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; BDI = Beck Depression Inventory; MADRS = Montgomery-Asberg Depression Rating Scale; TMT(−B) = Trail Making Test(−part B); WCST = Wisconsin Card sorting test; UPDRS = Unified Parkinson's Disease Rating Scale; HYS = Hoehn-Tahr Scale; TUG = timed up and go test; ADL = Activities of Daily Living; VAS = Visual Analog scale; ESS = Epworth Sleepiness Scale; VFT = Verbal Fluency Test; GDS = Geriatric Depression Scale; HAMD = Hamilton Depression Scale; WAIS-R = Wechsler Adult Intelligence Scale Revised; SDS = Self-rating Depression Scale; FIM = Functional Independence Measure; HAMD = Hamilton Depression Scale; BPRS = Brief Psychiatric Rating Scale; HAMA = Hamilton Anxiety Rating Scale; PDQ-39 = Parkinson's Disease Quality of Life; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; BTA = Brief Test of Attention; DRS = Mattis Dementia Rating Scale; COWA-FAS = Controlled Oral Word Assosiation Test; HVOT = Hooper Visual Organization Test; RCPM = Raven Colored Progressive Matrices; ↑improvement of.

described by Petersen et al. [3]. Low-frequency rTMS (1 Hz) of the left and right DLPFC was used in a study with MCI subjects to interfere with performance in a non-verbal recognition memory task. The authors demonstrated that rTMS of the right DLPFC improved recognition memory performance in healthy subjects and in MCI patients without any significant impact on the speed of response [39]. There are some additional study flaws that should be mentioned such as involvement of unbalanced samples with regard to their sizes: 100 healthy controls and only 8 patients with MCI. Moreover, different incomparable variants of the cognitive tests were used (a paper version versus a computerized version).

Elderly people with memory dysfunction (who scored at least −1 SD below standardized age-matched norms in at least one of the memory tests: Rey Auditory Verbal Learning Test, Visual Reproduction of Wechsler Memory Scale Revised or Benton Visual Retention Test) received a single session of rTMS in a study conducted by Solé-Padullés et al. (2006). Participants were randomly divided into active and sham rTMS group. Association memory performance improved significantly only in the active rTMS group after high-frequency stimulation of the prefrontal cortex site (5 cm anterior to the primary motor cortex) above the interhemispheric fissure [40]. Of note, association memory was studied by the task comprising only 10 pairs of name and face which might have been insufficient.

5. Alzheimer's disease

The number of studies that explore cognitive effects of rTMS in AD has recently increased. The characteristics of these studies are presented in Table 2.

In a randomized, double-blind study, Rabey et al. [41] combined high-frequency rTMS of six brain regions (left and right DLPFC, Broca's and Wernicke's areas, left and right parietal somatosensory association cortex) with cognitive training (rTMS-COG therapy) for a total of 54 sessions over four and half months. This stimulation period was divided into two phases: an intensive treatment phase (5 days/week for 6 weeks) and a maintenance treatment phase (biweekly for 3 months). Each day three brain regions were stimulated (Broca's and Wernicke's areas and right DLPFC or left and right parietal somatosensory association cortex and left DLPFC) and total number of pulses per day was 1300. In the placebo group, patients underwent the same procedure but the sham coil was used and nature movies were projected as a control activity instead of cognitive training. The results reveal significant improvement in the Alzheimer's Disease Assessment Scale, cognitive subsection (ADAS-cog) scores (primary outcome measure) and the Clinical Global Impression of Change (CGIC) score (secondary outcome measure) in the treatment group compared to the placebo group. The average ADAS-cog scores in the treatment group improved by 3.76 points compared to the placebo group (0.47 points) at six weeks. In the same way, at 4.5 months, the treatment group improved by 3.52 points compared to a deterioration (0.38) in the placebo group. An improvement of about four points is considered to be a clinically significant result [41]. The results of this study are very promising; however, it is difficult to distinguish between the pure effect of rTMS and the effect of cognitive therapy, since the authors focused on the synergistic effects of both treatments. On the other hand, it has to be said that the placebo group which received sham rTMS together with active cognitive training did not show any significant treatment effects. There are additional methodological points that have to be pointed out here. Stimulating more than one brain area at the same time might induce additional beneficial after-effects as compared to stimulating just one brain area [66] as well as no additional effect to the single-site rTMS stimulation [67,68]. Since stimulation of one brain area might change excitability (increase as well as decrease) of different brain areas that are functionally/anatomically interconnected with the stimulated area [8,9] the outcome of multi-site stimulation is uncertain. There is also an intercallosal effect that may increase or decrease excitability in the opposite brain hemisphere [69,70] and thus performing the stimulation bilaterally may be problematic. Moreover, in the methods section it is not clearly described how the cognitive stimulation was combined with TMS and how the coil was located over different brain regions in individual subjects. It is not indicated whether the order of stimulated regions was randomized. The size of the patients sample is very small. Taken together, results of this study are very preliminary. Hopefully other groups will be able to replicate these impressive results.

Ahmed et al. (2012) studied a larger sample of patients with AD ($n = 45$) who were divided into three main groups according to the type of stimulation they received (low-frequency rTMS, high-frequency rTMS, sham rTMS). Stimulation was applied bilaterally over the DLPFC. The authors demonstrated that the high-frequency rTMS group improved significantly more than the other groups in MMSE, Instrumental Daily Living Activity scale (IADL), and Geriatric Depression Scale (GDS). Interestingly, there was a difference between the subgroups of the mild/moderate and the severe AD patients in the achieved improvement of all rating scales. While the mild/moderate subgroup improved, no significant improvement was seen in the severe AD group [42]. Although clinically relevant scales/tests were used by the authors, the MMSE seems to be rather an unspecific instrument for detecting treatment-induced cognitive changes.

Cotelli et al. dealt with the effects of rTMS on language performance and naming in people with AD. A recent offline study by Cotelli et al. (2011) showed a significant effect of high-frequency rTMS to the left DLPFC on auditory sentence comprehension, with no effect on other cognitive functions. The authors claim that facilitation effect of left DLPFC rTMS on patients with AD seems specific to the language domain [43]. However, previous online studies demonstrated the positive effect of high-frequency rTMS over the left and right DLPFC on accuracy of action naming in AD patients [45]. These effects apply to the patients at different stages of cognitive decline in general, but object naming accuracy after left and right DLPFC rTMS improved only in the moderate to severe (MMSE < 17) group of patients [44]. Unfortunately, some important information is missing in the later studies such as the number of pulses used in a session.

6. Parkinson's disease

Several articles deal with different cognitive effects of rTMS in patients with PD. Some focus on depression as a primary outcome [48,51], assessing the cognitive functions of rTMS only as a secondary outcome.

Srovnalova et al. recently published two randomized, sham-controlled studies with a cross-over design that focused solely on cognitive functions in PD. The authors showed that high-frequency rTMS of the right DLPFC induced significant improvement in the Tower of London task performance, as expressed by total problem-solving time. No significant change was detected after left DLPFC rTMS or sham stimulation [46]. In a second study, the researchers demonstrated improvement in all Stroop subtests after active high-frequency rTMS applied sequentially over both the left and right inferior frontal gyri (IFG). The results indicated a nonspecific enhancement of the cognitive processing speed. No significant change was induced by active or sham rTMS on Frontal Assessment Battery scores [47]. However, the problem of bilateral stimulation and interpretation of the stimulation results have already been mentioned above. Previously, authors from the same lab had found no significant effect of left high-frequency stimulation of the dorsal premotor cortex (PMd) and DLPFC on cognitive functions as measured by the Verbal Fluency Test-category, Trail Making Test, or the Digit span in cognitively normal PD patients [49].

Koch et al. (2004) demonstrated that high-frequency rTMS improves time perception as measured by time reproduction task in patients with PD [52]. Pal et al. (2010) studied the effects of left high-frequency DLPFC rTMS in PD patients with depression. Significant improvement in depression rating scales – Beck Depression Inventory

(BDI) and Montgomery–Asberg Depression Rating Scale (MADRS) – and in Stroop test accuracy was identified. Other cognitive tests such as MMSE or TMT revealed no change after the stimulation [48]. Similar sample groups (depressed PD patients) were used in two other studies that compared the effects of rTMS and fluoxetine [50,51]. High-frequency rTMS of the left DLPFC significantly improved Stroop test performance after two weeks of treatment. There was also a significant improvement in Hooper Visual Organization Test (HVOT) after two weeks of stimulation that persisted for up to eight weeks after the initial stimulation. In eight weeks after stimulation, there was a significant decrease in perseverative errors in the Wisconsin Card Sorting Test (WCST) compared to the initial values [50].

In the other study [51], significant change was found eight weeks after rTMS in Activities of Daily Living (ADL) in comparison with baseline. There was also a significant difference in MMSE scores after two weeks of treatment, with more improvement in the group that received rTMS than the group that had taken fluoxetine [51]. The authors concluded that rTMS is effective in treating depression (BDI, Hamilton Depression Scale — HAMD) and improving some aspects of cognition in PD patients with depression and the effect seems to be similar to or even better than the effects of fluoxetine.

In the studies of Pal et al. [48], Boggio et al. [50] and Fregni et al. [51] the effect of rTMS was focused on depression in PD (a primary endpoint) while cognitive after-effects were also studied in these depressed PD cohorts. Another major limitation of studies of Boggio et al. [50] and Fregni et al. [51] is the lack of an appropriate placebo group.

7. Discussion

This review summarizes articles that study the cognitive effects of rTMS in patients with AD and PD and in patients with MCI preceding AD. We are aware of the existence of other reviews that partially address this issue [32,33,71–76], but this is the first comprehensive review that covers rTMS-induced cognitive changes focused on patients with the two most common neurodegenerative diseases, including MCI patients, and captures recent developments in this particular field.

On the whole results of the studies presented in this review show partial effect of rTMS on the cognitive performance of patients with neurodegenerative diseases including MCI. It has been repeatedly shown that rTMS has a potential to induce measurable behavioral effects that outlast the period of stimulation. However, the currently reviewed papers have many flaws. Almost all studies included in our review share one major limitation which is an inadequately powered sample size. Therefore, none of the studies can be assessed as Class I or Class II with regard to evidence of the treatment effect [77,78] despite the fact that some studies are randomized and controlled. Only few Class III studies have been available so far [39,44–47,49] and even this class evidence can be debated particularly due to small sample sizes included in majority of these studies. Thus no clear level of recommendation (effective, probably effective, possibly effective) can be proposed at the moment for the use of rTMS as a treatment for cognitive deficits in AD/PD based on the current reviewed literature.

We still do not understand the exact mechanisms accountable for these effects. Therefore, rTMS studies using electrophysiological methods (EEG, evoked potentials) as well as multimodal advanced imaging techniques (fMRI, FDG PET) prior to and after rTMS treatment are urgently needed to shed further light on mechanisms underlying the rTMS after-effects.

Another major problem is that we do not know which patients are more susceptible or more likely to profit from rTMS with respect to cognitive outcomes. There is high between-subject and within-subject variability in rTMS after-effects. It has been shown that a ceiling effect may occur in very mildly affected patients e.g. [48,49]. Moreover, it has been demonstrated that brain plasticity may no longer be modifiable in severely cognitively impaired patients e.g. [42,43]. Association between the AD/PD severity and motor cortex excitability has been clearly shown e.g. [79–81]. In AD patients and in healthy elderly participants, bilateral stimulation was needed to produce measurable rTMS effects [44,45,82], while only left DLPFC stimulation was necessary to produce similar effects in younger healthy participants [83]. This is consistent with the model of hemispheric asymmetry reduction in older adults (HAROLD) introduced by Cabeza [84].

But there are other important potential confounders that have to be considered such as patient's age, age at the disease onset, brain atrophy or genetic factors.

To our knowledge groups of AD, PD or MCI patients with different age at disease onset were not directly compared with respect to the therapeutic outcomes. But this parameter varies largely across reviewed studies which make the direct comparison of different studies difficult. In the reviewed articles patients with AD were older (in their mid-seventies) than patients with PD or MCI (in their mid-sixties). Although both age and disease duration were usually reported [34–37,49], the age of the disease onset was not indicated in some studies [38–41,43–45]. Indeed, early onset PD patients have different clinical symptoms as compared to the patients with late disease onset and a higher risk of bearing a known genetic mutation. In the same vein, in AD the likelihood of genetic cause (genes such as PSEN1, PSEN2, and APP) and non-memory symptoms is higher in early-onset, whereas memory problems are typical for late-onset AD [85]. Difference in glucose metabolism connected with age of onset was confirmed by several studies [86–88]. In PD, the side of the disease onset should also be considered particularly in patients at early stage of the disease [81]. Taken together, the age and side of disease onset in a very important variable that may influence the rTMS outcomes and should be either controlled for where possible or considered for the interpretation of the results.

There is also a potential influence of brain atrophy on rTMS results especially when dealing with patients with dementia. The decrease in magnitude of the current densities induced on the cortex depends on the distance to scalp, but also on anatomical and electrical features of the tissues [89]. The distance between the stimulated cortex and coil increases and the effects of rTMS may thus decrease dramatically [28,90]. Some authors even suggest higher intensities of stimulation in older patients with cerebral atrophy [91]. Prefrontal atrophy is also listed as a negative predictor of the prefrontal rTMS response in depressed patients [92] especially in patients with late-life depression. However, in the reviewed studies the brain atrophy as measure by MRI was mentioned in 6 studies [35,36,41,42,44,45] where it served for the probable diagnosis of Alzheimer's disease and for exclusion of other potential causes of dementia. This variable was not taken into account for further analysis of rTMS after-effects. In the future rTMS studies the intracranial/gray matter volume as measured by MRI or individual distance to coil as measured using the frameless stereotactic coil navigation should be carefully considered.

Differences in genetic factors may also play an important role in rTMS results. In fact, a recent study showed that apolipoprotein E (APOE) status modulates the changes in network connectivity induced by the high frequency rTMS in non-demented elderly with memory complaints [93]. Variability of response to rTMS could also result from polymorphism of the BDNF gene. The response of the Val66Met allele carriers to stimulation was different compared to the response of Val66Val individuals — the Val66Met allele carriers showed reduced or absent stimulation after-effects compared to Val66Val subjects [94,95]. Therefore, the impact of genetic factors on cortical plasticity should be considered in future research.

Taken together, the effect of rTMS may differ depending on the stage of the disease, age of the disease onset, the amount of brain atrophy and underlying brain changes, and the individual cognitive reserve. Other important confounders include genetic factors. Therefore, future studies should focus on these specific issues and explore possible confounders in more detail and in larger well described and thoroughly examined patient cohorts.

Of note, great variability in simulation parameters and study protocols designs was observed. Unlike in their online rTMS studies [44,45], Cotelli et al. showed [43] that rTMS of the left DLPFC did not have any significant effect on action or object naming when an offline approach was used. Conversely, the authors demonstrated that auditory sentence comprehension improved significantly [43]. The results of these studies teach us that the effects of online and offline rTMS may significantly differ and the outcomes of online stimulation may not predict the possible after-effects of repeated-sessions stimulation. This result has a practical consequence for designing future studies. Also, mechanisms underlying rTMS effects should be studied separately for online and offline approaches.

The duration of stimulation and the study follow-up varied a lot too. There were single session studies and studies that lasted for several months. Most studies exploring the stimulation effect duration lasted approximately 10 days. A limited number of studies have explored long-term effects based on follow up visits after the treatment. Some studies [42,43,48,50,51] included a follow-up measurement one to three months after the end of the treatment and showed that the positive effects on cognitive functions were maintained. The number of pulses ranged from a few hundred to a couple thousand. Researchers used high-frequency (25 Hz) and (although very rarely) low-frequency (1 Hz) stimulation. Intensity of stimulation ranged from 80% to 120%. There was no general agreement in the selection of the targeted area, although most of the researchers chose the DLPFC.

To summarize from all the studies included in this review, the parameters of stimulation that most likely result in significant cognitive improvement in patients with neurodegenerative diseases include high frequency (10–20 Hz) rTMS applied over the left DLPFC for at least 10 multiple sessions with the intensity between 80 and 110% of the individual motor threshold. These results are similar to the outcomes of the systematic review by Guse et al. [71], but those authors included a different range of population groups (mostly patients with depression and schizophrenia). Unfortunately, at the moment there is still no clear evidence for the superiority of specific protocols for inducing cognitive after-effects in patients with AD, PD or MCI since the direct comparisons of different protocols performed in one patient group sample are lacking. Some authors rather compare effects of rTMS applied over different brain areas using the same stimulation protocol e.g. [41,49]. But the situation is even more complicated since there are many potential confounders involved in clinical studies (see the text above). Of note, results of studies in PD cohorts have demonstrated that targeting different brain areas may lead to similar cognitive behavioral outcomes [47,48,50]. Conversely targeting the same brain area and using the same stimulation protocol may lead to different results in AD patients depending on the stage of the disease [44,45]. Stimulating more than one brain area at the same time might induce additional beneficial after-effects as compared to stimulating just one brain area [66] as well as no additional effect to the single-site rTMS stimulation [67,68]. Therefore, future research employing particularly EEG, functional MRI, PET/SPECT in combination with rTMS is needed to explore the exact mechanisms of different stimulation protocols and brain targets before the best stimulation protocols can be tested in larger double-blind studies. The individualized rTMS treatment tailored for specific diseases, patient groups or even individual subjects may be the right way forward [64].

The study design with respect to the controlling procedure is another important issue. rTMS may produce very high placebo effects [65], and therefore proper verification of the active stimulation is necessary in order to evaluate the real effects induced by specific rTMS. In our review, most of the studies used a tilted coil or the commercially available sham coils that do not produce the same sensory stimulus on the scalp as the active coils. This difference is more problematic when the high stimulation intensities are used. Success of blinding is indeed a very important part of part of double-blind studies. Assessment of a success of blinding was mentioned only in two controlled studies [48,51]. A systematic review [96] dealing with a blinding success of rTMS applied to the DLPFC showed that only 13 out of 96 studies reported the blinding success. Authors also stated that the most frequently used control paradigms such as tilting of the coil or even using a regular sham coil are not suitable for proper mimicking the real rTMS. Taken together, the placebo effect of active stimulation performed in these studies cannot be fully excluded. In this respect, the control site stimulation or the use of novel sham coils that produce the sensory stimulation of the scalp similar to that produced by active coils is recommended.

Different methods were also used for proper localization of the coil. The conventional 5 cm anterior to the "hand motor area hot spot" method and 10–20 EEG system are not considered to be precise in localizing the targeted area due to between-subject brain gray matter variability. For future research, modern frameless stereotaxic systems based on subject's brain MRI are recommended [62,97–99]. Furthermore, small clinical sample sizes, clinical heterogeneity within the specific patients groups and inconsistency of selection the neuropsychological methods that measure cognition and/or specific cognitive domains make the outcome results difficult to generalize and compare. In case that several cognitive tests are used for evaluation of cognitive outcomes the correction for multiple comparisons is needed to prevent false positive results. Of note, the Bonferroni correction was mentioned in only 5 controlled studies [43–45,47,50].

MMSE, as a basic screening tool for dementia and an elementary cognitive measure, and the activities of daily living (ADL) were used to measure global cognitive and functional status in four controlled studies: two in AD and two in PD patient populations [42,43,48,51]. rTMS induced some positive after-effects in people with neurodegenerative diseases in two studies [42,51] while no changes in the MMSE scores were observed in two other studies [43,48]. In studies involving AD patients, the global MMSE or ADL scores did not change after stimulation if these patients were in a severe dementia state [42,43]. Moreover, it has to be pointed out that MMSE is a very basic and unspecific measure that only reflects global cognition. It does not examine executive functions, and the memory evaluation is totally insufficient. Because of low sensitivity it is not recommended for use in PD and MCI patients. Rabey et al. (2012) used ADAS-cog as a more detailed and appropriate global cognitive measure in their rTMS controlled study in AD patients who scored an average 22 points on the MMSE [41]. Some clinically meaningful change was observed in that study (rTMS-induced mean change of 3.5 points on the ADAS-cog from the baseline) but the study lacks methodological clarity and it is performed in very small patient samples (see also the critical points mentioned above).

In addition to global cognitive measures, several studies tested the effects of rTMS on specific cognitive tasks including memory recognition [39], associative memory [40], episodic memory [100] or working memory [49,50,101], psychomotor speed [48,49], and executive functions [46–50,102–104]. These studies were conducted in different patient populations and in healthy volunteers, targeting particularly the left DLPFC. Although variable results were demonstrated, subtle possible effects of rTMS were observed in most of the studies. However, it is difficult to generalize the results of rTMS on specifically chosen cognitive test performance, mainly due to small sample sizes enrolled in these studies. In addition, clinical heterogeneity within the specific patients groups and inconsistency in the selection of the neuropsychological methods that measure cognition and/or specific cognitive domains make the study outcomes difficult to compare. Having said that, the observed results have to be considered as preliminary.

8. Conclusion, future directions

Despite the aforementioned limitations, rTMS is a noninvasive, non-anesthesia required, non-pharmacological tool representing an interesting area for research with possibly therapeutic implications in people with neurodegenerative diseases. For future research, people with mild to moderate stages of the disease should be included. We think that at

the moment there is neither a good rationale nor evidence for stimulating many brain regions simultaneously and bilaterally for prolonged periods of time in large heterogeneous patient samples. Conversely, for future studies we suggest rather a more precise scientific approach. We recommend the use of EEG and/or brain imaging (fMRI for studying brain activity and connectivity patterns and PET for studying metabolic changes) results in order to define the best targets for receiving optimal cognitive after-effect in individual subjects. These cognitive outcomes should be specific depending on the patient group and clinically relevant [47]. There is some evidence showing that the DLPFC stimulation may improve working memory, specific executive functions, memory recall and naming while the IFG stimulation may enhance cognitive speed in patients with AD and/or PD. Other brain regions should also be targeted including e.g. the temporo-parietal cortices. Multimodal brain imaging and EEG/evoked potentials or combination of both techniques (e.g. high density EEG-fMRI) may assist in studying the individual underlying mechanisms of rTMS effects. We recommend individual-based neuronavigation of the coil using frameless stereotaxy and a suitable control procedure. Multiple-session protocols may lead to improved efficacy and prolonged treatment duration. Watching for and studying potential confounders in larger well-characterized groups is another important topic for future research particularly in genetically and clinically heterogeneous cohorts of patients with neurodegenerative brain diseases.

Although some cognitive effects of rTMS in people with neurodegenerative diseases were observed in various studies, based on the current available literature we cannot recommend rTMS for treatment of cognitive deficits in patients with neurodegenerative brain diseases. In future research we should look for specific but clinically meaningful changes induced by specific rTMS that reflect everyday functioning in different groups of cognitively impaired and aged population.

Conflict of interest statement

The authors have no conflict of interest.

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