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Review Article

Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease

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Several Transcranial Magnetic Stimulation (TMS) techniques can be applied to noninvasively measure cortical excitability and brain plasticity in humans. TMS has been used to assess neuroplastic changes in Alzheimer's disease (AD), corroborating findings that cortical physiology is altered in AD due to the underlying neurodegenerative process. In fact, many TMS studies have provided physiological evidence of abnormalities in cortical excitability, connectivity, and plasticity in patients with AD. Moreover, the combination of TMS with other neurophysiological techniques, such as high-density electroencephalography (EEG), makes it possible to study local and network cortical plasticity directly. Interestingly, several TMS studies revealed abnormalities in patients with early AD and even with mild cognitive impairment (MCI), thus enabling early identification of subjects in whom the cholinergic degeneration has occurred. Furthermore, TMS can influence brain function if delivered repetitively; repetitive TMS (rTMS) is capable of modulating cortical excitability and inducing long-lasting neuroplastic changes. Preliminary findings have suggested that rTMS can enhance performances on several cognitive functions impaired in AD and MCI. However, further well-controlled studies with appropriate methodology in larger patient cohorts are needed to replicate and extend the initial findings. The purpose of this paper was to provide an updated and comprehensive systematic review of the studies that have employed TMS/rTMS in patients with MCI and AD.

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Key words: transcranial magnetic stimulation; Alzheimer's disease; mild cognitive impairment; cortical plasticity; intracortical inhibition; afferent inhibition

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Introduction

Alzheimer's disease (AD) is a neurodegenerative process characterized by progressive neuronal loss, reduced levels of several crucial neurotransmitters, and altered forms of synaptic plasticity. Mild cognitive impairment (MCI) is considered a transitional stage between normal aging and a diagnosis of clinically probable AD. Single and paired-pulse transcranial magnetic stimulation (TMS) can assess cortical excitability, thus representing a useful co-adjuvant diagnostic tool to noninvasively assess *in vivo* neuroplastic changes. Paired associative stimulation and cortical response to repetitive TMS (rTMS) have provided useful information about different aspects of cortical plasticity. The combination of TMS with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) can provide further information on local cortical excitability and functional connectivity between motor cortex and other cortical regions.

We review the most important TMS studies that have demonstrated abnormal cortical excitability, plasticity, or connectivity in patients with AD and MCI.

If delivered repetitively, TMS can also induce long-lasting effects, noninvasively modulating the cortical excitability. rTMS was widely used to assess and modulate a variety of cognitive functions (sustained attention/concentration, executive functions/working memory verbal fluency/retrieval, problem solving/reasoning) in patients with degenerative diseases, patients with psychiatric disorders and in healthy subjects (for a review, see 1). Memory impairment is usually the first and more severe cognitive manifestation of these neurodegenerative processes, and rTMS studies have confirmed the role of the prefrontal cortex (PFC) during the encoding and retrieval of verbal or nonverbal material in healthy participants (2–6). By combining fMRI and rTMS, Manenti et al. (7) also provided evidence of a causal role of not only the PFC but also parietal cortices during word retrieval. It should be considered that the research in the field of memory is limited by the poor penetration depth of TMS (8).

In this review, we will also focus on the present, initial, findings showing that rTMS has the potential to enhance performances in cognitive functions that are impaired in MCI and patients with AD.

We update here previous important reviews (i.e., 9, 10) because in the last few years, other studies have significantly expanded the previous findings. We aimed thus to provide a comprehensive perspective of past and current research and to help guide future studies.

The MEDLINE, Pubmed (1966–July 2013), and EMBASE (1980–July 2013) electronic databases were searched using the medical subject headings (MeSH) 'dementia,' 'Alzheimer's disease,' 'mild cognitive impairment,' 'transcranial magnetic stimulation,' 'repetitive transcranial magnetic stimulation,' 'cortical excitability,' 'cortical plasticity,' 'motor threshold,' 'intracortical inhibition,' 'afferent inhibition,' and 'connectivity.'

Two review authors (SG and FB) screened the titles and abstracts of the initially identified studies to determine whether they satisfied the selection criteria. Any disagreement was resolved through consensus. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were searched for additional publications. In case of missing or incomplete data, principal investigators of included trials were contacted and additional information requested. No language restrictions were applied.

The two reviewers independently assessed the methodological quality of each study and risk of bias, focusing on blinding and other potential sources of bias. The search strategy described previously yielded 48 results. Only articles reporting data on studies using TMS techniques in patients with AD or MCI were considered eligible for inclusion. We excluded 3 studies after reading the full published papers; thus, 45 studies contributed to this review: the earliest was published in 1997 and the most recent in 2013.

Transcranial magnetic stimulation techniques

Measures of cortical excitability

Resting motor threshold (RMT) is defined as the minimum stimulus intensity that produces a motor evoked potential (MEP) of more than 50 μV in 50% of 10 trials in a relaxed muscle, whereas active motor threshold (AMT) is the minimum stimulus intensity required to generate a MEP (about 200 μV in 50% of 10 trials) during isometric contraction of the tested muscle at about 10% maximum. RMT provides information about a central core of neurons in the muscle representation in the motor cortex. RMT is increased by drugs that block voltage-gated sodium channels (11, 12), but is not affected by drugs with effect on GABAergic transmission (11, 12), and is lowered by drugs that increase non-N-methyl-D-aspartate (NMDA) glutamatergic transmission (13, 14). Therefore, RMT is thought to reflect both neuronal membrane excitability and non-NMDA receptor glutamatergic neurotransmission. AMT differs from RMT in that excitability of motoneurons in the spinal cord is enhanced by the voluntary muscle contraction, and thus provides a measure of corticospinal excitability with greater dependence on the spinal segmental-level excitability (15–17).

The amplitude of the MEP reflects not only the integrity of the corticospinal tract and the excitability of motor cortex and spinal level, but also the conduction along the peripheral motor pathway to the muscles. That is, a dysfunction along the corticospinal tract may therefore reveal abnormal MEPs, while the absence of MEPs abnormalities suggests integrity of the pyramidal tract (15–17). It has been recently demonstrated (18) that changes in MEP amplitudes and motor threshold represent two different indices of motor cortex plasticity. Whereas increases and decreases in MEP amplitude are assumed to represent LTP-like or LTD-like synaptic plasticity of motor cortex output neurons, changes in motor

threshold may be considered as a correlate of intrinsic plasticity.

Transcranial magnetic stimulation enables mapping of motor cortical outputs. Cortical mapping procedures, performed through single TMS pulses applied on several scalp positions overlying the motor cortex, may be obtained with an accurate assessment of the number of cortical sites eliciting MEPs in a target muscle, the site of maximal excitability (hot spot), and the 'center of gravity' of motor cortical output, as represented by the excitable scalp sites (19).

Besides evoking MEPs, single TMS pulses delivered during voluntary muscle contraction produce a period of EMG suppression known as cortical silent period (cSP). Moreover, through single-pulse TMS, it is possible to investigate inhibitory motor cortical processes ipsilateral to the stimulation side (ipsilateral silent period, iSP), which are considered to reflect the functional integrity of the callosal fibers connecting corresponding motor cortices (20).

Transcranial magnetic stimulation may also be used to assess the intracortical facilitatory and inhibitory mechanisms that influence the cortical motor output. Some of these TMS techniques involve paired stimuli based on a conditioning-test paradigm (21). Stimulation parameters such as the intensity of the conditioning (CS) and test stimulus (TS), together with the time between them (interstimulus interval, ISI), determine interactions between stimuli. When the CS is below and the TS is above the MT, the CS inhibits the response to TS at ISIs of 1–5 ms (short-latency intracortical inhibition, SICI), inducing an increase in the test MEP amplitude at ISIs of 7–20 ms (intracortical facilitation, ICF). CS at suprathreshold intensity inhibits the TS at ISIs of 50–200 ms and this is termed long-interval intracortical inhibition (LICI). Both SICI and cSP are thought to reflect the excitability of inhibitory GABAergic cortical circuits (15), and SICI is considered to reflect mostly the $GABA_A$-mediated intracortical inhibitory interactions (22). Whereas spinal inhibition contributes to the early phase of the cSP (for its first 50–75 ms), the late part of the SP, as well as LICI, reflect a long-lasting cortical inhibition mediated by $GABA_B$ most likely in the motor cortex (23).

Conversely, ICF is believed to reflect intracortical excitatory neurotransmission, which is largely mediated by NMDA receptors (24).

Short-latency afferent inhibition (SAI) refers to the suppression of the amplitude of a MEP produced by a conditioning afferent electrical stimulus, usually applied to the median nerve at the wrist approximately 20 ms prior to TMS of the hand area of the contralateral motor cortex (25). As SAI is decreased by the muscarinic receptor antagonist scopolamine in healthy individuals (26) and can be positively modulated by acetylcholine (Ach) in healthy individuals (27, 28), this measure is thought to be a non-invasive way of testing central cholinergic activity. However, SAI may also depend on the integrity of circuits connecting sensory input with motor output (29), and other neurotransmitters, especially dopamine, are supposed to play a modulatory role on the cholinergic neurotransmission.

Cortical connectivity and plasticity

Real-time integration of TMS with electroencephalography (EEG) (30–32) can provide further information on local cortical excitability and widespread network dynamics. As a matter of fact, EEG has an excellent temporal resolution, whereas TMS can be applied to study local reactivity of the brain and interactions between different brain regions with directional and precise chronometric information. The effects of several experimental manipulations including TMS in rodents on EEG rhythms have been recently reviewed to build a knowledge platform for innovative translational models for drug discovery in AD (33).

Several other TMS techniques are currently used to noninvasively modulate the cortical excitability, thus shedding light on mechanisms of cortical plasticity in humans.

Paired associative stimulation (PAS) and cortical responses to rTMS also provide information about different aspects of cortical plasticity (34). Through PAS procedure, an electrical stimulus is delivered to a peripheral nerve (usually the median nerve), followed by a single TMS pulse applied over the hand area of the primary motor cortex (M1) (35). When appropriately timed, PAS induces an increase in corticospinal excitability over a period of time which is interpreted as a marker of motor cortical plasticity, where long-term plasticity (LTP)-like processes are thought to play a major role (35). A new repetitive PAS (rPAS) protocol facilitates and prolongs the effects of electrical peripheral nerve stimulation and rTMS on cortical excitability. Submotor threshold 5-Hz repetitive electrical nerve stimulation of the right median nerve is synchronized with subthreshold 5-Hz rTMS of the left M1 at a constant interval for 2 min. The ISI between the peripheral stimulus and the transcranial stimulation is set at 10 ms (5-Hz rPAS10 ms) or 25 ms (5-Hz rPAS25 ms) (36).

If delivered repetitively, TMS can influence brain function. Through rTMS, a train of TMS pulses of the same intensity are applied to a single brain area at a given frequency ranging from 1 to 20 or more stimuli per second. Depending on the stimulation parameters, particularly the frequency of stimulation, cortical excitability can be modulated, thus obtaining a facilitating or suppressing effect. RTMS can be applied as continuous trains of low-frequency (1 Hz) or bursts of higher-frequency ($\geq$ 5 Hz) rTMS. Generally, low-frequency rTMS (stimulus rates $\leq$1 Hz) induces inhibitory effects on motor cortical excitability leading to a reversible 'virtual lesion' (37, 38), whereas high-frequency rTMS (5–20 Hz) usually promotes an increase in cortical excitability (39, 40). This modulation can last for several minutes (depending on the overall duration of the train itself) and provides an index of cortical plasticity. A novel protocol of rTMS named theta burst stimulation (TBS) (41) employs low intensities and has a robust, long-lasting effect in normal subjects (41, 42). Different patterns of delivery of TBS (continuous vs intermittent) produce opposite effects on synaptic efficiency of the stimulated cortex.

Studies on cortical plasticity, excitability, and connectivity

The major findings of TMS studies published on cortical excitability and plasticity in AD/MCI, as well as demographic and clinical characteristics of sample populations, are presented in Table 1.

Motor threshold

A consistent finding among TMS studies performed in patients with AD is the decreased RMT. Most of them found significantly reduced RMT in patients with AD compared with healthy controls (43–55), or a tendency toward a reduced RMT even if without statistically significant difference (56–64). Only one study noted no difference in RMT between patients with AD and controls (65), and one found increased RMT in AD (66).

It has been hypothesized that mechanisms related to RMT are preserved in the early stages (65). RMT was found to be normal also in patients with MCI (61). Alternatively, RMT changes might reflect a functional change, but not structural damage of cortical motor neurones. In the disease progression, the RMT decrease may be compensatory to the loss of motor cortical neurones (44, 58). Perretti et al. (66) suggested that, in the most advanced disease stage, the increase in RMT can be related to cortical atrophy. In a recent combined TMS-MRI study (67) in AD and mild cognitive impairment (MCI), the cortical thinning was found to be related to decreased cortical excitability, especially on the precuneus and cuneus. In patients with AD, the hyperexcitability on the sensorimotor cortex may represent a protective mechanism that counteracts the prominent loss of cortical volume. This supposed protective mechanism was found neither on the precuneus or cuneus, nor in the MCI group. Therefore, the authors concluded that the progression of the dementia proceeds differently in the structure and function of neuronal circuits from normal condition via MCI to AD.

The AMT was assessed in fewer studies, and the results are somewhat divergent from those for RMT. Only two studies found significant decreases in AMT in patients with AD as compared to healthy subjects (44, 49). These results suggest that the excitability of spinal projections is relatively preserved during early-course AD.

The increased excitability to TMS in patients with AD may be the consequence of an abnormality within the glutamatergic system, and this hypothesis was supported by a study demonstrating an abnormal response to rTMS in patients with AD (53).

Most of the studies found no significant differences in MEP amplitude between patients with AD and healthy individuals (46, 47, 49, 53, 54, 65, 66); significant increases in MEP amplitude in patients with AD were detected in 3 studies (43–45). Overall considered, the integrity of the corticospinal tract seems not to be compromised, at least in earlier stages of AD.

Interestingly, the 'center of gravity' of motor cortical output shows a frontal and medial shift, without changes in the hot spot location in patients with AD (58), thus indicating functional reorganization. The dysregulation of the inhibitory frontal centers and their integration in the excitatory network underlying motor output was thought to account for this finding (58).

Silent period, intracortical inhibition, and facilitation to paired TMS

Transcranial magnetic stimulation studies exploring the inhibitory circuits by means of cSP and SICI to paired-pulse TMS have yielded more divergent results.

A significant reduction in SICI has been reported in several studies (51, 55, 56, 59, 64, 65), whereas most studies did not find any significant

Table 1 Main findings of the studies on cortical excitability and plasticity in patients with Alzheimer's disease and mild cognitive impairment

			Demographic, clinical, and radiological features					TMS findings	
Authors	Grp	No	Age (y)	Gender (%F)	Education (y)	Disease duration (mo)	Radiology	Abnormal	Normal
Alagona et al., 2001	AD	21	72.2 ± 7.5	65.0	–	–	MRI	RMT ↓, I/O, MEP ↑	CMCT
Alberici et al., 2008	AD	8	74.5 ± 7.3	62.5	4.8 ± 0.4	30.7 ± 7.3	MRI		RMT, SICI, ICF
Battaglia et al., 2007	AD	10	70.1 ± 7.4	40	–	14.4 ± 6.7	MRI	PAS ↓	
De Carvahlo et al., 1997	AD	14	67.8 ± 6.0	72.7	–	–	CT	RMT ↓, MEP ↑	CMCT
Di Lazzaro et al., 2002	AD	15	69.0 ± 5.3	40	9.3 ± 3.4	28.4 ± 14.6	–	RMT, SAI ↓	AMT, I/O curve, SP, SICI, ICF
Di Lazzaro et al., 2004	AD	28	71.3 ± 2.9	–	8.2 ± 2.3	32.0 ± 16.8	–	RMT, SAI ↓	SICI
Di Lazzaro et al., 2005	AD	20	70.5 ± 6.9	60	7.9 ± 2.9	26.8 ± 16.4	–	SAI ↓	
Di Lazzaro et al., 2006	AD	20	69.5 ± 6.5	50	8.9 ± 4.5	31.9 ± 16.3	–	RMT, SAI ↓	
Di Lazzaro et al., 2007	AD	10	72.1 ± 4.4	40	9.2 ± 4.9	32.0 ± 13.1	MRI	RMT, AMT, SAI ↓	SICI
Di Lazzaro et al., 2008	AD	12	69.3 ± 7.3	–	9.1 ± 4.3	32.0 ± 13.1	MRI	RMT, SAI ↓	AMT, SICI
Ferreri et al., 2003	AD	16	75.0 ± 6.9	61.5	–	(> 4 yrs)	Head techn. or MRI	RMT ↓	
Liepert et al. 2001	AD	11	74.8 ± 9.7	70	–	–	CT or MRI	SICI ↓	MT,CMCT, cSP, ICF
Martorana et al. 2008	AD	11	73.0 ± 9.2	–	–	–	MRI	RMT, SICI ↓	ICF
Martorana et a. 2009	AD	10	71.7 ± 4.9	–	–	–	MRI	RMT, SAI ↓	
Nardone et al., 2006	AD	13	69.6 ± 4.9	46.15	14.2 ± 2.8	32.2 ± 15.5		SICI, SAI ↓	RMT, AMT, CMCT, ICF
Nardone et al., 2008	AD	17	68.4 ± 4.8	41.1	–	(>6 mo)	–	SAI ↓	RMT, AMT, CMCT, SICI, ICF
Nardone et al., 2011	MCI	40	68.2 ± 3.6	35.0	9.6 ± 3.4	12.4 ± 4.5	–	SAI ↓ in aMCI–MD	RMT, AMT, CMCT, SICI, ICF
Olazaran et al., 2010	AD	11	77.2 ± 4.4	54.5	–	2.7(1.9)		SICI ↓	RMT, ICF, LICI
Pepin et al., 1999	AD	17	68.5 ± 9.2	72.7	–	–	MRI	RMT, AMT ↓, MEP ↑	SICI, ICF
Perretti et al., 1996	AD	15	67.2 ± 7.8	73.3	7.3 ± 4.3	(>1 yr)	MRI	RMT ↑, cSP ↓	I/O curve, MEP
Pierantozzi et al., 2004	AD	12	65.2 ± 3.2	–	–	–	MRI	SICI ↓	RMT, AMT, I/O, ICF
Sakuma et al., 2007	AD	12	–	–	–	–	MRI	SAI ↓ in AD	RMT in AD RMT, SAI in MCI
	MCI	16							
Terranova et al., 2013	MCI	10	79.7 ± 2.6	40	–	33.8 ± 16.4	–	PAS, SAI ↓	RMT, SAI in MCI

All values are expressed as mean (SD). No, number of subjects; y, years; mo, months;%F, percentage female; CT, computed tomography; MRI, magnetic resonance imaging; AD, Alzheimer's disease; MCI, mild cognitive impairment; aMCI-MD, amnestic MCI- multiple domain; RMT, resting motor threshold; AMT, active motor threshold; MEP, motor evoked potential; I/O curve, input/output curve; cSP, cortical silent period; SICI, short-latency intracortical inhibition; LICI, long-latency intracortical inhibition; ICF, intracortical facilitation; SAI, short-latency afferent inhibition; PAS, paired associative stimulation (induced changes in MEP amplitude); ↑, increase; ↓, decrease.

difference in SICI between patients with AD and controls (44, 47–50, 60, 63). The amount of disinhibition can correlate with the severity of AD (56). Conversely, most studies assessing cSP failed to find significant abnormalities in this measure (43, 52, 53, 56). Peripheral silent period was examined in one single study and found not to be altered. Taken together, these findings do not support the possibility of an impairment in cortical GABAergic synaptic transmission. On the other hand, a dysfunction of GABA system has not been proven to represent a satisfactory alternative explanation for the cortical hyperexcitability in AD. In fact, biological investigations of biopsy brain tissue in patients with AD failed to demonstrate alterations in the GABA concentration or disturbance of GABA transporters (68, 69).

Significant ICF changes in AD subjects have never been observed (44, 47, 51, 56, 59, 63, 65), thus pointing to a normal NMDA receptor-dependent glutamate excitatory activity in AD. However, several studies suggest that abnormalities of glutamatergic neurotransmission might play a relevant role in AD. The glutamatergic hypothesis of AD, which has been proposed as an auxiliary mechanism to the cholinergic hypothesis (58), is possibly related to an imbalance between the non-NMDA and NMDA neurotransmission (13, 14, 58, 70, 71).

Recently, Hoeppner et al. (55) found a significantly prolonged iSP-latency in patients with AD compared with controls, with no differences in iSP-duration; in this study, the iSP-latency correlated significantly with the SICI. These effects appear to be independent from the degree of cognitive impairment and the presence of clinical signs of motor dysfunction. Results of this study suggest subclinical dysfunctions of motor cortical inhibition in mild to moderate clinical AD stages, with relevant interactions between intra- and interhemispheric inhibitions.

Both the amount of IHI and SAI were found to be significantly reduced also in patients with MCI as compared to control subjects, whereas SICI or ICF did not differ between them (72). The degree of IHI significantly correlated with neither the mini-mental state examination score

nor the degree of SAI. Our results suggest that transcallosal connection between bilateral M1 is primarily involved in MCI, regardless of SAI dysfunction.

Short-latency afferent inhibition

Among the parameters of motor cortical reactivity/excitability, the most consistent abnormal finding in AD regards SAI. All the studies assessing SAI found significant decreased SAI values as compared to healthy subjects (47–50, 59–62, 73). These findings are consistent with postmortem studies showing central cholinergic impairment in AD (74–76).

A negative correlation was found between SAI and performance in abstract thinking (49, 50) and long-term memory (50). The reduction in this putative marker of cholinergic activity is also correlated with euphoric manic state and disinhibition (77) in AD. This correlation can be explained by the prevalent cholinergic dysfunction of temporo-limbic area (including hippocampus, entorhinal cortex, and amygdala), particularly in the early stage of the disease. SAI testing may therefore represent a useful marker of central cholinergic dysfunction even in the initial stages of AD (60).

By contrast, SAI was found not to be significantly reduced in subjects with amnestic MCI (61). However, it is noteworthy to consider that in this study, the diagnosis of amnestic MCI was based on the criteria proposed by Petersen in 1999 rather than on the revised ones (78), and that the relationship to the different MCI subtypes was not defined. It has been recently demonstrated (79) that SAI is significantly reduced in patients with amnestic MCI-multiple domain when compared with the controls, while it is not significantly different in patients with amnestic MCI-single domain patients and in patients with non-amnestic.

By using the neurophysiological determination of SAI, the activation of the cerebello–thalamo–cortical pathway by means of continuous (inhibitory) cerebellar TBS was found to modulate central cholinergic functions (80).

Pharmacological effects

Several studies examined the acute effects of drugs enhancing acethylcholine neurotransmission on motor cortical excitability in patients with AD. The effect of the acethylcholinesterase inhibitor (AchEI) rivastigmine on cortical excitability was extensively studied by Di Lazzaro and co-workers (27, 47, 48). The AchEI galantamine was administered in another study (65). A reversal of SICI abnormalities was also detected following administration of galantamine (65), but not after rivastigmine (48). In one study, a smaller dose of the AchEI donezepil was given to 10 patients and a higher dosage to five (56). SICI was increased only in patients who were given the higher dose of donezepil (10 mg). Rivastigmine appeared to increase SAI in patients with AD (27, 47, 48), with no effect on healthy subjects (47), while neither rivastigmine nor galantamine had effect on RMT (27, 47, 48, 65).

Pennisi et al. (57) found that mean RMT correlated positively with disease severity at baseline and significantly decreased over both hemispheres after 1 year of treatment with AChEIs administered at different dosages.

Di Lazzaro et al. (27) also reported that most patients with abnormal SAI at baseline and who had had an acute increase in SAI after a single oral dose of rivastigmine benefited from prolonged administration of rivastigmine. In contrast, a normal SAI in baseline conditions, or an abnormal SAI in baseline conditions that was not greatly increased by a single oral dose of rivastigmine, was invariably associated with poor response to long-term treatment. The acute change in SAI correlated positively with an improvement in neuropsychological tests after 1 year of treatment.

Ferreri et al. (81) compared motor cortex functionality in 10 patients with AD before and after long-term AchEIs therapy to monitor potential drug-related effects on cortical physiology. The examined parameters of motor cortex excitability remained unchanged in patients with stabilized cognitive performances during the therapy. These results support the theory that the frontal lobes are among the specific targets of the neurophysiological stabilization induced by AchEIs, in agreement with quantitative EEG and SPECT studies (82, 83). Furthermore, Trebbastoni et al. (84) investigated changes in cortical excitability and short-term synaptic plasticity by delivering 5-Hz rTMS over the primary motor cortex in 11 patients with mild to moderate AD before and after chronic therapy with rivastigmine and found that chronic treatment with rivastigmine has no influence on altered cortical excitability and short-term synaptic plasticity. The authors concluded that the limited clinical benefits related to cholinesterase inhibitor therapy in patients with AD depend on factors other than improved plasticity within the intracortical excitatory glutamatergic circuits. Martorana and co-workers

assessed in two studies the acute effects of dopaminergic modulation on motor cortex excitability. In the first study, the authors examined the effects of a single dose of melevodopa on motor threshold, SICI, and ICF in patients with AD and healthy elderly controls (51). While melevodopa had no significant effect on RMT, AMT, and ICF in either group, it significantly reversed the abnormal SICI reduction in the patients with AD, with no changes in control group. These results suggest that dopamine may modulate cortical excitability in AD through intracortical inhibitory circuits. In a subsequent study, Martorana et al. (52) measured SAI after administration of a single dose of L-dopa in both AD and healthy subjects. Normalization of SAI was observed in AD, but no effect was noted in control subjects.

Cortical connectivity and plasticity

Inghilleri et al. (53) tested the effects of modulation of cortical motor areas induced by suprathreshold high-frequency (5 Hz) rTMS. Whereas in controls 5-Hz rTMS elicited normal MEPs that progressively increased in amplitude, in patients with AD, it elicited MEPs that decreased in size. These findings suggest the presence of an altered cortical plasticity in excitatory circuits within motor cortex in patients with AD. Conversely, 5-Hz rTMS induced an increase in cortical SP in both groups, thus suggesting a normal plasticity in cortical inhibitory circuits in the patients. Koch et al. (85) also found that low-frequency (1 Hz) rTMS did not induce in patients with AD the inhibitory effects which are observed in healthy subjects. L-Dopa did not modulate the effects of rTMS in patients with AD, showing that synaptic potential plasticity, such as long-term depression (LTD) may play an important role in the pathogenesis of this disease. Performing PAS with interval between peripheral nerve stimulation and TMS set at 25 ms (PAS25), Battaglia et al. (62) studied corticomotor LTP-like plasticity in patients with AD and healthy controls and also performed biochemical analyses in brain slices of amyloid precursor protein (APP)/presenilin-1 (PS1) mice, an AD animal model. PAS-induced plasticity was found to be significantly reduced in patients with AD. Moreover, 4–4.5-month-old APP/PS1 mice exhibited deficits of NMDAR-dependent neocortical (motor and medial prefrontal) and hippocampal LTP, and a significant alteration of NMDAR activity. Overall considered, these findings suggest that decreased plasticity might underlie motor symptoms in AD, resulting from a deficit of NMDAR-dependent neurotransmission. Also different protocols of theta burst stimulation (TBS) are known to induce plastic changes resembling the LTP and LTD mechanisms described in animal models. Koch et al. (86) were able to demonstrate the impairment of LTP-like together with normal LTD-like cortical plasticity in patients with AD. In fact, patients with AD showed consistent LTD-like effects that were comparable to those obtained in healthy controls when submitted to continuous TBS, while they did not show any LTP-like aftereffect when submitted to TBS protocols that induced an LTP-like effect in healthy controls such as intermittent TBS.

Recently, Terranova et al. (87) employed rPAS to investigate whether abnormal M1 synaptic plasticity is present at an early stage of AD. In the control subjects, rPAS induced a significant increase in MEP amplitudes and a decrease in SAI in the APB muscle persistently for up to 1 h. Conversely, 5-Hz rPAS did not induce any significant changes in MEP amplitudes and SAI in mild patients with AD. These findings suggest that sensory-motor plasticity is impaired in the motor cortex of AD at an early stage of the disease.

Julkunen et al. (54) studied functional connectivity between the motor cortex and other cortical areas. Fifty single TMS pulses 3 s apart were delivered to the motor cortex to assess spreading of navigated TMS-evoked EEG responses throughout the brain and found significant differences in motor cortical reactivity from averaged left and right hemispheres in patients with AD. In addition, using real-time integration of TMS and EEG prominent changes in cortical connectivity in subjects with AD have been demonstrated. In particular, the TMS-evoked response at 30–50 ms decreased significantly in patients with AD compared with both healthy controls and subjects with MCI over widespread brain regions; significant differences were found in the ipsilateral parietal cortex and contralateral frontocentral areas. These findings of diminished reactivity and connectivity between regions point to a dysfunction of large-scale sensorimotor networks, perhaps with reduced synchronization of EEG activity in patients with AD. In a subsequent study, the same authors (88) investigated the sensitivity of the TMS-EEG to discriminate control subjects from MCI and patients with AD and to evaluate how the TMS-EEG response related to the scores of the dementia rating scales used to evaluate the severity of cognitive impairment in these subjects. The authors found that

the TMS-EEG response P30 amplitude correlated with cognitive decline, showing good specificity and sensitivity in differentiating healthy subjects from those with MCI or AD. Recently, Bonnì et al. (89) explored by means of bifocal TMS parieto-frontal functional connectivity in 15 patients with AD and 12 healthy control subjects. Conditioning stimuli were applied over the right posterior parietal cortex (PPC) at different intensities (90% and 110% of RMT). MEPs were then recorded from the ipsilateral M1 at different ISIs ranging between 2 and 15 ms. Results showed that in healthy subjects, a conditioning TMS pulse applied over the right PPC at 90% (but not at 110%) of RMT intensity was able to increase the excitability of the homolateral M1. This functional interaction peaked at ISI 6 ms. Conversely, in patients with AD, the facilitatory pattern of parieto-motor connections was evident only when TMS was delivered at an intensity of 110% of RMT with a peak at ISI 8 ms. Interestingly, treatment with AchEI did not modify significantly the strength of the connection in patients with AD. Furthermore, the effects induced by PPC conditioning at 110% RMT correlated with neuropsychological measures of episodic memory and executive functions; the patients with better cognitive performance had thus less impaired connectivity. These findings suggest that parieto-frontal cortico-cortical functional connectivity is altered in patients with AD.

In patients with MCI, Bracco et al. (90) found that, unlike healthy subjects, linguistic task performance did not produce any significant MEP modulation in patients with aMCI. These findings suggest that functional connectivity between the language-related brain regions and the dominant M1(hand) may be altered in aMCI.

Neuromodulation and therapeutic interventions

In the last years, new non-invasive neurostimulation techniques have gained increased attention. In particular, two techniques of non-invasive brain stimulation – rTMS and tDCS – can modulate cortical excitability, inducing lasting effects (91, 92) both have been shown to have a potential therapeutic role in cognitive neuroscience (93).

Both techniques are known to involve mechanisms of synaptic plasticity, specifically LTP and LTD. A link between the aftereffects induced by rTMS and the induction of synaptic plasticity has been recently identified (94). We focus in this review the attention on the therapeutic applications of rTMS in patients with AD and MCI.

Several neuroimaging studies have demonstrated that the increased activation in right dorsolateral prefrontal cortex (DLPFC) is one of the functional brain abnormalities associated with memory deficits in MCI and AD (95–97); these findings have been interpreted as demonstrating recruitment of compensatory networks (98, 99). DLPFC is a common target for rTMS experiments and therapeutic protocols.

Turriziani et al. (100) investigated whether rTMS, given as inhibitory and excitatory TBS, over the left and right DLPFC modulates recognition memory performances in 100 healthy controls and in 8 subjects with MCI. Recognition memory tasks of faces, buildings, and words were used in different experiments. In the healthy control subjects, inhibitory TBS of the right DLPFC improved recognition memory performance for both verbal and nonverbal memoranda, while inhibitory TBS of the left DLPFC had no effect in the recognition memory performance; in contrast, excitatory TBS of the right DLPFC impaired nonverbal recognition memory performance in control subjects, while iTBS-excitation of the left DLPFC had no effect on recognition memory performance.

Repetitive transcranial magnetic stimulation (rTMS)–inhibition of the right DLPFC thus improved the recognition memory performance of patients with MCI with memory deficits while, in both the MCI and control subjects, the performance did not improve after rTMS-inhibition of the left DLPFC. Therefore, this study revealed a beneficial effect on memory performance when there is reduced activity in the right DLPFC during recognition memory tasks in patients with memory impairments.

It can be hypothesized that the previously reported additional activation in DLPFC in MCI and patients with AD reflects a dysfunctional use of brain resources rather than reflecting the recruitment of cognitive resources to maintain task performance (e.g., 98,99). Inhibitory rTMS over the right DLPFC may have the potential to modulate the activity in this dysfunctional network, enhancing function in healthy subjects or restoring an adaptive equilibrium in patients with MCI (101).

Three studies by Cotelli and colleagues have assessed the effects of rTMS on naming and language performance in patients with AD. In two crossover, sham-controlled, single-session studies (102, 103), rTMS was applied to the DLPFC during the execution of naming tasks. In the first study, high-frequency rTMS of either left or right DLPFC lead to a significantly improved accuracy

in action naming, but not in object naming (102). In the second study, Cotelli et al. (103) found that the results of the previous study were replicated only in patients with mild AD (Mini-Mental-State Examination (MMSE) $\geq$ 17/30); conversely, both action and object naming were facilitated in patients with moderate to severe AD (MMSE < 17/30) after left and right DLPFC rTMS.

In a subsequent study, Cotelli et al. (104) investigated whether the application of high-frequency rTMS to the left DLPFC would lead to significant facilitation of language production and/or comprehension in patients with moderate AD. Ten patients were assigned to one of two groups in which they received either 4-week real rTMS, or 2 weeks of sham rTMS followed by 2 weeks of real rTMS stimulation. No significant effects were observed on naming performance, while a significant effect was observed on auditory sentence comprehension after 2 weeks of real rTMS sessions. After two additional weeks of daily rTMS sessions, there was no further improvement, but a significant benefit on auditory sentence comprehension was still detected 8 weeks after the end of the rTMS intervention. Important findings were the absence of any effects on memory and executive functions, as well as the absence of any side effects of the rTMS applications.

In a single-case study, Cotelli et al. (105) aimed to assess whether rTMS could improve memory performance in an individual with amnestic MCI. Stimulation of the left parietal cortex increased accuracy in an association memory task, and such an improvement was still significant 24 weeks after stimulation began.

The objective of another study (106) was to compare the long-term efficacy of high- versus low-frequency rTMS applied bilaterally over the DLPFC, on cortical excitability and cognitive function of patients with AD. All patients received one session daily for five consecutive days. The group which received five daily sessions of high-frequency rTMS group improved significantly more than the low-frequency and sham groups in all assessed rating scales (MMSE, Instrumental Daily Living Activity Scale and the Geriatric Depression Scale) after treatment. This improvement was maintained for 3 months. The authors thus concluded that high-frequency rTMS may be considered as a useful adjuvant treatment of patients with mild to moderate AD.

Bentwich et al. (107) also investigated the combination of brain stimulation with cognitive rehabilitation (the so-called neuroAD-system) in patients with AD. In particular, they aimed to obtain a synergistic effect of cognitive training (COG) associated with rTMS (rTMS-COG). Eight subjects with mild to moderate AD were subject to daily rTMS-COG sessions (5/week) for 6 weeks, followed by maintenance sessions (2/week) for additional 6 months. rTMS was applied over Broca and Wernicke areas, right and left DLPFC, right and left parietal somatosensory association cortex, and COG tasks were developed to fit these regions. Improvements of Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) and of Clinical Global Impression of Change (CGIC) were found. Also MMSE, the Alzheimer Disease Assessment Scale -Activities of Daily Living (ADAS-ADL), and the Hamilton Depression Scale improved, but a statistical significance was not achieved, while Neuropsychiatric Inventory (NPI) did not change.

In a successive randomized, double-blind, controlled study, the same research group (108) aimed at examining the safety and efficacy of rTMS-COG in AD. Fifteen patients with AD received 1-h daily rTMS-COG or sham treatment, five sessions/week for 6 weeks, followed by bi-weekly sessions for 3 months. There was an improvement in the average ADAS-cog score and in the average CGIC after 6 weeks and after 4.5 months of treatment in the group receiving real rTMS-COG compared with the placebo group. NPI improved non-significantly. Therefore, the authors concluded that NeuroAD-system offers a novel, safe, and effective therapy for improving cognitive function in AD.

Haffen et al. (109) reported in a single-case study that rTMS treatment may improve cognitive skills. rTMS was applied in the patient with initial AD over the left DLPFC for ten stimulation sessions over 2 weeks. Cognitive improvements were noted especially in tests of episodic memory and speed processing. This study showed possible effects 1 month after rTMS, and their findings suggest that brain stimulation might facilitate cognitive processes partly depending on DLPFC.

Overall considered, these studies suggest that rTMS may be helpful in restoring brain functions, given its potential to recruit compensatory networks that underlie the memory-encoding and the other cognitive functions (110).

Table 2 summarizes the main findings of studies aiming at improving cognitive functions in patients with AD and MCI using rTMS.

Discussion

The reviewed studies aiming to explore cortical excitability and plasticity in AD illustrate that

Table 2 Main findings of studies aiming at improving cognitive performances in patients with Alzheimer's disease and mild cognitive impairment using repetitive transcranial magnetic stimulation (rTMS)

			Demographic features					Brain stimulation–Study design			
Authors	Grp	No	Age (y)	Gender (%F)	Education (y)	Disease duration (y)	Diagnosis	Parameters	Brain target	No. of sessions	Cognitive function
Cotelli et al., 2006	AD	15	76.6 ± 6.0	–	6.0 ± 2.0	–	NINCDS-ADRADA	20 Hz, 90% MT, 600 ms (+ sham)	L/R DLPFC	1	↑: Action naming NSE: Object naming
Cotelli et al., 2008	AD	12 12	75.0 ± 6.2 77.6 ± 5.8	–	6.8 ± 3.1 5.7 ± 2.6	–	NINCDS- ADRADA	20 Hz, 90% MT, 500 ms (+ sham)	L/R DLPFC	1	↑: Action naming (Mi); ↑: Action-object naming (M-S)
Cotelli et al., 2010		5(Real) AD5 (sham)	75.0 ± 6.2 77.6 ± 5.8		6.4 ± 1.3 4.8 ± 0.4	–	NINCDS- ADRADA	20 Hz, 100% MT, 2000 stim/s (+sham)	L DLPFC	20	↑: Auditory comprehension NSE: Naming
Ahmed et al., 2011	AD	15 (h-f) 15 (l-f) 15 (sham)	65.9 ± 5.9 68.6 ± 6.7 68.3 ± 4.9	66.6 60.0 66.6	> 6 20%	3.9 ± 2.3 4.1 ± 2.3 4.4 ± 2.5	NINCDS-ADRADA	20 Hz, 90% MT, 1 Hz 100% MT (+ sham)	L/R DLPFC	5	↑: MMSE, IALD, GDS (h-f rTMS) NSE: MMSE, ADAS-ADL, HAMILTON, NPI
Bentwich et al., 2011	AD	8	75.5 ± 4.3	12.5	10.9 ± 2.2	2.6 ± 0.6	DMS-IV	10 Hz, 90–110% MT, 2 s.	Broca's Wernicke'sareas, L/R DLPFC L/R pSAC	54	↑: ADAS-COG, CGIC
Haffen et al., 2012	AD	1	75	0	–	2	NINCDS-ADRADA	10 Hz, 100% MT, 5 s	L/R DLPFC	10	↑: MMSE, MIS, Free and Cued Recall Test, IST, TMT NSE: Picture naming, Copy
Turriziani et al. 2012	MCI	8	66 ± 5.7	20	13.6 ± 3.7	–	Diagnostic criteria for MCI*	1 Hz, 90% MT; iTBS	L/R DLPFC		
Rabey et al., 2013	AD	15	–	–	–	–	DMS-IV	10 Hz, 90–110% MT, 2 s	Broca's Wernicke'sareas, L/R DLPFC L/R pSAC	54	↑: ADAS-COG, CGIC

All values are expressed as mean (SD). No, number of subjects;%F, percentage of female; y, years; L, left, R, right; MCI, mild cognitive impairment; Mi, mild (Alzheimer's disease); M-S, moderate to severe (Alzheimer's disease); h-f, high frequency; l-f, low frequency; Hz, Herz; MT, motor threshold; DLPFC, dorsolateral prefrontal cortex; TPC, temporoparietal cortex; TC, temporal cortex; pSAC, parietal somatosensory association cortex; ↑, enhancement; NSE, no significant effect; NINCDS-ADRDA (national institute of neurological and communicative diseases and stroke/Alzheimer's disease and related disorders association); DMS-IV, diagnostic and statistical manual of mental disorders, 4th edition; CDR, clinical dementia rating; MMSE, mini-mental state examination; IALD, instrumental daily living activity; GDS, geriatric depression scale; ADAS-COG, Alzheimer's disease assessment scale–cognitive; CGIC, clinical global impression of change; NPI, neuroropsychiatric inventory test; *, criteria of Petersen (2001).

several TMS techniques may represent a useful additional tool for the functional evaluation of patients with MCI and AD. Also integrated approaches using TMS together with others neurophysiological techniques (such as high-density EEG) have been recently proposed as promising tools for noninvasive evaluation of subjects with cognitive impairment.

Among the studies focusing on motor cortical excitability parameters, the most consistent finding is the reduction in SAI in patients with AD. The SAI technique can also be used to monitor AD progression and response to treatment (27). Both *in vivo* and postmortem studies on cholinergic involvement in early AD are inconclusive (111–113), and it remains still relatively unclear how early in the course of the disease neurochemical and neuropathological alterations occur. On the other hand, neurobiological changes should be examined earlier in the disease process, at a stage when presumably they are more relevant for the pathogenesis of AD. Therefore, the finding that TMS abnormalities can also be observed in patients with early diagnosis of AD (60, 64) and in patients with amnestic MCI-multiple domains (79) has potentially relevant diagnostic and therapeutic implications. In particular, identification of SAI abnormalities occurring early in the course of AD or even in patients with MCI will allow earlier diagnosis and treatment with cholinergic agents.

Several TMS techniques, as well as the combination of TMS and EEG, also enable the exploration of plasticity across different brain regions and the characterization of the functional connectivity between different neural networks. Encouraging findings, showing impaired cortical plasticity and functional connectivity between motor and non-motor brain regions in AD, have been obtained.

Overall, there are several issues that should be more carefully addressed in future studies. First, brain atrophy is known to occur in AD, often in the initial stages of the disease (114, 115). Nevertheless, the potential influence of regional cortical thinning on the TMS findings has been so far not adequately considered. However, as the effects of TMS depend on the distance between cortex and scalp (93, 116), cortical thinning can significantly modify the impact of TMS (117) because of the greater scalp-to-brain distance. Therefore, some reported TMS abnormalities in patients with AD might be simply related to tissue shrinkage and brain atrophy. In a recent study (118), higher cortical excitability was found to be associated with lower cortical thickness and lower learning ability in healthy older adults, in agreement with the previous reports of increased cortical excitability in patients with AD with cortical atrophy and cognitive deficits.

Moreover, distinct cortical regions are differently affected in AD, especially in the earlier stages of the disease, and in non-motor cortical areas (e.g., temporoparietal and frontal association cortices), the abnormalities may be particularly profound and occur early in the course of the disease, while so far principally the motor cortex has been assessed (8).

Notably, most of the TMS findings show considerable variability between studies. TMS methodological issues, age at disease onset, duration of disease, and also genetic factors may account for such a marked inter-study variability. In fact, a common single nucleotide polymorphism of the brain-derivated neurotrophic factor (BDNF) gene due the valine-to-methionine substitution at codon 66 (BDNF-Val66Met) is known to differentially modulate cortical plasticity (119). Moreover, functional neuroimaging showed that the presence of Apolipoprotein E (*APOE*) and its $\varepsilon 4$ allele also distinctively modulate the clinical phenotype of AD (120); therefore, similar to the presence of BDNF-Val66Met polymorphism, also this genetic factor could influence the cortical reactivity and the response to rTMS. Koch et al. (121) also investigated the correlation between motor cortical plasticity, measured with 1-Hz rTMS, and the levels of Aβ(1–42), total tau (t-Tau), and phosphorylated tau detected in CSF of patients with AD. These authors found that higher CSF t-Tau levels were associated to a stronger inhibition of the MEPs, implying that the expected effects of the 1-Hz rTMS protocol were more evident in patients with more pathological t-Tau CSF levels. These findings suggest that also CSF t-Tau modulates excitatory activity and may alter mechanisms of cortical plasticity.

As rTMS is capable of modulating cortical excitability and inducing lasting effects, some researchers have tried to therapeutically use this neuromodulatory technique to improve cognitive performances in AD. This treatment shows considerable promise to reduce cognitive impairments, but results of the initial studies have to be considered as still preliminary at the present time. rTMS appears to be safe in patients with AD, even if long-term risks have not been sufficiently considered in all studies.

There is high between-subject and within-subject variability also in the observed rTMS aftereffects. Stimulation parameters and study protocol designs varied considerably in the previous studies. Single-session studies as well as

months-lasting studies have been performed. The typical treatment consists of daily sessions (five times a week) for 2 weeks. Some studies (98, 100) have explored long-term effects up to 3 months after the end of the rTMS intervention, and these showed the persistence of the beneficial effects on cognitive functions. Some rTMS interventions were of short duration; their effects seem to be short-lasting, and need to be replicated after longer-duration interventions (8). Moreover, some effects were obtained after longer-lasting applications, but not observed after a single rTMS session (102–104).

High-frequency stimulation has been used in most of the studies, and the intensity of stimulation ranged from 80% to 120% of the RMT. Important methodological differences can be observed with regard to the coil positioning and targeted localization. The DLPFC is the most common target for rTMS experiments and therapeutic protocols. The coil was placed 5 cm anterior from the hand motor area on the left and right hemispheres and held parallel to the midsagittal line.

However, the 10–20 EEG system and the conventional coil placement 5 cm anterior from the 'hand motor area hot spot' method cannot be considered a precise localization of this area. For future studies, a frameless stereotaxic navigation system based on subject's brain MRI is strongly recommended (122). Interestingly, bilateral stimulation was found to be necessary to produce measurable rTMS effects in some studies (102, 103).

The effects of online and off-line rTMS also may differ significantly. Cotelli and colleagues (104) were able to demonstrate a significant improvement in auditory sentence comprehension only when an off-line approach was used, while they failed to detect any significant effect on action or subject naming in their online studies (102, 103).

Furthermore, the heterogeneity in the selection of neuropsychological tests that measure cognitive functions renders the findings difficult to generalize. Two global cognitive measures, the MMSE and ADL, were used in some controlled studies (104, 106). In both studies, MMSE and ADL did not change in patients with severe cognitive impairment, thus suggesting that brain plasticity may no longer be modifiable in these patients. It should be considered that MMSE is a simple very basic screening test for dementia; it is not sensitive enough to detect subtle memory deficits and did not examine the executive functions. For future studies, an adequate and uniform choice of neuropsychological outcome measures would be of great importance to enable comparison across different studies. In particular, the outcome scales commonly used in trials of pharmacological agents for AD, such as the cognitive subscale of the ADAS-Cog, should also be employed to examine the therapeutic effects of rTMS (8). Several studies evaluated the effects of rTMS on specific cognitive functions including associative memory (123) and memory recognition (100), while the effects on other cognitive functions such as episodic and working memory, psychomotor speed and executive functions have not yet been examined in controlled studies.

Also control procedures to avoid placebo effects can be ameliorated. Therefore, in future research, the novel sham coils that produce an identical scalp sensory stimulation should be employed or a control site stimulation should be performed.

In the vast majority of the performed studies, high-frequency rTMS was applied; only in one controlled study (100), low-frequency rTMS was used. Therefore, even if TMS studies showed cortical hyperexcitability in patients with AD, the therapeutic attempts by means of rTMS are aimed at further increasing cortical excitability. Moreover, high-frequency rTMS might not enhance cortical excitability in patients with AD (8). Indeed, rTMS effects depend on the state of activity of the brain at the time of stimulation (124). For this reason, the baseline cortical excitability should be appropriately examined before and after therapeutic interventions. Finally, it seems unlikely that rTMS stimulation over a single brain area may lead to a real cognitive enhancement of patients with AD, particularly for those patients in more advanced stages of AD and multiple cognitive deficits (8).

Obviously, the new safety guidelines for the application of TMS in research and clinical settings (125) should be more thoroughly applied in all future studies.

In conclusion, several studies from the literature suggest that TMS may contribute to better understand the changes in cortical plasticity underlying MCI and AD, shedding light on the pathogenesis of the neurodegenerative process, and might also represent a promising therapeutic tool with potentially beneficial effects on the impaired cognitive functions.

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Conflict of interest

None.

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