

Review

Noninvasive brain stimulation in Alzheimer's disease: Systematic review and perspectives for the future

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ABSTRACT

Background: A number of studies have applied transcranial magnetic stimulation (TMS) to physiologically characterize Alzheimer's disease (AD) and to monitor effects of pharmacological agents, while others have begun to therapeutically use TMS and transcranial direct current stimulation (tDCS) to improve cognitive function in AD. These applications are still very early in development, but offer the opportunity of learning from them for future development.

Methods: We performed a systematic search of all studies using noninvasive stimulation in AD and reviewed all 29 identified articles. Twenty-four focused on measures of motor cortical reactivity and (local) plasticity and functional connectivity, with eight of these studies assessing also effects of pharmacological agents. Five studies focused on the enhancement of cognitive function in AD.

Results: Short-latency afferent inhibition (SAI) and resting motor threshold are significantly reduced in AD patients as compared to healthy elders. Results on other measures of cortical reactivity, e.g. intracortical inhibition (ICI), are more divergent. Acetylcholine-esterase inhibitors and dopaminergic drugs may increase SAI and ICI in AD. Motor cortical plasticity and connectivity are impaired in AD. TMS/tDCS can induce acute and short-duration beneficial effects on cognitive function, but the therapeutic clinical significance in AD is unclear. Safety of TMS/tDCS is supported by studies to date.

Conclusions: TMS/tDCS appears safe in AD, but longer-term risks have been insufficiently considered. TMS holds promise as a physiologic biomarker in AD to identify therapeutic targets and monitor pharmacologic effects. In addition, TMS/tDCS may have therapeutic utility in AD, though the evidence is still very preliminary and cautious interpretation is warranted.

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1. Introduction

Alzheimer's disease (AD) is the most common type of dementia worldwide, currently affecting 5.3 million people in the US alone (Alzheimer's Association's Facts and Figures' Report, 2010). Approximately one in every eight individuals age 65 have AD and the prevalence rises steeply to 40–50% by the age of 85. Progressive episodic memory loss is a clinical hallmark of AD (Dickerson and Eichenbaum, 2010), associated with decline in other cognitive domains (e.g., word retrieval, language comprehension, calculation, visuospatial orientation, learning capacity, abstract thinking and judgment), as well as deterioration of sensory and motor functions. In addition, with disease progression, behavioral symptoms such as delusions, agitation, changes in personality, and mood disturbances may also occur (Cummings et al., 1998). AD has devastating effects on

patients and their caregivers, and poses a tremendous socioeconomic impact on families and the health systems around the world. Presently, there is no cure for AD and existing interventions (including medications) can at best delay progression by 6–12 months in half of the patients (Alzheimer's Association's Facts and Figures' Report, 2010). The search for causes of AD, a detailed characterization of the progression of the disorder, and an improved understanding of the contributions of diverse genetic and environmental factors remain essential. However, given the increasing prevalence and debilitating impact of AD, successful diagnostic and therapeutic interventions are of immediate relevance.

Noninvasive brain stimulation with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) is valuable in research and has potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology (Wagner et al., 2007). TMS is a technique for noninvasive stimulation of the human brain and modulation of brain activity, while tDCS is a purely neuromodulatory intervention (Wagner et al., 2007). TMS is based on electromagnetic induction and can be used to examine brain-behavior relations, map sensory, motor, and cognitive

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functions, and explore the excitability of different cortical regions (Hallett, 2007). Repetitive TMS (rTMS) and tDCS have therapeutic potential in patients with neurologic and psychiatric disorders, as both can induce lasting modulation of brain activity in the targeted brain region and across brain networks through transcranial induction of electric currents in the brain (Wagner et al., 2007). It is not, however, completely understood by which mechanisms of action TMS and tDCS induce these lasting effects on the brain. There is burgeoning evidence to suggest that the physiologic impact of both techniques involves synaptic plasticity, specifically long-term potentiation (LTP) and long-term depression (LTD). For instance, Hoogendam et al. (2010) recently identified seven lines of evidence that strongly suggest a link between the after-effects induced by rTMS and the induction of synaptic plasticity. Similarly, Stagg and Nitsche (2011) brought together the results from pharmacological, neurophysiological, and imaging studies to conclude that tDCS may indeed modulate synaptic strength within the cortex, with evidence pointing to the involvement of intracortical neurons. At present, nevertheless, it is impossible to demonstrate a direct link between rTMS or tDCS and synaptic plasticity. Therefore, the effects of rTMS and tDCS are often described as LTP- and LTD-like effects.

TMS may offer a reliable means to characterize important neurophysiologic and pathophysiologic aspects of AD. To date, several reports using TMS have claimed the detection of abnormalities in cortical reactivity, plasticity, and connectivity in AD patients, and revealed differences between patients with AD, those with other dementias, and healthy elder individuals. Moreover, noninvasive brain stimulation, including TMS and tDCS, might hold therapeutic promise in AD. Herein, we review all studies that have applied noninvasive brain stimulation in AD to provide a comprehensive perspective of past and current research, and to help guide future studies.

2. Methods

2.1. Selection of studies and inclusion criteria

A systematic search of the literature was conducted using Web of Science and PubMed databases (until November 30th, 2010). The identification of English language articles was based on the following keywords: 'Alzheimer*' and 'magnetic stimulation' or 'direct current stimulation'. In addition, reference lists in retrieved reports were examined. Peer-reviewed studies were included if they met the following criteria: (a) human subjects were involved; (b) patients with AD were included in study samples; (c) studies were prospective in nature; and (d) TMS or tDCS was applied.

2.2. Collection of data

The data were collected using a semi-structured form for each study by one of the authors and checked by another. The following variables were extracted from all studies when pertinent and available: (a) Demographic and clinical characteristics: number of participants; study group; mean age; gender; educational level; mean duration of illness; neurologic, neuropsychiatric, and neuropsychological evaluation, including establishment of diagnosis and staging, neuropsychological testing, anatomical scanning, and medication; (b) Identification of all specific measures of cortical reactivity performed in each study; if TMS had been applied to the motor cortex, muscle from which neurophysiologic measures were obtained; (c) Mean and standard deviation (SD) of cortical reactivity measure(s) achieving statistical significance as compared with healthy elders; (d) Dose and duration of administration of pharmacological drugs; (e) Effects of pharmacological challenges on measures of cortical reactivity, and mean and SD of cortical reactivity measure(s) achieving statistical significance after the administration of medication, as opposed to

before; (f) Any significant correlations between neurophysiologic findings and demographic or psychosocial characteristics (e.g., age and years of education), neuropathology (staging or duration of disease) or neuropsychological scorings; and (g) Adverse events/safety considerations. Note that we extracted approximate mean and SD from graphs when data were not provided otherwise.

3. Results

3.1. Selected studies

A flow diagram reflecting the process of identification and selection of studies is provided in Fig. 1. The initial strategy yielded 225 and 88 peer-reviewed papers in Web of Science and PubMed, respectively, when combining 'Alzheimer*' and 'magnetic stimulation', and 21 and 4 peer-reviewed papers in Web of Science and PubMed, respectively, for the combination of 'Alzheimer*' and 'direct current stimulation'. During the initial review of retrieved papers, we excluded nearly 35% from Web of Science and about 11% from PubMed as they represented review or opinion articles, or were written in languages other than English. Of these, we further excluded approximately 83% and 66% of Web of Science and PubMed retrieved articles, respectively, during a more detailed screening as TMS/tDCS were not used as a diagnostic or therapeutic tool, or patients with AD had not actually been included. Ultimately, when combining both databases, our search identified 29 articles, of which 24 were TMS studies devoted to the measurement of motor cortical reactivity, local plasticity and connectivity in patients with AD, and 5 addressed the therapeutic application of TMS or tDCS to enhance cognitive function in AD. Among the studies exploring diagnostic applications of TMS, 23 compared findings in patients with AD with those in healthy controls, while 1 study included only AD patients but presented a longitudinal, long-term follow-up (Pennisi et al., 2002). Overall, 7 studies examined acute effects of pharmacological agents on motor cortical excitability in AD patients. Moreover, 1 study examined the predictive value of one TMS measure for the clinical response to a long-term pharmacological treatment (Di Lazzaro et al., 2005).

3.2. Studies on cortical reactivity, local plasticity, and connectivity in AD

Demographic and clinical characteristics of sample populations, as well as major findings of TMS studies published to date on cortical reactivity and plasticity in AD are presented in Table 1. Overall, results on a total of 317 patients with AD were contrasted to 298 healthy older individuals. We excluded from these numbers 20 AD patients and 12 healthy controls from one study (Table 1; study #11) (Di Lazzaro et al., 2005), since they appear to be the same participants included in a previous study (study #9) (Di Lazzaro et al., 2004).

3.2.1. Cortical reactivity measures

3.2.1.1. Short-latency afferent inhibition. The most consistent finding of altered motor cortical reactivity in AD regarded short-latency afferent inhibition (SAI). SAI refers to the suppression of the amplitude of a motor evoked potential (MEP) produced by a conditioning afferent electrical stimulus applied to the median nerve at the wrist approximately 20 ms prior to TMS of the hand area of the contralateral motor cortex (Tokimura et al., 2000). Fig. 2A provides a schematic illustration of the experimental set-up. SAI is thought to reflect the integrity of central cholinergic neural circuits, as it has been shown to be reduced or abolished by the muscarinic antagonist scopolamine in healthy subjects (Di Lazzaro et al., 2000). It has long been suggested that the pathogenesis of AD may involve deficits in the cholinergic circuits (Davies and Maloney, 1976; Coyle et al., 1983), and agents that enhance cholinergic neurotransmission – e.g., acetylcholine-esterase inhibitors (AChEIs) – are associated with

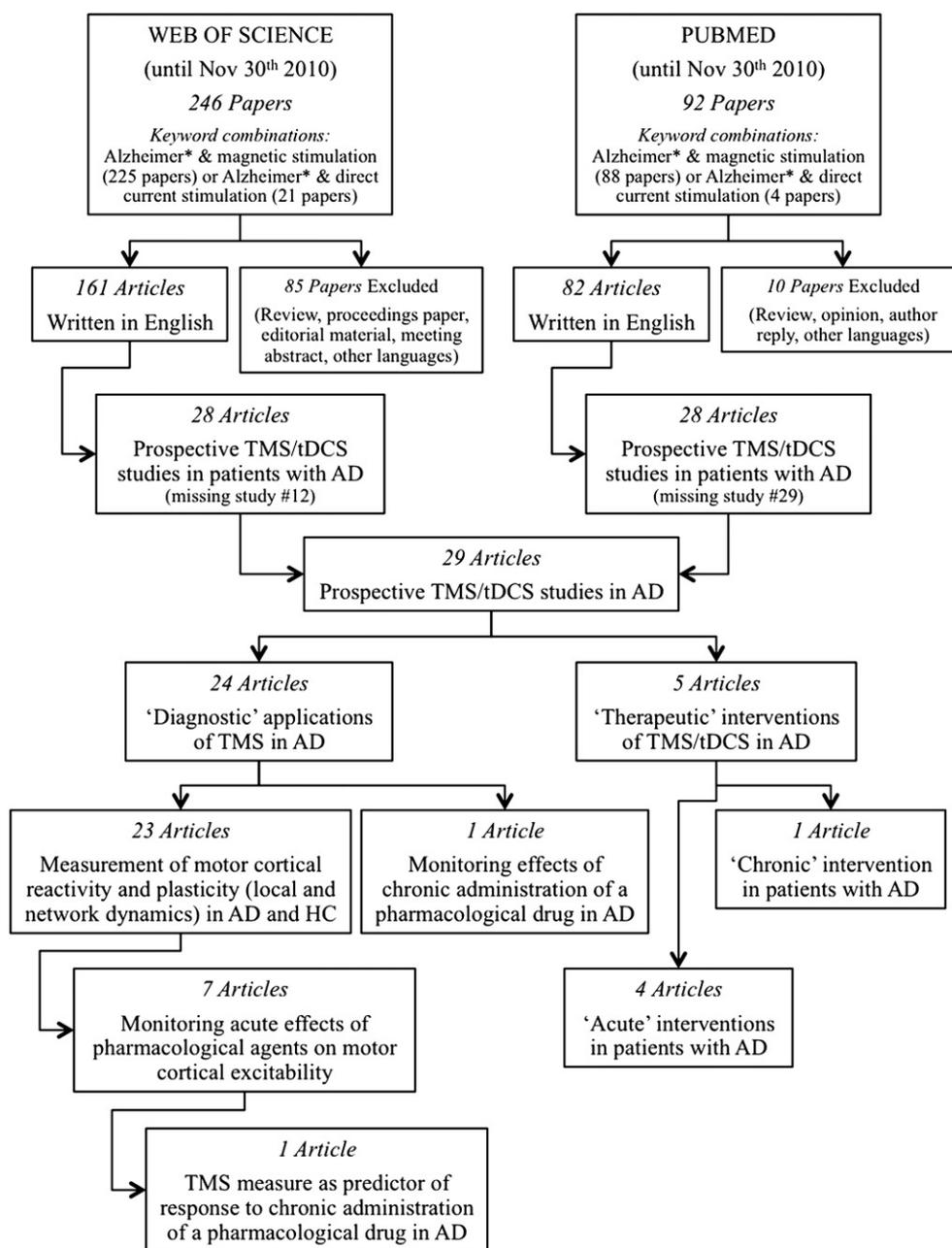


Fig. 1. Flow diagram of the selection process of peer-reviewed articles for systematic review.

improvements in cognitive function and activities of daily living (Birks et al., 2009). All 10 identified studies assessing SAI (Fig. 3A) found significant reductions in AD as compared to healthy individuals (studies #6, 9, 11, 12, 14, 16, 17, 19, 22, and 23) (Di Lazzaro et al., 2002, 2004, 2005, 2006, 2007, 2008; Nardone et al., 2006, 2008; Sakuma et al., 2007; Martorana et al., 2009). Results from TMS studies measuring SAI thus suggest that afferent inhibition may be a useful marker of central cholinergic dysfunction even in early stages of AD (Nardone et al., 2008).

Abnormal SAI may differentiate AD from frontotemporal dementia (study #12) (Di Lazzaro et al., 2006) or vascular dementia (study #19) (Di Lazzaro et al., 2008). However, in neurodegenerative dementias in which cholinergic deficits have been demonstrated, such as dementia with Lewy bodies (DLB), results to date are conflicting. Nardone et al. (2006) (study #14) found that SAI could differentiate AD from DLB, the latter presenting with normal SAI, although a clear tendency toward a reduced SAI was present in DLB patients as compared to

controls. Di Lazzaro et al. (2007) (study #16) showed a significant reduction in SAI in both AD and DLB patients, thus suggesting that SAI testing may be useful in differentiating cholinergic versus non-cholinergic forms of dementia. The discrepancy between studies might be due to major limitations in Nardone et al.'s study that make their results less conclusive: (a) SAI testing was performed without randomization of different conditions, which might have resulted in less accurate SAI evaluation; (b) patient selection seems to have been less strict than in the study by Di Lazzaro and co-workers because the diagnosis of DLB was based on criteria proposed in 1996 instead of the revised ones (McKeith et al., 2005); (c) neuroradiological studies, which are extremely helpful to support the diagnosis, appear not to have been conducted; (d) given the less strict patient selection, it is possible that some patients with Parkinson's disease (PD) associated with dementia might have been included in the DLB group, and since SAI appears to be normal or even enhanced in PD, this may have resulted in an overall normal mean; (e) it should also be noted that

#13 Inghilleri et al., 2006	20	AD	71.0 ± 2.1	.	-	44.0 ± 18.9	DSM-IV	CT and/or MRI	MMSE: 16.4 ± 3.5 ADAS-Cog: 38.7 ± 10.9 + Others	No AChEIs / no other 2 wks	Right FDI	SIGN [RMT ↓ in AD]	N.S. [I/O curve]	-	N.S. [before or after rTMS]	-	-	-	SIGN 5 Hz rTMS: lack of MEP ↑ in AD] N.S. [1 Hz]	No correlation w/ clinical scores
	20	HC	69.0 ± 1.6	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
#14 Nardone et al., 2006	13	AD	69.6 ± 6.6	53.85	14.2 ± 2.8	32.2 ± 15.5	NINCDS-ADRADA [Probable] DRs: 125.8 ± 8.0	-	MMSE: 24.2 ± 2.8	No AChEIs, dopamin /no other 2 wks	Domin FDI	N.S. [RMT & AMT]	-	N.	-	SIGN [↓ in AD]	SIGN [SICI ↓ in AD]	N.	-	SAI & SICI not correlated w/ age, disease duration, MMSE, DRs
	15	HC	67.5 ± 7.2	53.33	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
#15 Battaglia et al., 2007	10	AD	70.1 ± 7.4	60.0	-	[1.2 ± 0.7 yrs]	DSM-IV NINCDS-ADRADA [Probable]	MRI	MMSE: 20.02 ± 3.9 ADAS-Cog: 24.4 ± 8.0 MADRS	No AChEIs / no other 2 wks	Right APB	N.S. [RMT]	N.S. [I/O curve]	-	-	-	-	-	SIGN [PAS: LTP-like plasticity ↓ in AD]	-
	10	HC	68.4 ± 6.1	60.0	-	-	-	-	MMSE: 27.9 ± 1.8 ADAS-Cog: 8.8 ± 3.5 MADRS	-	-	-	-	-	-	-	-	-	-	-
#16 Di Lazzaro et al., 2007	10	AD	72.1 ± 4.4	60.0	9.2 ± 4.9	32.0 ± 13.1	NINCDS-ADRADA [Probable]	MRI	MMSE: 17.8 ± 1.8 RAVLT + Others	Naive to AChEIs/no other 2 wks	Left FDI	SIGN [RMT & AMT ↓ in AD]	N.S. [I/O curve]	-	SIGN [↓ in AD]	N.S. [SICI]	-	-	SAI negatively correlated w/ Raven matrices	
	10	HC	72.0 ± 5.1	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
#17 Sakuma et al., 2007	12	AD	.	.	-	-	NINCDS-ADRADA [Probable]	MRI	MMSE: 21.8 ± 2.8	No AChEIs	Right FDI	N.S. [RMT]	-	-	SIGN [↓ in AD]	-	-	-	-	-
#18 Alberici et al., 2008	15	HC	.	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	8	AD	74.5 ± 7.3	37.5	4.8 ± 0.4	30.3 ± 7.3	NINCDS-ADRADA	MRI	MMSE: 20.2 ± 4.0 UPDRS IADL/ BADL/FBI DeRenzi	Chronic AChEIs	Right/ Left FDI	N.S. [RMT]	-	-	-	N.S. [SICI]	N.	-	-	-
#19 Di Lazzaro et al., 2008	8	HC	63.1 ± 7.5	50	7.1 ± 2.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	12	AD	69.3 ± 7.3	.	9.1 ± 4.3	32.0 ± 13.1	NINCDS-ADRADA [Probable] [HIS]	MRI	MMSE: 22.7 ± 2.7 MDB + other GDS	Naive to AChEIs/no other 2 wks	Left FDI	SIGN [RMT ↓ in AD]	-	-	SIGN [↓ in AD]	N.S. [SICI]	-	-	SAI negatively correlated w/ RAVLT delayed, Raven + other	
#20 Julkunen et al., 2008	12	HC	73.1 ± 5.4	.	.	-	-	-	MMSE: ≥ 29	-	-	-	-	-	-	-	-	-	-	-
	5	AD	73.2 ± 8.1	60.0	9.6 ± 2.1	-	NINCDS-ADRADA [Probable] CDR: 0.6 ± 0.2	MRI	MMSE: 22.0 ± 5.1	AChEIs	Right/ Left Hypo thenar	SIGN [Aver both R/L ↓ in AD]	N.S. [I/O curve]	-	-	-	-	-	SIGN [EEG: TMS-evoked P30 ↓ in AD; ≠ FC & TPC; less sync?]	-
#21 Martorana et al., 2008 [Melevod]	4	HC	77.8 ± 2.6	25.0	6.5 ± 1.0	-	CDR: 0 ± 0	-	MMSE: 27.0 ± 4.1	-	-	-	-	-	-	-	-	-	-	-
	11	AD	73.0 ± 9.2	.	-	-	DSM-IV NINCDS-ADRADA CDR: ≥ 1.5	MRI	MMSE: 15.74 ± 1.6 NPB/NPI UPDRS	No AChEIs or others	Right APB	SIGN [RMT ↓ in AD]	-	-	-	SIGN [↓ in AD]	N.	-	-	-
#22 Nardone et al., 2008	12	HC	68.0 ± 5.8	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	17	AD	68.4 ± 58.82	.	-	[Sympt > 6 mo]	NINCDS-ADRADA [Probable] CDR: 0.5-1	-	-	Naive to AChEIs/no other 2 wks	Domin FDI	N.S. [RMT & AMT]	-	N.	-	SIGN [↓ in AD]	N.S. [SICI]	N.	-	SAI not correlated w/ age, disease duration, CDR
#23 Martorana et al., 2009 [L-dopa]	22	HC	70.4 ± 54.55	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	10	AD	72.5 ± 6.1	.	-	-	NINCDS-ADRADA [Probable] CDR: 1.75 ± 1.6 [HIS]	MRI	MMSE: 18.23 ± 3.2 NPB	Naive to AChEIs/no other 30 days	Right FDI	SIGN [RMT ↓ in AD]	-	-	-	SIGN [↓ in AD]	-	-	-	-
10	HC	71.7 ± 4.9	.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Legend. n: Number of subjects; yrs: Years; % M: Percentage of males; mo: Months; Anat scan: Anatomical scanning; NeuroΨ: Neuropsychologic; Meds: Medications; Pharmacol: Pharmacological; MT: Motor threshold; MEP: Motor evoked potential; mV: Microvolts; CMCT: Central motor conduction time; SP: Silent period; ms: Milliseconds; SAI: Short-latency afferent inhibition; ICI: Intracortical inhibition; ICF: Intracortical facilitation; Connectiv: Connectivity; AD: Alzheimer's disease; HC: Healthy controls; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; GDS¹: Reisberg's Global Deterioration Scale; HIS: Hachinski Ischemic Score; MRI: Magnetic resonance imaging; MMSE: Mini-Mental State Examination; NTB: Neuropsychological Test Battery; TOKEN: Token Test; CNS: Central Nervous System; APB: Abductor pollicis brevis; TA: Tibialis anterior; SIGN: Significant; RMT: Resting motor threshold; N.S.: Non significant; I/O curve: Input-output curve; per M: peripheral M response; cSP: Central silent period; pSP: Peripheral silent period; NINCDS-ADRADA: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; [Probable/Possible]: Probable/possible AD; BDS: Blessed Demential Scale; CT: Computerized tomography; ADM: Abductor digiti minimi muscle; R: Right; L: Left; AMT: Active motor threshold; SICI: Short latency intracortical inhibition; FDI: First dorsal interosseus muscle; CDR: Clinical Dementia Rating; WMT: Wechsler Memory Test; RAVLT: Rey Auditory Verbal Learning Test; AChEIs: Acetylcholinesterase Inhibitors; Symptoms: Symptoms; MDB: Mental Deterioration Battery; IADLS: Instrumental Activity of Daily Living scale; GDS²: Geriatric Depression Scale; ECD: Extensor digitorum communis; mo: Months; NPB: Neuropsychological battery; BDI: Beck depression inventory; NPI: Neuropsychiatry Inventory; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ADAS-Cog: Cognitive subscale of the Alzheimer Disease Assessment Scale; wks: Weeks; PAS: Paired associative stimulation; LTP: Long-term potentiation; plat: Plasticity; UPDRS: Unified Parkinson Disease Rating Scale; BADL: Basic Activities of Daily Living; FBI: Frontal Behavioral Inventory; FC: Frontocentral; TPC: Temporoparietal cortex; sync: Synchronization; Domin: Dominant. *Symbols.* †: Mean ± standard deviation; %: Percent; >: more than; ≤: equal or less than; ≥: equal or more than; .: No data; -: Not done or not applicable; ‡: Increased; *: 14 out of the initial 20 received single-dose of rivastigmine, specifically those who had low baseline SAI; **: 16 out of the initial 20 received rivastigmine for 1 year (treatment stopped in 4); ↓: Decreased.

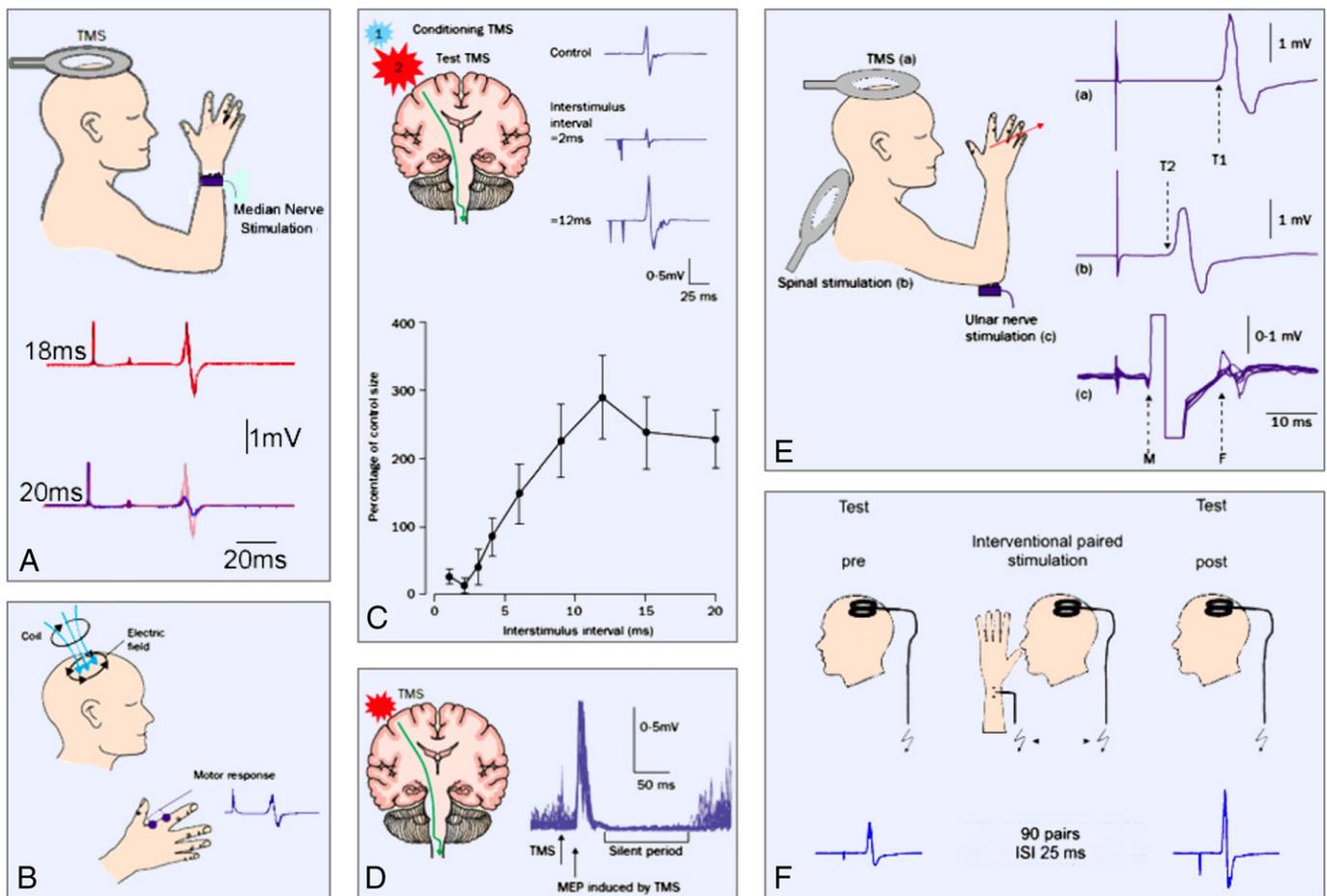


Fig. 2. Schematics of TMS measures of cortical reactivity (A–E) and plasticity (F). A: short-latency afferent inhibition (SAI); B: motor evoked potential (MEP); C: intracortical inhibition (ICI) and intracortical facilitation (ICF), represented at inter-stimulus intervals of 2 ms and 12 ms, respectively; D: cortical silent period (CSP); E: central motor conduction time (CMCT); F: paired associative stimulation (PAS). Schematic A partially composed Tokimura et al. (2000); schematics B–E adapted from Kobayashi and Pascual-Leone (2003); schematic F adapted from Stefan et al. (2000).

the mean values of SAI reported are different (for each ISI) from those reported by Di Lazzaro and colleagues (grand mean of all ISIs), making it difficult to evaluate them.

On the other hand, SAI appears to be normal in patients with mild cognitive impairment (MCI) (study #17) (Sakuma et al., 2007) and may thus not be useful to anticipate risk for development of AD. Similarly, no significant correlations were shown between SAI and age or duration and staging of AD (study #22) (Nardone et al., 2008). Nevertheless, SAI was found to be negatively correlated with performance in abstract thinking (studies #16 and 19) (Di Lazzaro et al., 2007, 2008) and long-term memory (study #19) (Di Lazzaro et al., 2008) in AD patients.

3.2.1.2. Motor threshold. Another particularly consistent result across studies of TMS in AD regards resting motor threshold (RMT). When TMS is applied to the motor cortex at appropriate stimulation intensity, MEPs can be recorded from contralateral extremity muscles (Fig. 2B). RMT refers to the lowest TMS intensity necessary to evoke MEPs in the target muscle when single-pulse stimuli are applied to the motor cortex, and it is commonly defined as the minimum stimulus intensity required to elicit MEPs of more than 50 μ V peak-to-peak amplitude in at least 50% of successive trials, in resting target muscles (Kobayashi and Pascual-Leone, 2003).

One study (study #11) (Di Lazzaro et al., 2005) did not report data on this measure, but of the others, most (14 of 22) found significantly reduced RMT in AD as compared with healthy controls (studies #2, 3, 4, 6, 7, 8, 9, 12, 13, 16, 19, 20, 21, and 23) (Di Lazzaro et al., 2002, 2004, 2006, 2007, 2008; Martorana et al., 2008, 2009; de Carvalho et al.,

1997; Pepin et al., 1999; Alagona et al., 2001, 2004; Ferreri et al., 2003; Inghilleri et al., 2006; Julkunen et al., 2008) (Fig. 3B). However, in one study (study #1) (Perretti et al., 1996), RMT was found to be higher in AD patients than controls (Fig. 3B). RMT is believed to reflect membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the motor cortex (Kobayashi and Pascual-Leone, 2003). Overall, findings to date on this TMS measure suggest an increased excitability of the corticospinal projections or motor cortical outputs in AD.

Active motor threshold (AMT) differs from RMT in that excitability of motoneurons in the spinal cord is enhanced by voluntary contraction of the target muscle, thus providing a measure of corticospinal excitability with greater dependence on the spinal segmental level excitability (Kobayashi and Pascual-Leone, 2003). AMT is usually defined as the minimum stimulus intensity to produce MEPs of approximately 200 μ V in 50% of consecutive trials during isometric contraction of the tested muscle, at about 20% of maximum voluntary contraction. AMT was assessed in 9 studies, with results being somewhat divergent from those for RMT, even within the same study. Two studies found significant decreases in AMT, along with RMT, in AD patients as opposed to healthy controls (studies #3 and 16) (Di Lazzaro et al., 2007; Pepin et al., 1999). The remaining studies found no significant differences in AMT in AD versus controls. However, while in 4 studies that absence of differences was paralleled by a lack of difference in RMT (studies #5, 10, 14, and 22) (Nardone et al., 2006, 2008; Liepert et al., 2001; Pierantozzi et al., 2004), 3 other studies reported significant decreases in RMT but no differences in AMT findings (studies #6, 19, and 21) (Di Lazzaro et al., 2002, 2008;



Fig. 3. Measures of cortical reactivity found in all (SAI) or most (RMT) studies to be significantly different in patients with AD as compared to healthy elders. As for ICI, although fewer studies found significant differences than those that did not, significant results are also presented. A: neurophysiologic findings for SAI in 9 out of the 10 studies measuring it, all showing significantly reduced SAI in AD as opposed to healthy elderly; study #23 (Martorana et al., 2009) was not included for lack of data conform with all others. B: neurophysiologic findings (means and SDs) for RMT of all 15 studies of 22 finding significant differences between AD versus healthy elder individuals. C: neurophysiologic findings for ICI of 4 studies, from a total of 11, in which significant differences between AD versus healthy elder individuals were obtained. Study numbers correspond to studies presented in Table 1. Results are presented in means and SDs. Note: A few studies did not provide exact means and SDs; we thus extracted approximate values from graphs whenever necessary.

Martorana et al., 2008). Thus, it seems that the excitability of spinal projections is relatively preserved during early-course AD.

3.2.1.3. Motor evoked potential amplitude. 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, dysfunction at any level along the corticospinal pathway may reveal abnormal MEPs, while the presence of intact MEPs suggests integrity of the pyramidal tract (Kobayashi and Pascual-Leone, 2003). The amplitude of MEPs can

be assessed in relation to the maximal MEP amplitude to progressively higher TMS intensities (input–output curve; Fig. 2B) or to the maximum peripheral M response. Either way, 11 studies measuring MEP amplitude in AD were identified. When using the former approach, most of the studies (7 of 8) found no significant differences between AD patients and healthy individuals in MEP amplitude (studies #1, 6, 10, 13, 15, 16, and 20) (Di Lazzaro et al., 2002, 2007; Inghilleri et al., 2006; Julkunen et al., 2008; Perretti et al., 1996; Pierantozzi et al., 2004; Battaglia et al., 2007), whereas one study found MEP amplitude to be significantly higher among patients with AD than healthy controls (study #4) (Alagona et al., 2001). When using the latter approach, significant increases in MEP amplitude in AD patients were found in 3 studies (studies #2, 3, and 4) (de Carvalho et al., 1997; Pepin et al., 1999; Alagona et al., 2001), whilst in 2 other studies (studies #1 and 8) (Alagona et al., 2004; Perretti et al., 1996) no significant differences were detected. Overall, however, these results suggest that the integrity of the corticospinal tract is not compromised in earlier stages of AD.

3.2.1.4. Central motor conduction time. Central motor conduction time (CMCT) is defined as the latency difference between the MEPs induced by stimulation of the motor cortex and those evoked by spinal (motor root) stimulation, and is calculated by subtracting the latency of the motor potential induced by stimulation of the spinal motor root from that of the response to motor cortex stimulation (Fig. 2E). Lengthening of CMCT suggests demyelination of pathways, while low amplitude responses with little delay or absence of responses are more suggestive of loss of neurons or axons (Kobayashi and Pascual-Leone, 2003). None of the 7 studies that examined CMCT in AD (studies #1, 2, 4, 5, 6, 14, and 22) (Di Lazzaro et al., 2002; Nardone et al., 2006, 2008; de Carvalho et al., 1997; Alagona et al., 2001; Perretti et al., 1996; Liepert et al., 2001) found statistically significant differences between patients and healthy elders. Once again, these results support that the integrity of the corticospinal tract is unaffected in mild-to-moderate stages of AD.

3.2.1.5. Intracortical inhibition and silent period. More divergent results between studies have been obtained for intracortical inhibition (ICI; Fig. 2C) and silent period (SP; Fig. 2D) measures. Both short-latency ICI (SICI) and cortical SP (cSP) are thought to reflect the excitability of inhibitory GABAergic cortical circuits (Hallett, 2000). In SICI, inhibitory interactions in the cortex can be studied by combining a subthreshold (60–80% of RMT) conditioning stimulus with a suprathreshold test stimulus, a technique known as paired-pulse TMS, at different short inter-stimulus intervals. Maximum inhibitory effects are generally found with interstimuli intervals between 1 and 4 ms, and the maximum amount of this inhibition is commonly 20–40% of the test MEP. SICI is thought to reflect mostly GABA_A-mediated intracortical inhibitory interactions (Paulus et al., 2008). In SP, when an individual is instructed to maintain muscle contraction and a single suprathreshold TMS pulse is applied to the motor cortex contralateral to the target muscle, the electromyographic (EMG) activity is arrested for a few hundred milliseconds after the MEP. This period of EMG suppression is referred to as a silent period, normally defined as the time from the end of the MEP to the return of voluntary EMG activity (Kobayashi and Pascual-Leone, 2003). Whereas spinal inhibition contributes to the early part of the SP (its first 50–75 ms), the late part originates most likely in the motor cortex (Ziemann, 2008).

Significant reductions of SICI (Fig. 3C) to paired-pulse TMS were found by some investigators (studies #5, 10, 14, and 21) (Nardone et al., 2006; Martorana et al., 2008; Liepert et al., 2001; Pierantozzi et al., 2004). However, most (7 of 11) studies did not find differences in SICI between AD patients and controls (studies #3, 6, 9, 16, 18, 19, and 22) (Di Lazzaro et al., 2002, 2004, 2007, 2008; Nardone et al., 2008; Pepin et al., 1999; Alberici et al., 2008). Nonetheless, when present, the amount of disinhibition can correlate with the severity of AD (study #5) (Liepert et al., 2001). On the other hand, of the 6 studies assessing

cSP, most (studies #5, 6, 8, and 13) (Di Lazzaro et al., 2002; Alagona et al., 2004; Inghilleri et al., 2006; Liepert et al., 2001), but not all (studies #1 and 4) (Alagona et al., 2001; Perretti et al., 1996), failed to find a significant deficit in this measure in AD versus healthy participants. Peripheral SP, assessed in a single study, was not altered in AD patients (study #1) (Perretti et al., 1996). Taken together, these findings do not strongly support impairments in GABAergic inhibition in AD.

3.2.1.6. Intracortical facilitation. Intracortical facilitation (ICF) is studied with paired-pulse TMS (Fig. 2C), but the inter-stimulus intervals at which facilitatory effects of the conditioning subthreshold TMS pulse on the suprathreshold test MEP can be observed are longer, usually between 7 and 20 ms. The magnitude of this facilitation can be quite variable among individuals, from 120% to 300% of the test MEPs (Kobayashi and Pascual-Leone, 2003). ICF is thought to reflect excitatory neurotransmission in human motor cortex largely mediated by N-methyl-D-aspartate receptors (NMDARs) (Ziemann, 2008). No study has found significant changes in ICF in AD patients as compared to healthy controls volunteers (studies #3, 5, 6, 10, 14, 18, 21, and 22) (Di Lazzaro et al., 2002; Nardone et al., 2006, 2008; Pepin et al., 1999; Martorana et al., 2008; Liepert et al., 2001; Pierantozzi et al., 2004; Alberici et al., 2008). Findings of all 8 studies point, therefore, to a normal NMDAR-dependent glutamate excitatory activity in AD, as tested by this cortical reactivity measure.

3.2.2. Cortical plasticity and functional connectivity

Three studies have examined cortical plasticity (studies #13 and 15) (Inghilleri et al., 2006; Battaglia et al., 2007) or functional connectivity (study #20) (Julkunen et al., 2008) in AD, involving a total of 35 patients with AD and 34 healthy elders. Several TMS techniques can be used to measure brain plasticity noninvasively in humans. These include cortical responses to repetitive TMS (rTMS) and paired-associative stimulation (PAS), and each provides information about different aspects of cortical plasticity (Hallett, 2000; Ziemann et al., 2008; Chen and Udupa, 2009).

Repetitive TMS consists of the application of a train of TMS pulses of the same intensity to a single brain area at a given frequency that can range from 1 to 20 or more stimuli per second. Such a train of rTMS can induce a modulation of cortical excitability beyond the duration of the train itself. Depending on the stimulation parameters, particularly frequency of stimulation, cortical excitability is rendered facilitated or suppressed. In general, a continuous train of lower frequencies of rTMS, in the 1 Hz range, leads to a transient suppression of excitability in the targeted cortical area, while bursts of high-frequency stimulation (≥ 5 Hz) lead to a temporary increase in cortical excitability (Kobayashi and Pascual-Leone, 2003). This modulation can last for several minutes (depending on the duration of the train itself) and provides an index of plasticity.

PAS (Fig. 2F) refers to a paradigm consisting of pairing low-frequency repetitive median nerve electric stimulation with timed TMS over the contralateral the motor cortex, resembling models of associative LTP as developed in animal studies (Classen, 2008). PAS was shown to be able to modulate the excitability of the motor system, leading to a lasting (≥ 60 min) increase in MEP amplitude, when the interval between peripheral nerve stimulation and TMS was set at 25 ms (PAS25), an inter-stimulus interval slightly longer than the time needed for the afferent inputs to reach the cerebral cortex (Stefan et al., 2000). However, changing the interval between the two associative stimuli to 10 ms (PAS10), i.e., an inter-stimulus interval shorter than the time needed for the afferent inputs to reach the cerebral cortex, leads to a depression of TMS-evoked MEPs (Wolters et al., 2003).

3.2.2.1. Studies of plasticity in motor cortical areas. Inghilleri et al. (2006) tested the effects of modulation of cortical motor areas induced by

suprathreshold high-frequency (5 Hz) rTMS. During rTMS, the amplitude of MEPs progressively decreased in patients while increasing in controls. Interestingly, 5 Hz rTMS induced an increase in cSP in both groups, thus pointing to normal plasticity in cortical inhibitory circuits in the patient group. These findings suggest that the mechanisms supporting facilitatory cortical plasticity might be abnormal in AD. It is noteworthy, though, that such modulatory effects of rTMS show great inter-individual variability (Maeda et al., 2000).

Other findings (Battaglia et al., 2007) seem to support impaired glutamatergic neurotransmission in AD, likely through NMDAR dysfunction. Employing PAS25, Battaglia and colleagues (Battaglia et al., 2007) studied corticomotor LTP-like plasticity in AD and healthy individuals, and also performed biochemical analyses in brain slices of a symptomatic APP/PS1 model. PAS-induced plasticity was found to be significantly reduced in AD patients. Moreover, the authors also showed that 4–4.5 month-old APP/PS1 mice exhibited deficits of NMDAR-dependent neocortical (motor and medial prefrontal) and hippocampal LTP, and a marked alteration of NMDAR activity. Therefore, it was suggested that decreased plasticity might underlie motor symptoms in AD and result from a deficit of NMDAR-dependent neurotransmission.

3.2.2.2. Studies of connectivity between motor and non-motor cortical areas. To date, no study has measured cortical reactivity or plasticity outside the motor cortex. However, Julkunen et al. (2008) have studied functional connectivity between the motor cortex and other cortical regions. They delivered 50 single TMS pulses 3 s apart to the motor cortex to assess spreading of navigated TMS-evoked electroencephalography (EEG) responses throughout the brain. They found significant differences in motor cortical reactivity (decreased MT from averaged left and right hemispheres) in AD subjects as compared with healthy controls. In addition, they obtained proof-of-concept findings of prominent changes in cortical connectivity in patients with AD using real-time integration of TMS and EEG. In particular, the TMS-evoked response at 30–50 ms decreased significantly in AD patients compared to both healthy elders and subjects with MCI over widespread brain regions, with significant differences detected in the ipsilateral parietal cortex and contralateral frontocentral areas (Fig. 4A). These findings of diminished reactivity and connectivity between regions suggest a dysfunction of large-scale sensorimotor networks perhaps with reduced synchronization of EEG activity in patients with AD. Moreover, amplitudes of P30 and P200 in MCI patients were halfway between the values of AD and control groups, thus suggesting that the combination of EEG with rTMS might detect abnormalities during prodromal stages of AD.

3.3. Studies on the monitoring of effects of pharmacological agents on motor cortical excitability

Table 2 presents major findings of TMS studies published to date assessing the acute and long-term effects of pharmacological agents, along with demographic and clinical characteristics of study samples. Overall, 77 patients with AD and 25 healthy, age-matched subjects have been tested before and after the administration of a single oral dose of medication, while 33 AD patients were tested prior to and following prolonged treatment.

3.3.1. Acetylcholine-esterase inhibitors (AChEIs)

Five studies examined the acute effects of AChEIs on motor cortical excitability in patients with AD (Table 2; studies #5, 6, 9, 10, and 11) (Di Lazzaro et al., 2002, 2004, 2005; Liepert et al., 2001; Pierantozzi et al., 2004). Specifically, single doses of rivastigmine were administered in 3 studies (Di Lazzaro et al., 2002, 2004, 2005), galantamine in another (Pierantozzi et al., 2004), and in one study a smaller dose of donepezil was given to 10 patients and a higher dosage to five (Liepert et al., 2001). In this latter study, SICI was increased in patients who were given the higher dose of donepezil (10 mg). A reversal of SICI was also detected following administration of galantamine (Pierantozzi et al., 2004), but not after rivastigmine (Di Lazzaro et al., 2004). In contrast, rivastigmine appears to augment SAI (Di Lazzaro et al., 2002, 2004, 2005), while having no effects on healthy controls (Di Lazzaro et al., 2004). Neither rivastigmine nor galantamine changed MT (studies #6, 9, and 10) (Di Lazzaro et al., 2002, 2004; Pierantozzi et al., 2004).

3.3.2. Dopaminergic agents

Two studies assessed the acute effects of dopaminergic challenges on motor cortical excitability (studies #21 and 23) (Martorana et al., 2008, 2009) in AD patients. The studies were motivated by the hypothesis that the dopaminergic system, involved in learning and memory processes, might be dysfunctional in patients with AD, eventually disrupting the cholinergic system. In the first study, Martorana et al. (2008) examined the effects of a single dose of melevodopa on RMT, AMT, ICI, and ICF in patients with AD and healthy elders. While melevodopa had no significant effect on RMT, AMT, and ICF in either group, it significantly changed SICI in AD patients, whereas no changes were observed among controls. Therefore, dopamine may modulate cortical excitability in AD via intracortical inhibitory circuits. In a second intervention, Martorana et al. (2009) measured SAI after administration of a single dose of L-dopa in both AD and healthy individuals. Normalization of SAI was observed in AD, while no effect was noted in controls. This suggests that the relationship between acetylcholine and dopamine systems may be

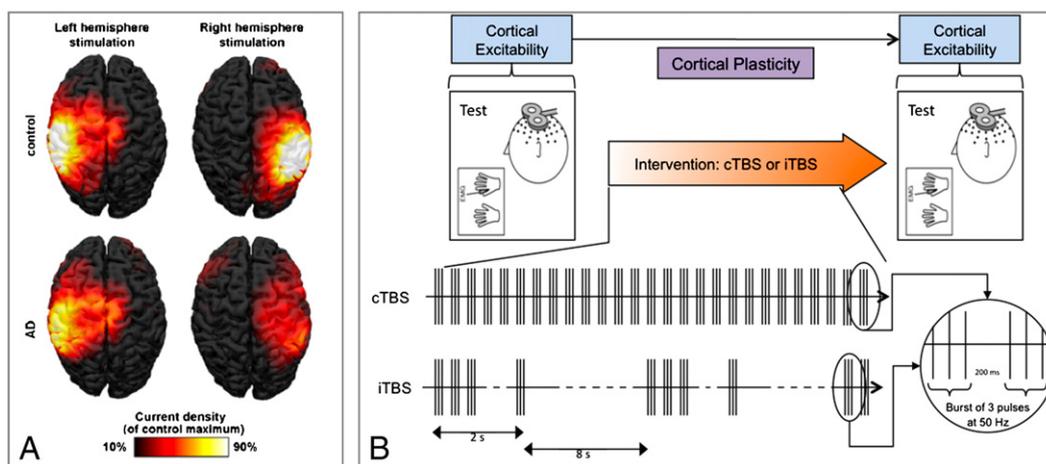


Fig. 4. Measuring cortical reactivity and plasticity, and functional connectivity and synchrony with TMS-EEG. A: results from study #20 (Julkunen et al., 2008) to illustrate the feasibility of combining TMS with EEG; B: schematic representation of experimental paradigm to measure local and network plasticity in motor (TMS-EMG and TMS-EEG) and non-motor (TMS-EEG) cortical regions.

Table 2
Major findings of peer-reviewed papers assessing the effects of acute and chronic administration of pharmacological drugs on cortical reactivity in Alzheimer's disease (AD), and assessing the predictive value of TMS measures for response to chronic administration of medication.

Paper	n	Age (yrs †)	Gender (% M)	Education (yrs†)	Disease duration (mo †)	Neurologic, neuropsychiatric, and neuropsychological evaluation				Pharmacol challenge	Effects on cortical reactivity					ICI	ICF	
						Diagnosis and staging	Anat scan	NeuroΨ testing	Meds		Muscle	MT (%)	MEP (mV)	CM CT	SP (ms)			SAI
<i>Acute administration of pharmacological drugs</i>																		
#5 Liepert et al., 2001	10	[n = 11: 74.8 ± 9.7]	[n = 11: 18.18]	-	-	[n = 11: CDR: 1.64 ± 0.64]	CT or MRI	MMSE WMT + other	No drugs affecting CNS	Donepezil 1 wk [5 mg/d] + 1 wk [10 mg/d] in 5 patients	Right FDI	-	-	-	N.S.	-	SIGN [SICI ↑ after 10 mg]	N.S.
#6 Di Lazzaro et al., 2002	6	[n = 15: 69.0 ± 5.3]	[n = 15: 60.0]	[n = 15: 9.3 ± 3.4]	[n = 15: 28.4 ± 14.6]	NINCDS-ADRADA [Probable]	-	MMSE: 18.6 ± 3.5 RAVLT + Others	Naïve to AChEIs	Rivastigmine Single-dose [3 mg]	Left FDI	N.S. [RMT, AMT]	-	-	-	SIGN [↑ in AD] N.S. [HC]	-	-
#9 Di Lazzaro et al., 2004	3 [HC] 14	[n = 28: 71.3 ± 6.8]	.	[n = 28: 8.2 ± 2.3]	[n = 28: 32.0 ± 16.8]	NINCDS-ADRADA [Probable]	-	MMSE: [n = 28: 19.35 ± 3.8] RAVLT + Others	Naïve to AChEIs/ no other 30 days	Rivastigmine Single-dose [3 mg]	Left FDI	N.S. [RMT]	-	-	-	SIGN [↑]	N.S. [SICI]	-
#10 Pierantozzi et al., 2004	12	65.2 ± 3.5	.	-	[Sympt not > 18 mo]	NINCDS-ADRADA [Possible] CDR: ≤ 1	MRI	MMSE: 21.8 ± 2.1 NPB BDI/NPI	No AChEIs or other	Galantamine Single-dose [4 mg]	Right/Left APB	N.S. [RMT & AMT]	N.S. [MEP amp]	-	-	-	SIGN [↑ SICI]	-
#11 Di Lazzaro et al., 2005	14* [↓ bas SAI]	[n = 20: 70.5 ± 6.9]	[n = 20: 40.0]	[n = 20: 7.9 ± 2.9]	[n = 20: 26.8 ± 16.4]	NINCDS-ADRADA [Possible]	-	MMSE [n = 20: 19.1 ± 5.5] RAVLT + Others	Naïve to AChEIs/ no other 30 days	Rivastigmine Single-dose [3 mg]	Left FDI	-	-	-	-	SIGN [↑]	-	-
#21 Martorana et al., 2008	11	73.0 ± 9.2	.	-	-	DSM-IV NINCDS-ADRADA CDR: ≥ 1.5	MRI	MMSE: 15.74 ± 1.6 NPB/NPI UPDRS	No AChEIs or others	Melevodopa Single-dose [250 mg] + [Placebo in AD]	Right APB	N.S. [RMT & AMT in AD or HC]	-	-	-	-	SIGN [↑ SICI in AD] N.S. [HC]	N.S. [AD & HC]
#23 Martorana et al., 2009	12 [HC] 10	68.0 ± 5.8 72.5 ± 6.1	.	-	-	NINCDS-ADRADA [Probable] CDR: 1.75 ± 1.6	MRI	MMSE: 18.23 ± 3.2 NPB	Naïve to AChEIs/ no other 30 days	L-dopa Single-dose [125 mg]	Right FDI	N.S. [RMT in AD or HC]	N.S. [MEP amp in AD or HC]	-	-	SIGN [↑ in AD] N.S. [HC]	-	-
<i>Chronic administration of pharmacological drugs</i>																		
#24 Pennisi et al., 2002	17	[Range: 55–82]	41.2	-	-	NINCDS-ADRADA [Probable]	CT/MRI [diffuse atrophy in all; repeated at 1 yr]	MMSE: 11.76 ± 5.68 MMSE (1 yr): 8.53 ± 5.14	-	AChEIs 1 yr	Right/Left FDI	SIGN [↓ R/L RMT]	N.S.	N.	-	-	-	-
<i>Predictors of response to chronic administration of pharmacological drugs</i>																		
#11 Di Lazzaro et al., 2005	16**	[n = 20: 70.5 ± 6.9]	[n = 20: 40.0]	[n = 20: 7.9 ± 2.9]	[n = 20: 26.8 ± 16.4]	NINCDS-ADRADA [Possible]	-	MMSE [n = 20: 19.1 ± 5.5] RAVLT + Others	-	Rivastigmine 1 yr chronic tt	Left FDI	-	-	-	-	SIGN [↑ in those w/ ↓ bas SAI or ↑ after s-d]	-	-

Legend. n: Number of subjects; yrs: Years; % M: Percentage of males; mo: Months; Anat scan: Anatomical scanning; NeuroΨ: Neuropsychologic; Meds: Medications; Pharmacol: Pharmacological; MT: Motor threshold; MEP: Motor evoked potential; mV: Microvolts; CMCT: Central motor conduction time; SP: Silent period; ms: Miliseconds; SAI: Short-latency afferent inhibition; ICI: Intracortical inhibition; ICF: Intracortical facilitation; CDR: Clinical Dementia Rating; CT: Computerized tomography; MRI: Magnetic resonance imaging; MMSE: Mini-Mental State Examination; WMT: Wechsler Memory Test; CNS: Central nervous system; wk: Week; mg/d: Milligram/day; FDI: First dorsal interosseus muscle; N.S.: Non-significant; SIGN: Significant; HC: Healthy control; NINCDS-ADRADA: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; [Probable]: Probable AD; RAVLT: Rey Auditory Verbal Learning Test; AChEIs: Acetylcholinesterase Inhibitors; RMT: Resting motor threshold; AMT: Active motor threshold; SICI: Short-latency intracortical inhibition; Sympt: Symptoms; [Possible]: Possible AD; NPB: Neuropsychological battery; BDI: Beck Depression Inventory; NPI: Neuropsychiatry Inventory; APB: Abductor pollicis brevis muscle; amp: Amplitude; bas: baseline; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; UPDRS: Unified Parkinson Disease Rating Scale; R/L: Right/left; tt: Treatment; w/: With; s-d: Single-dose. *Symbols.* †: Mean ± standard deviation; %: Percent; >: more than; ≤: equal or less than; ≥: equal or more than; .: No data; -: Not done or not applicable; †: Increased; *: 14 out of the initial 20 received single-dose of rivastigmine, specifically those who had low baseline SAI; **: 16 out of the initial 20 received rivastigmine for 1 year (treatment stopped in 4); ↓: Decreased.

abnormal in AD. Interestingly, the amount of increase of SAI by L-dopa correlated with cognitive impairment, as assessed by the Mini-mental State Examination (MMSE).

3.3.3. Long-term effects of medications on motor cortical excitability in AD

One study has investigated the effects of long-term administration of AChEIs on motor cortical excitability. Indeed, Pennisi et al. (2002) (study #24) showed that mean RMT, which was positively correlated with disease severity at baseline, significantly decreased over both hemispheres after 1 year of treatment with AChEIs at various dosages, while no significant changes were observed on MEP amplitude or CMCT.

3.3.4. Predictors of response to chronic administration of medications

Di Lazzaro et al. (2005) (study #11) assessed the predictive value of SAI for positive clinical response to 1 year of treatment with rivastigmine in patients with AD. They found 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, patients with normal SAI at baseline or abnormal SAI at baseline but presenting a small change in SAI after a single dose of rivastigmine showed progression of disease. Moreover, patients with abnormal SAI at baseline improved or remained stable on average in almost three-fold more neuropsychological tests than patients with normal baseline SAI. The acute change in SAI after single-dose rivastigmine was positively correlated with an improvement in a number of neuropsychological tests after 1 year of treatment. It was, therefore, suggested that abnormal baseline SAI – conceivably reflecting dysfunction in central cholinergic circuits – and a positive response to the acute effects of a single dose of rivastigmine may be predictive of long-term response to rivastigmine, so that the evaluation of SAI and the effects of a single dose of rivastigmine on SAI could be useful to identify responders. Eventually, similar strategies may prove to be similarly useful with other pharmacological agents for AD.

3.4. Studies on the enhancement of cognitive function in AD

Table 3 compiles major findings of TMS and tDCS studies published to date to enhance cognitive function in AD, as well as demographic and clinical characteristics of study samples. Overall, 54 patients with AD have been studied (this includes 9 new patients in study #26, as the remaining were the same 15 patients of study #25).

Both, rTMS and tDCS are noninvasive brain stimulation techniques capable of modulating cortical excitability and inducing lasting effects (Pascual-Leone et al., 1998; Nitsche and Paulus, 2000). The mechanisms of action of rTMS and tDCS remain unclear, but both show promise as therapeutic applications in neuropsychiatric disorders (Miniussi et al., 2008; Sparing and Mottaghy, 2008; Nitsche et al., 2009; Slotema et al., 2010), including the approval by the US Food and Drug Administration of the Neuronetics' Neurostar TMS intervention for the treatment of medication-resistant depression (O'Reardon et al., 2007). Repetitive TMS can be applied as continuous trains of low-frequency (1 Hz) or bursts of higher frequency (≥ 5 Hz) rTMS, while tDCS can be applied as anodal or cathodal stimulation (Wagner et al., 2007). In general, low frequency rTMS and cathodal tDCS are thought to reduce, and high-frequency rTMS and anodal tDCS to enhance excitability in the targeted cortical region.

Three studies, all conducted by the same group (Table 3; studies #25, 26, and 29) (Cotelli et al., 2006, 2008, 2010), have been carried out to assess the effects of rTMS over the dorsolateral prefrontal cortex (DLPFC) on naming and language performance in patients with AD. Two crossover, sham-controlled, single-session studies (Cotelli et al., 2006, 2008) used online rTMS, i.e., rTMS was applied during the execution of naming tasks. Significant improvements in action

naming, but not in object naming, were found following high-frequency stimulation of either left or right DLPFC in each of the 15 AD patients in the earlier study (Cotelli et al., 2006). In their second study, when dividing AD patients according to disease staging based on MMSE scoring, Cotelli et al. (2008) found that previous results were replicated only in mild AD patients (MMSE $\geq 17/30$). In contrast, in patients with moderate-to-severe AD (MMSE $< 17/30$), both action and object naming were improved after both left and right DLPFC rTMS. This led the investigators to suggest that the lack of benefit of rTMS on object naming in early-stage AD might be related to a 'ceiling' effect. In a later, parallel study (Cotelli et al., 2010), no significant effects of off-line rTMS were observed on naming performance (rTMS intervention consisted of a total of 4 weeks of daily stimulation) in moderate AD. A significant effect was nonetheless observed on auditory sentence comprehension after 2 weeks of real rTMS sessions, as compared to sham. Two additional weeks of daily rTMS sessions resulted in no additional improvements, although a significant benefit on auditory sentence comprehension was still detected 8 weeks after the end of the rTMS intervention as compared to baseline. These results were thought to be specific to the language network, therefore not due to a non-specific effect on cognitive processing in general, as no effects on memory and executive functions were found. None of these three studies reports any side effects of the intervention, but it is not clear what safety evaluations (if any) were completed.

Two other, crossover-designed studies used tDCS to enhance recognition memory in patients with AD (studies #27 and 28) (Ferrucci et al., 2008; Boggio et al., 2009). Ferrucci et al. (2008) also studied patients with mild AD before and after 3 sessions of tDCS targeting bilateral temporoparietal areas with anodal, cathodal, or sham tDCS. In either case, a third electrode (second cathodal) was placed over the right deltoid muscle (extracerebral reference). Separate sessions (15 min at 1.5 mA) were at least one week apart. Anodal tDCS to the temporoparietal region significantly increased accuracy in a word recognition task; cathodal tDCS significantly decreased accuracy, while sham tDCS did not change it. Moreover, no effects were observed in a visual attention task, suggesting that the effects of tDCS were likely specific for recognition memory. No safety considerations were reported, and no modeling of the actual current distributions was presented. Boggio et al. (2009) exposed patients with mild to moderately severe AD to a session of anodal tDCS to the left DLPFC, anodal tDCS to the left temporal cortex (cathodal electrode was placed over the right supraorbital area for these 2 sessions), or a session of sham stimulation. Sessions were 48 h apart, and patients were tested during each of the stimulation sessions, starting 10 min after stimulation onset and lasting until the end (30 min at 2 mA). No adverse effects occurred. Stimulation over both prefrontal and temporal areas resulted in a significant improvement of visual recognition memory, which was not attributable to attentional, non-specific processes, as assessed by the Stroop task. Nevertheless, contrary to the investigators' expectations, no effects were obtained on working memory, which was however measured by a digit span task, more indicative of attentional than working memory functions.

4. Discussion

We performed a systematic review of prospective studies using noninvasive brain stimulation in AD. Overall, 388 patients with varying stages of severity of AD were involved in 29 studies, and 298 healthy elders served as controls. A number of studies have applied TMS to physiologically characterize AD and to monitor effects of pharmacological agents, while others have begun to therapeutically use TMS or tDCS to improve cognitive function in AD. We thus report on two main types of studies: neurophysiologic measures and therapeutic applications. The former comprise either diagnostic studies, in which comparisons were made between patients with AD and age-matched healthy controls (though generally not against patients with other forms of dementia or neurodegenerative illnesses), or studies monitoring the effects of

Table 3
Major findings of peer-reviewed papers aiming at enhancing cognitive function in patients with Alzheimer's disease (AD) using noninvasive brain stimulation.

Paper	Study design	n	Age (yrs f)	Gender (% M)	Education (yrs f)	Disease duration (yrs f)	Neurologic, neuropsychiatric, and neuropsychological evaluation			Noninvasive modality	Study design		No. of sessions	Cognitive function enhanced
							Diagnosis and staging	Anat scan	NeuroVr testing		Meds	Parameters		
#25 Cotelli et al., 2006	Crossover Sham-controlled	15	76.6±6.0	.	6.0±2.0	–	NINCDS-ADRADA [Probable]	MRI [all atrophy MTL & TPC]	MMSE: 17.8±3.7	AChEIs [don/ riv; no memant]	rTMS [online]	20 Hz 90% MT 600 ms (+ sham)	Left/ Right DLPFC	1 ↑ action naming; no effects on object naming
#26 Cotelli et al., 2008	Crossover Sham-controlled	12 [Mi] 12 [M-S]	75.0±6.2 77.6±5.8	.	6.8±3.1 5.7±2.6	–	NINCDS-ADRADA [Probable]	MRI	MMSE: 19.7±1.6 MMSE: 14.3±2.6	AChEIs [don/ riv; no memant]	rTMS [online]	20 Hz 90% MT 500 ms (+ Sham)	Left/ Right DLPFC	1 ↑ action naming in Mi AD; ↑ action & object naming in M-S AD
#27 Ferrucci et al., 2008	Crossover Sham-controlled	10	75.2±7.3	30	10.9±4.8	–	DSM-IV NINCDS-ADRADA [Probable]	–	MMSE: 22.7±1.8	Stable on AChEIs for 3 mo.	tDCS	Anodal/cathodal/sham 1.5 mA, 15 m	Left/ Right TPC	3 ↑ word recognit memory [after anodal tDCS]
#28 Boggio et al., 2009	Crossover Sham-controlled	10	79.1±8.8	40	8.7±4.9	4.5±2.2	NINCDS-ADRADA [Probable]	–	MMSE: 17.0±4.9	AChEIs + others	tDCS	Anodal/sham 2 mA, 30 m	Left DLPFC	3 ↑ visual recognit memory; no effect on working memory
#29 Cotelli et al., 2010	Parallel Sham-controlled	5 [Real] 5 [Sham]	71.2±6.1 74.4±3.8	.	6.4±1.3 4.8±0.4	–	NINCDS-ADRADA [Probable]	–	MMSE: 16.2±2.7 + Others MMSE: 16.0±2.0 + Others	Stable on AChEIs [don/ riv] for 6 mo.	rTMS [off-line]	20 Hz 100% MT 2000 stim/s (+ sham)	Left DLPFC	20 [Follow-up 8 wks after] ↑ auditory sentence comprehension; no effect on naming perform

Legend: n: Number of subjects; yrs: Years; % M: Percentage of males; Anat scan: Anatomical scanning; NeuroVr: Neuropsychological; Meds: medications; No.: Number; NINCDS-ADRADA: National Institute of Neurological and Communicative Disorders and Stroke — Alzheimer's Disease and Related Disorders Association; Probable AD: MRI: Magnetic resonance imaging; MTL: Medial temporal lobe; TPC: Temporo-parietal cortex; MMSE: Mini-Mental State Examination; AChEIs: Acetylcholinesterase inhibitors; don: Donepezil; riv: Rivastigmine; memant: Memantine; rTMS: Repetitive transcranial magnetic stimulation; Hz: Hertz; MT: Motor threshold; ms: Milliseconds; DLPFC: Dorsolateral prefrontal cortex; CDR: Clinical Dementia Rating; tDCS: Transcranial direct current stimulation; mA: Milliampere; m: Minutes; TC: Temporal cortex; recognit: Recognition; Mi: Mild; M-S: Moderate-to-severe; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; mo.: Months; stim/s: Stimuli per second; wks: Weeks. Symbols: †: Mean ± standard deviation; .: No data; -: Not done or not applicable; %: Percent; ↑: Increase/improvement.

certain drugs, in which within subject comparisons were made between pre- and post-drug intake. The therapeutic application studies were sham-controlled, but they were small proof-of-principle trials, not adequately powered to establish evidence for therapeutic efficacy. Furthermore, given the difficulties of a reliable sham TMS intervention, some of these studies lacked reliable blinding of subjects and none seem to have blinded the technicians or experimenters applying the TMS (though the clinical raters were blinded). Overall, applications of TMS to characterize motor system pathophysiology in AD appear to be safe and may be developed in valuable biomarkers. Among the studies focusing on motor cortical reactivity measures, the most consistent finding is a significant reduction of SAI in AD patients in comparison to healthy elders. The reduction of SAI in AD was found in all studies that assessed it, and thus appears to provide a reliable marker of cortical cholinergic dysfunction in AD, eventually capable of monitoring the effect of AChEIs and dopaminergic drugs (Di Lazzaro et al., 2002, 2004, 2005; Martorana et al., 2009). Significantly lower RMT in AD patients as compared to age-matched controls was detected in about 2/3 of the studies. This seems to support the hypothesis of cortical hyperexcitability in AD and may inversely relate to the stage of severity of cognitive involvement (Pennisi et al., 2002; Alagona et al., 2001). However, the reason for somewhat variable results is worth considering in relation to this and other neurophysiologic measures. Encouraging findings, showing impaired functional connectivity between motor and non-motor brain regions in AD, have also been obtained (Julkunen et al., 2008). Finally, TMS and tDCS therapeutic approaches seeking to enhance cognitive function in AD appear safe and promising, but have to be considered very preliminary.

In the following subchapters, we shall discuss several different topics which we think are scarcely, if at all, addressed in studies conducted to date, while some others may provide lines in which future research can be of interest.

4.1. The role of atrophy

Although some studies have conducted magnetic resonance imaging (MRI) scanning to rule out other potential causes of dementia (e.g., vascular lesions) or to assess anatomical brain atrophy in AD patients, no study has performed more detailed analyses of the potential influence of brain atrophy or distance-to-coil on their results. It has been shown that the impact of TMS depends on the distance between cortex and scalp, as the magnetic field (i.e., the induced current in the brain) decreases with distance (Wagner et al., 2004, 2008). Furthermore, modeling work suggests that current density distribution is critically influenced by brain morphology and tissue characteristics (Wagner et al., 2007, 2008). Brain atrophy can thus substantially alter the effect of TMS (Wagner et al., 2007), not only because of greater scalp-to-brain distance but also due to increased current shunting in the CSF compartment. On the other hand, regional cortical thinning has been demonstrated in AD (Dickerson et al., 2009) and even during prodromal stages (Bakkour et al., 2009). Therefore, it is worth considering the possibility that the differences of TMS effects in patients with AD versus healthy elders might simply be confounded by and possible be simply the consequence of brain atrophy and tissue shrinkage. Volumetric studies of cerebrospinal fluid (CSF) layer, white matter volume, and cortical thinning should be included in future studies and will assist in the interpretation of TMS results involving subjects with cerebral atrophy.

4.2. Role of cortical target

Neuropathologic and neuroimaging studies in AD suggest that distinct cortical areas are differently affected. For instance, positron emission tomography (PET) studies with the amyloid-β binding ¹¹C-labeled Pittsburgh Compound B (PiB) show that patients with AD

have higher ^{11}C -PiB binding in prefrontal, precuneus and cingulate, and lateral temporal and parietal cortices, with minimal binding differences in medial temporal lobe and visual, sensory, and motor cortices (Klunk et al., 2004; Rowe et al., 2007; Devanand et al., 2010). PET studies with the glucose ligand ^{18}F -labeled fluorodeoxyglucose (FDG) show characteristic patterns of cerebral glucose hypometabolism (Mosconi et al., 2008), with primary cortices being relatively spared. In addition, metabolic deficits appear to occur in a progressive manner, from the hippocampus to temporoparietal and posterior cingulate cortices (Ziemann et al., 2008), to frontal lobes (Mosconi, 2005), and eventually extending to the occipital lobes (Mosconi et al., 2008). Furthermore, even during transitional stages between normal aging and AD, including patients with MCI converting to AD, an 'AD-like' pattern of FDG hypometabolism – in hippocampus, posterior cingulate and temporoparietal cortex, with milder magnitude of reduced metabolism than in clinical AD patients – is frequent (for review, Herholz, 2010). Similarly, PiB retention follows an intermediate pattern between healthy controls and AD (Forsberg et al., 2008), being significantly increased in frontal, parietal, and lateral temporal association cortices, and precuneus in amnesic MCI patients converting to AD as compared to healthy control individuals (Kemppainen et al., 2008; Wolk et al., 2009). A similar distribution is also observed in PiB-positive non-amnesic MCI patients (Wolk et al., 2009). Based on such neuroimaging findings, the motor cortex does not seem to be the best cortical area to assess in prodromal and early stages of AD. Rather, non-motor cortical regions where abnormalities may be particularly profound or early in the course of disease, e.g. lateral temporoparietal and frontal association cortices, may provide earlier physiologic biomarkers.

Cortical reactivity and plasticity measures outside the motor cortex are possible when combining TMS with EEG (Thut et al., 2005; Ives et al., 2006; Thut and Pascual-Leone, 2010a). EEG provides exquisite temporal resolution, a direct measure of neuronal activity, and is capable of differentiating between inhibitory and facilitatory effects. The TMS-EEG integration provides real-time information on cortical reactivity and connectivity. A noninvasive input (TMS) of known spatial and temporal characteristics can be applied to study local reactivity of the brain and interactions between different brain regions with directional and precise chronometric information. Thus, measures of cortical reactivity, including ICI or ICF, can be obtained in non-motor cortical areas with TMS-EEG looking at TMS-evoked potentials (EPs). Analysis of time-domain phase synchrony and coherence between different cortical regions can be directly estimated from high-density EEG recording (Jing and Takigawa, 2000; Strens et al., 2002; Oliviero et al., 2003; Schindler et al., 2008). Further, a variety of sophisticated techniques is available to identify and characterize connectivity networks using EEG data (Sameshima and Baccala, 1999; Kaminski et al., 2001; Kramer et al., 2009). Additionally, the study of cortical plasticity mechanisms outside the motor cortex is also possible. In particular, the application of theta burst stimulation (TBS), a unique rTMS protocol capable of more robustly inducing LTP- and LTD-like plasticity than traditional rTMS protocols (Rossi et al., 2009), followed by TMS-EPs over time can provide an index of synaptic and neuronal plasticity, analogously to the approach in animal models and brain slice preparations. Thus, contrasting the results of TMS on EEG before and after TMS can provide information about cortical reactivity and plasticity (depending on the TMS protocols applied) at the site of stimulation and resulting network dynamic adaptation (Thut and Pascual-Leone, 2010a, 2010b). In addition to enabling the systematic exploration of local cortical reactivity and plasticity across different brain regions, the combination of TMS with EEG is promising as it allows the characterization of functional connectivity and synchrony across different neural networks. Such findings may promote the understanding of the neurobiological underpinnings of AD, while eventually constituting valuable biological markers of AD risk and progression.

4.3. Population variability

The studies reviewed reveal that most of the TMS measures show considerable variability between studies. The cause for such variability remains unclear, but some factors, in addition to TMS methodological issues, are worth discussing. Baseline assessment of patients using standardized evaluations, as suggested by The Alzheimer's Disease Centers' Uniform Data Set (UDS; Initial Visit Packet and Neuropsychological Test Battery; www.alz.washington.edu; see also Weintraub et al., 2009) might be worth implementing to enable comparison between studies.

Genetic factors may contribute significantly to variability in TMS findings. For instance, the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene has been shown (Cheeran et al., 2008) to differentially modulate human cortical plasticity and the response to noninvasive brain stimulation. Furthermore, the impact of the BDNF Val66Met polymorphism might differ according to the noninvasive brain stimulation technique utilized (Antal et al., 2010). In the context of AD research, the low-activity Met66 allele was shown to be an additional risk factor for rapid disease progression during the preclinical period of AD (Hashimoto et al., 2009), and may also constitute a risk factor for the development of psychotic symptoms in AD (Pivac et al., 2010). Conceivably, the presence of BDNF Val66Met polymorphism may have distinct repercussions in the studied measures of reactivity and plasticity in normal and pathologic aging, thus deserving particular attention in future studies.

Apolipoprotein E (*APOE*) and its $\epsilon 4$ allele are thought to raise the risk of AD (Corder et al., 1993) in a dose-dependent manner (Bertram et al., 2007), and may also influence brain responses to TMS measures. *APOE*- $\epsilon 4$ allele is associated with an earlier age of AD onset (Farrer et al., 1997; Sando et al., 2008), an accelerated onset of amyloid- β deposition into amyloid plaques (Tiraboschi et al., 2004), higher amyloid load (Drzezga et al., 2009), and lower glucose metabolism (Drzezga et al., 2005; Rabinovici and Roberson, 2010). Moreover, while some studies have found that the *APOE* gene does not influence the rates of disease progression in cognitive and functional domains (Growdon et al., 1996; Murphy et al., 1997; Kleiman et al., 2006), others have associated an accelerated cognitive (Dal Forno et al., 1996; Craft et al., 1998; Martins et al., 2005) and motor (Buchman et al., 2009) decline to the *APOE*- $\epsilon 4$ allele. *APOE* status, and the resulting differences in cognitive and motor decline, may be associated with differences in brain activity. Indeed, Wolk and Dickerson (2010) recently showed that the presence of *APOE*- $\epsilon 4$ distinctively modulates the clinical phenotype of AD by differentially influencing large-scale brain networks as assessed by functional neuroimaging. It is, therefore, also plausible that the presence of *APOE*- $\epsilon 4$ may influence cortical reactivity and local and network plasticity as measured by TMS. Research on the impact of *APOE*- $\epsilon 4$ in TMS measures in AD seems, thus, to be of great importance.

Age at disease onset may also contribute to the prominent between-study variability. Mean patient age in some studies was in the mid-sixties, in others in the mid-seventies. Moreover, duration of illness was not always reported and varied considerably across studies. Age-at-onset for patients in some studies was in the 50s, while in others it was past 70 years of age. Rabinovici and Roberson (2010) showed that sporadic AD patients with early-onset of disease (<65 years) have decreased glucose metabolism in posterior regions as compared to those with late-onset of disease (>65 years), whilst there is no difference in burden and distribution of amyloid- β as measured by PiB. Age-of-onset may also relate to the concept of cognitive reserve, the brain's capacity to minimize the clinical manifestations of cerebral damage. For instance, high-educated mild AD patients have more advanced pathological (increased PiB uptake in the lateral frontal cortex) and functional (lower glucose metabolic rate in the temporoparietal cortex) brain changes than less educated patients with the same degree of cognitive deterioration (Kemppainen

et al., 2008). Therefore, age at disease onset and the associated differences in brain network dynamics seem important to control for in future studies.

Assessing cognitive performance, particularly for domains associated to the function of the TMS targeted brain region, may also help explain some of the between-study discrepancies. Some studies have investigated the relationship between TMS findings and staging of disease (Pennisi et al., 2002; Nardone et al., 2006, 2008; Alagona et al., 2001; Ferreri et al., 2003; Inghilleri et al., 2006; Liepert et al., 2001) or performance in neuropsychological tests (Di Lazzaro et al., 2005, 2007, 2008). However, the results have been conflicting, perhaps because of lack of specificity of the tasks used. Since motor cortex was targeted in all TMS measures reviewed, quantitative evaluation of motor function, either with specific motor skill tasks (Crutch et al., 2007), measures of performance on daily activities (Bouwens et al., 2008), or motor learning tasks (Brown et al., 2009), particularly relevant in plasticity studies, seem important to include in future studies. Such measures will address the functional significance of the neurophysiologic findings and potentially disentangle some of the discrepancies observed among study populations.

4.4. Finding the earliest biomarkers of AD pathology

SAI shows very consistent results among patients with AD, and can be used to predict medication effects, but appears to be normal in MCI (Sakuma et al., 2007). Thus, it would be desirable to consider noninvasive neurophysiologic measures that could show earlier abnormalities. Animal studies reveal that the neurobiological substrate of age-associated cognitive decline likely involves an alteration of synaptic plasticity. For instance, deficits in late maintenance of hippocampal LTP in older rodents are characterized by a more rapid decay of LTP (Barnes, 1979, 1988, 2003), and fastest decay rates of LTP are associated with greater degree of forgetfulness (Barnes and McNaughton, 1980; Kelly et al., 2006). Additionally, deficits in the balance between LTP and LTD may lead to impaired learning and memory (Larson et al., 1986; Roman et al., 1987; Bliss et al., 2003), therefore potentially underlying deterioration of cognitive functions.

Aberrantly reduced local and network plasticity, promoted by a plethora of factors (genetic influences such as *APOE-ε4*, and biological and environmental factors such as age, poor cognitive reserve, traumatic brain injury, diabetes mellitus, chronic adverse stress, poor diet, etc.), may also be related to age-related cognitive decline in humans. In addition, recent evidence demonstrates that oligomers of soluble amyloid- β disrupt LTP and LTD (Shankar et al., 2008; Li et al., 2009), and thus altered plasticity may critically contribute to the development of AD. TMS paradigms to study brain plasticity, particularly outside the motor cortex, might therefore be particularly worth investigating.

TBS is thought to mimic paradigms used to induce LTP and LTD in slice preparations and animal models (Huang et al., 2005, 2008). When applied to the motor cortex, this TMS protocol has been shown to induce robust responses across subjects and to lead to enhancement or depression of MEP amplitudes to about half, depending on stimulation parameters. Physiologic and pharmacologic studies of TBS in humans show involvement of glutamatergic and GABAergic mediators, and the effects and their time-course are consistent with the notion that TBS does indeed engage mechanisms of cortical synaptic plasticity (Cardenas-Morales et al., 2010). Thus, post-TBS enhancement (following intermittent TBS) or suppression (after continuous TBS) of the cortical activity is considered an index of LTP or LTD-like induction of synaptic plasticity, respectively, in the targeted brain area. On the other hand, as noted above, real-time integration of image-guided TMS with EEG can provide information about the integrity of human brain plasticity (Thut and Pascual-Leone, 2010a), and is well suited for parallel studies in animals. Such an experimental approach, combining TMS protocols capable of inducing plasticity with other methods able to register changes throughout the brain, likely offers a potential metric of

local and network plasticity. Fig. 4B displays a schematic representation of this experimental paradigm.

4.5. Designing robust therapeutic interventions

Although promising, results of noninvasive stimulation to enhance cognitive function in AD to date have to be considered extremely preliminary. Most interventions have been acute or of short-duration, the effects seem short-lived, and were not replicated after longer-duration interventions. On the other hand, some of the effects obtained after longer-lasting interventions were not detected after single stimulation session (Cotelli et al., 2006, 2008, 2010). Others failed to show predicted improvements (Boggio et al., 2009), stressing the importance of careful choice of outcome measures. Overall, short studies are essential (for safety, for proof-of-principle, for cost efficacy). However, the translation to long-term studies has to be done carefully. For example, the specific intervention that helps in short-term studies may not help in long-term ones (though this should be experimentally tested). In long-term studies, multiple TMS or tDCS sessions may interact, and metaplasticity effects may affect outcome.

Thus, it seems that careful experimental design is needed and it should consider patient selection aspects, stimulation parameters, and clinical, cognitive and behavioral assessment tools. For example, it would be valuable for all future studies examining therapeutic efficacy of TMS or tDCS in AD to employ (in addition to any other desired outcome measures) the neuropsychological battery of the UDS or outcome scales commonly used in trials of pharmacological agents for AD, such as the Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen et al., 1984), despite its several limitations (Cano et al., 2010). This will enable comparison across studies.

Furthermore, the rationale for treating AD with neuromodulatory techniques remains debatable, and it might be a paradox that, while TMS studies show cortical hyperexcitability, the therapeutic attempts are based on techniques aimed at *enhancing* cortical excitability (anodal tDCS, high-frequency rTMS). It is plausible that hyperexcitability may be the consequence of other underlying pathophysiologic mechanisms, such as decreased synaptic efficiency or *hypoplasticity*. If so, appropriately testing cortical physiology before and after therapeutic interventions would make sense. In addition, the assumption that high-frequency rTMS, for instance, will enhance cortical excitability in AD patients may be wrong. Indeed, rTMS effects are thought to be state-dependent, dependent on the state of activity of the brain at the time of stimulation (Silvanto and Pascual-Leone, 2008). High-frequency rTMS has also been shown to have desirable symptomatic effects on other conditions characterized by cortical hyperexcitability, such as auditory verbal hallucinations (Montagne-Larmurier et al., 2009; Dollfus et al., 2008). It is, therefore, possible that the effects of neuromodulatory techniques in the brain of AD patients may differ to those in normal subjects, and studies to physiologically characterize this would be important to guide future therapeutic trials.

Importantly, studies to date have failed to be evidence-based. For example, the assumption that the mechanisms of plasticity might be aberrantly diminished in the DLPFC or temporoparietal regions (brain areas targeted in the published studies) in AD is yet to be demonstrated and, thus, the concomitant assumption that plasticity enhancement is needed for amelioration of the AD condition remains conjectural. Consequently, whether plasticity-based interventions with high-frequency rTMS or anodal tDCS, or other protocols, would result in benefit to the patients seems to require more solid investigation before embarking upon long-standing treatments. Furthermore, it seems questionable whether improving performance in one task actually represents cognitive enhancement. More comprehensive outcome measures are needed to assess the clinical significance of TMS or tDCS in AD and appropriately powered studies with sound blinding procedures are necessary. Moreover, although merely speculative, it is unlikely that stimulations over a single brain

area will heavily contribute to betterment of the cognitive status of AD patients, particularly those with more advanced disease. Eventually, well-planned, multiple-target stimulation protocols may be necessary in order to overcome the multitude of cognitive deficits characterizing moderate or severe AD.

5. Conclusions and perspectives for the future

Noninvasive stimulation has been steadily increasing its potential utility for the diagnosis, monitoring, and enhancement of cognitive function in AD. TMS may contribute to the understanding of the neurobiological substrates underlying cognitive decline and AD pathology. However, establishment of noninvasive brain stimulation techniques as diagnostic and therapeutic tools in AD requires systematic and thorough investigation of a variety of factors (e.g., volumetric studies of cortical thinning, white matter volume and integrity, genetic variants, learning capacity, age at disease onset, and cognitive reserve) and novel TMS protocols (e.g., TBS, assessment of non-motor cortical regions, and TMS combined with EEG or other neuroimaging modalities). We thus envision future novel diagnostic and therapeutic interventions for not only clinical AD but also its prodromal stages, including MCI, based on the overarching hypothesis that aberrant mechanisms of cortical plasticity and altered brain networks are the proximal causes of cognitive decline and critical contributors to the development of AD. If so, assessment of cortical plasticity mechanisms and network dynamics might ultimately provide an earliest predictive biomarker of cognitive decline and AD, and lead to novel interventions that might forestall neurocognitive decline during aging and prevent, or at least drastically delay, development of symptomatic AD.

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Conflict of interest

APL serves on the scientific advisory board for Nexstim, Neuronix, Starlab, and Neosync, and holds IP for the combination of TMS with EEG.

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