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Transcranial Magnetic Stimulation in Alzheimer's Disease and Cortical Dementias

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Abstract

Transcranial magnetic stimulation (TMS) has become a safe, noninvasive, and promising tool to assess specific cortical circuits in the central nervous system. Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience, and psychiatry has spread widely, leading to important findings on cortical function in physiological and pathological conditions. Indeed, numerous studies have described abnormalities in specific cortical circuits using particular TMS stimulation paradigms, which allow the indirect assessment of inhibitory and excitatory interneuronal activity, mainly dependent on GABA receptors, of central cholinergic activity, and of cortical plasticity. The objective of the present work is to examine the utility of TMS as a means to support and predict the clinical diagnosis of Alzheimer 's disease and other cortical dementias, in a setting where our understanding of neurodegenerative diseases is far from adequate.

Keywords: Transcranial magnetic stimulation; Brain stimulation; Alzheimer's disease; Dementia with Lewy bodies; Frontotemporal lobar degeneration

Abbreviations: AD: Alzheimer's Disease; DLB: Dementia with Lewy bodies; PDD: Parkinson's Disease Dementia; FTD: Frontotemporal Dementia; CBD: Corticobasal Degeneration; PSP: Progressive Supranuclear Palsy; rMT: Resting Motor Threshold; CSP: Cortical Silent Period; SICI: Short Interval Intracortical Inhibition; ICF: Intracortical Facilitation; LICI: Long Interval Intracortical Inhibition; SAI: Short Latency Afferent Inhibition

Introduction

Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), Parkinson's disease dementia (PDD) and frontotemporal lobar degeneration (FTLD), account for the predominant cause of dementia in the population aged ≥ 60 years, with an estimated prevalence of 5-7% in this age-group [1], escalating to about 30% in the people older than 85 [2]. With the progressive aging of the population, the prevalence of dementia is estimated to double every 20 years [3], thus becoming a health- and social-care priority for many high-income countries. Numerous studies have tried to address the challenge of identifying early biological or neuroimaging markers in order to unravel the physiopathological processes underlying these disorders and to correctly recognize the earliest stages of disease, when the neurodegenerative process is still limited and possibly reversible [4].

In this view, also neurophysiological techniques, particularly transcranial magnetic stimulation (TMS), have become promising tools to assess specific cortical circuits in the central nervous system. Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience, and psychiatry has spread widely, leading to important findings on cortical function in physiological and pathological conditions [5].Indeed, with the contribution of pharmacological studies, numerous TMS stimulation paradigms have been developed to assess, non-invasively and in-*vivo*, the function of GABAergic, glutamatergic and cholinergic cortical circuits [6]. Furthermore, specific paradigms of paired associative stimulation (PAS) [7] or repetitive TMS (rTMS) [8,9] have shown to increase or decrease the excitability of corticospinal projections of the primary motor cortex (M1), representing a form of long-term potentiation (LTP) or depression (LTD) and thus a method of assessing synaptic plasticity [10].

The objective of the present review is to examine the utility of TMS as a means to aid and predict the early diagnosis of AD and other cortical dementias, bearing in mind that a precise and prompt diagnosis will be critical in the prospect of future disease-modifying therapies.

Transcranial Magnetic Stimulation Techniques

Single-pulse stimulation

Motor threshold (MT): MT is defined as the minimal intensity of motor cortex stimulation required to elicit a reliable motor evoked potential (MEP) of minimal amplitude in the target muscle. It is considered a reliable global measure of corticospinal excitability and depends on the excitability of axons activated by the TMS pulse, as well as the excitability of synaptic connections at both the cortical and spinal level [11-14]. Resting MT (RMT) is determined while the target muscle is completely at rest, while the active MT (AMT) is usually determined during a slight tonic contraction of the target muscle at approximately 20% of the maximal muscle strength [11,12].

RMT is considered as a global parameter of human brain excitability as it mainly reflects the membrane excitability of corticospinal neurons, cortico-cortical axons and their excitatory synaptic contacts, mediated by voltage-gated sodium channels and by ionotropic glutamatergic non-NMDA receptors [15].

Motor evoked potential amplitude: The MEP is typically recorded over the target muscle using surface electrodes in a bipolar belly-tendon arrangement, applying a single TMS pulse to the contralateral primary motor cortex (M1) at adequate stimulator intensity [16]. Extrinsic factors, as conditioning stimuli preceding a test TMS

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stimulus, and intrinsic factors, as mental activity, can modulate the cortico-motor excitability and change MEP amplitude [12]. MEP amplitude increases gradually with TMS intensity, with a relationship between stimulus intensity and MEP amplitude described by a sigmoid curve, also known as the "stimulus-response curve" or "recruitment-curve". MEP amplitude evoked by above threshold stimuli clearly reflects trans-synaptic activation of cortico-spinal neurons through a complex network of excitatory circuits controlled by inhibitory circuits. Pharmacological studies showed that this network is regulated by glutamatergic, GABAergic and neuromodulating (in particular noradrenergic and serotonergic) neurotransmitters [15]. The versatile modulation of the stimulus-response function by physiological variables explains why the measurement of MEP amplitude is the most widespread electrophysiological method to assess after-effects of repetitive TMS and other non-invasive brain stimulation protocols applied over M1 on corticospinal excitability [12,17,18].

Cortical silent period (CSP): The CSP is a period of electrical silence lasting up to 100-300 ms in the surface electromyographic activity [19], that can be evoked using TMS at suprathreshold intensities. The duration of the CSP gradually increases with the intensity of TMS and is mediated by intra-cortical inhibitory phenomena [20-25]. Pharmacological studies suggested that at the lower range of stimulus intensities, CSP duration reflects the activation of $GABA_A$ receptors, while at higher range of stimulus intensities, it reflects the activation of $GABA_B$ receptors [12,26-32].

Paired-pulse stimulation

Paired-pulse stimulation TMS usually involves a conditioning stimulus (CS) followed by a test stimulus (TS), and MEP amplitudes are compared to those produced by the TS alone as a reference condition. Many paradigms have been developed by varying the intensity of the CS and the interval between the pair of TMS pulses, or interstimulus interval (ISI). Different paired-pulse TMS paradigms allow the non-invasive assessment of inhibitory and excitatory interneuronal activity within the human cortex [12].

Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF): SICI is elicited when a subthreshold CS is followed by a suprathreshold TS at an ISI of 1-6 ms and likely reflects intracortical post-synaptic inhibition mediated by $GABA_A$ receptors, positively modulated by dopamine and nicotine, and decreased by noradrenaline [14,15,33-35]. ICF can be elicited with a similar protocol as SICI but at longer ISIs of 6-30 ms and, although poorly understood, may reflect excitatory glutamatergic circuits in M1 [12,15,33,36-38].

Long interval intracortical inhibition (LICI): LICI is tested by applying two suprathreshold stimuli at long ISIs of 50-200 ms, leading to inhibition of the TS by the CS, and is likely mediated by $GABA_B$ receptors [15,27,30,34,39-42].

Paired-associative stimulation (PAS): PAS involves a TMS stimulus preceded by a conditioning electrical stimulus of a peripheral nerve at different ISIs [43]. This paradigm, consisting of low-frequency repetitive stimulation of the median nerve (typically 90-200 stimuli) combined with a TMS stimulus over the contralateral motor cortex, may induce persistent and reversible excitability changes in the motor cortex [10,44]. PAS with an ISI of 25 ms (PAS25) leads to a strong facilitation of MEPs, mainly dependent on NMDA receptors, while an ISI of 10 ms (PAS10) causes inhibition [7,45]. It has been suggested that these effects represent, respectively, a form of associative LTP and LTD, and thus a method of assessing cortical synaptic plasticity [7,44-48].

Short latency afferent inhibition (SAI): SAI is elicited if median nerve stimulation precedes contralateral M1 TMS at ISIs around the latency of the N20 component of the somatosensory evoked potential, with a maximum inhibition occurring at about N20 latency plus 2 ms [43,49], and is likely mediated by cholinergic [50,51] and $GABA_A$ergic circuits [52]. SAI decreases with normal aging [53,54] and in neurodegenerative disorders of the central cholinergic system, such as AD [51,55-57].

Repetitive TMS

Repetitive TMS (rTMS) can be applied at various stimulation frequencies or as a patterned train of pulses, and has a modulatory effect on cortical excitability, which outlasts the stimulation period. Stimulation frequencies below 1 Hz are mainly inhibitory [8,58], while repetition rates above 5 Hz are mainly facilitatory [8,59]. Recently, newer patterned protocols such as theta burst stimulation (TBS) have been developed to modulate cortical excitability [60]. TBS consists of TMS pulses delivered as a 3-pulse 50-Hz burst applied at 5 Hz. Intermittent TBS (iTBS) involves 600 pulses delivered as 2-sec trains of TBS repeated every 10 sec for about 3 min, producing LTP-like plasticity in the cortex. In contrast, continuous stimulation for 40 sec of TBS (cTBS) results in a LTD-like decrease in motor cortex excitability [60]. Most rTMS paradigms are NMDA-receptor activity dependent [61] and are modulated by prior synaptic activation [62].

The Role of TMS in the Diagnosis of Dementia

Alzheimer's disease

Several studies have identified an enhanced cortical excitability in AD, assessed by a reduction in the MT [55,63-83], even in the early phases of disease [31,55,56,64,66-75,77,78,81-88], albeit studies in patients with mild cognitive impairment (MCI) have reported contrasting results [87-89]. The gradual reduction in MT seems to correlate with disease progression [79,90], although a subsequent increase in MT has been identified in advanced stages of disease, possibly secondary to severe cortical atrophy [91].

Studies regarding the duration of the CSP have found contrasting results, with the majority of studies showing no significant alterations [55,64,74,75,82,86], while two studies showed a significant reduction in the duration of the CSP [63,91].

Contrasting results have been reported regarding SICI, with some studies showing normal inhibition [55,56,67,69-71,80,84,92], while others showing a reduction of SICI [73,78,86,87,93,94]. ICF seems to be unaffected in AD [31,55,56,71,78,80,84,86,87,92-94].

LICI was significantly reduced in one study in patients in therapy with memantine, thus no clear associations can be made on the role of the underlying pathology or the effect of the drug [65].

The dysfunction of the cholinergic system, highlighted by a reduction in SAI, has been widely reported in patients with AD [52,55,56,67-71,77,81,88,93,95]. Moreover, the restoration of SAI after the use of acetylcholinesterase inhibitors [51,55,67] and L-dopa [77] further supports this hypothesis, and seems to correlate with the response to treatment [51,55]. Cerebrospinal fluid (CSF) levels of amyloid $beta_{42}$ and phosphorylated tau significantly correlate with the decrease in SAI, suggesting that these peptides may have some influence on the cholinergic dysfunction in AD [96]. Interestingly, as recently reported, a single session of cerebellar cTBS partially restored SAI in AD patients, suggesting that the cerebellum may have a direct influence on the cholinergic dysfunction in AD [71].

The decrease in SAI has also been reported in a single study on MCI patients, in particular in the amnestic presentations, while it was not significantly different in the non-amnestic form, thus suggesting possible at risk patients which will convert into dementia [57].

Cortical plasticity, as assessed by rTMS or PAS, also seems to be altered in patients with AD. Indeed, inhibitory and excitatory rTMS paradigms have shown reduced LTD- and LTP-like cortical plasticity, respectively [74,82,97]. The amount of rTMS-induced inhibition correlated with the CSF levels of total tau, but not with amyloid beta$_{42}$, possibly suggesting an involvement of tau on the abnormal excitatory activity and thus on the mechanisms of cortical plasticity [98]. Likewise, iTBS and cTBS protocols have revealed a reduced LTP-like cortical plasticity with a normal LTD-like effect [99].

Pharmacological modulation of cortical plasticity could provide novel implications in disease pathophysiology; indeed, rotigotine administration was shown to restore LTP-like cortical plasticity in AD patients, as assessed by iTBS, thus providing novel implications for therapies based on dopaminergic stimulation [100].

Similarly to studies with rTMS, PAS protocols have shown impairment in cortical plasticity in mild and moderate AD, highlighting the involvement not only of the motor cortex but also of sensorimotor integration [81,85].

Dementia with lewy bodies and parkinson's disease dementia

The rMT and SICI [70,93] seems to be unaffected in DLB. The cholinergic dysfunction, which is a hallmark of DLB and PDD, has been further corroborated by a series of studies that demonstrated a significant decrease in SAI, in both DLB [70,95] and PDD [101-103]. These findings have been confirmed also in patients with Parkinson's disease and MCI [104-106].

In DLB patients, the defect of cholinergic activity, assessed by SAI, strongly correlated with visual hallucinations [95], while visual cortical excitability correlated with the severity of visual hallucinations [107].

Frontotemporal lobar degeneration

Frontotemporal dementia (FTD): Only five studies to date have assessed neurophysiological characteristics in patients with FTD. These studies have been hindered by the small number and by the selection of patients, which has been exclusively clinical and not taking into account the importance of CSF proteins (amyloid beta$_{42}$, total and phosphorylated tau) to exclude possible focal variants of AD, or the genetic contribution of known pathogenic mutations.

These studies have shown central motor circuit abnormalities, even in cases without clinical evidence of motor involvement [31,68,75,84,108]. No significant alterations in MT [31,37,75,84,108], SICI or ICF [31,68,84], and SAI [68] have been shown in FTD.

However, recent studies have revealed a significant decrease in SICI, in particular in the progressive non-fluent aphasia subgroup, in contrast to the behavioral variant FTD and semantic dementia subgroups [84,108].

Corticobasal degeneration (CBD): Patients with CBD show significant higher MT, in agreement with the frequent involvement of motor areas in this disorder [84,109,110]. As a result, many cortical inhibitory mechanisms are altered in CBD, as CSP [109,111,112] and SICI [84,109,110,113,114]. No significant differences in ICF have been reported in CBD patients [84,109]. As with studies in FTD patients, diagnosis was exclusively made on clinical basis, not taking into account CSF values to exclude focal variants of AD, which have been reported in up to 50% of patients with corticobasal syndrome [115,116].

Progressive supranuclear palsy (PSP): Neurophysiological studies revealed a rMT within normal range and a reduced CSP in PSP patients [109,117]. Inhibitory mechanisms were also reduced, as assessed by SICI [109,117,118] and SAI [118], while ICF di not differ significantly from healthy subjects [117].

Cortical plasticity, as assessed by iTBS, elicited a significantly larger MEP facilitation in patients than in healthy subjects [117]. On the other hand, cTBS showed a paradoxical facilitation of MEPs in PSP patients, which correlated with disease progression [117].

The involvement of cerebellar structures and of the dentato-thalamo-cortical pathway in PSP has been assumed based on the reduction in MEP inhibition following TMS of the cerebellum, accounting for the so called cerebellar brain inhibition (CBI) [118,119]. Moreover, cerebellar iTBS modulated this altered functional cerebellar-motor connectivity, as assessed by an increase in CBI [118].

Discussion

TMS is a non-invasive and effective methodology with the potential to assess the functional integrity of cortical networks, in particular with the use of paired-pulse paradigms, which selectively target precise neurotransmitters and receptors.

Several studies have shown that TMS techniques may represent an additional tool for the functional assessment of patients with dementia (Table 1). In summary, the studies reviewed so far have consistently found a significant reduction of SAI in patients with AD [55], DLB [69] and PDD [103], which all have an established cholinergic deficit that responds to cholinergic medications [120].

Conversely, in other non-cholinergic forms of dementia, as in FTD, SAI was found to be normal [68]. Therefore, SAI testing could be used as a non-invasive *in vivo* assessment for cholinergic dysfunction in patients with dementia, representing a useful tool in differentiating between the cholinergic and the non-cholinergic forms of dementia. Moreover, TMS could thus be used to identify patients at increased risk to convert into dementia [57], monitor disease progression and response to treatment [51].

Cortical hyperexcitability consistently found in AD patients, assessed by a reduction of the rMT [121], could be the result of a glutamatergic overactivation, possibly secondary to an imbalance between NMDA and non-NMDA neurotransmission [122].

	rMT	CSP	SICI	ICF	LICI	SAI	Plasticity
AD	▼	=/▼	=/▼	=	▼	▼	▼
DLB	=	*	=	*	*	▼	*
PDD	=	*	=	=	*	▼	*
FTD	=	=	=/▼	=	*	=	*
CBD	▲	▼	▼	=	*	*	*
PSP	=	=/▲	▼	=	*	▼	▼

AD: Alzheimer's Disease; DLB: Dementia with Lewy Bodies; PDD: Parkinson's Disease Dementia; FTD: Frontotemporal Dementia; CBD: Corticobasal Degeneration; PSP: Progressive Supranuclear Palsy; Rmt: Resting Motor Threshold; CSP: Cortical Silent Period; SICI: Short Interval Intracortical Inhibition; ICF: Intracortical Facilitation; LICI: Long Interval Intracortical Inhibition; SAI: Short Latency Afferent Inhibition; Plasticity: LTD- Or LTP-Like Cortical Plasticity; ▼: Decrease; ▲: Increase; =: Non Significant Difference from Healthy Controls; *: Parameter has not been assessed in available published studies.

Table 1: Predominant neurophysiological parameters in dementias.

Studies assessing intracortical inhibition (CSP and SICI) have reported contrasting results in many cases; these parameters seem to be more often altered in patients with dementia associated with parkinsonian features, as in DLB, PDD, PSP and CBD, suggesting an involvement of GABAergic circuits in these disorders [70,109,111,112,117,123]. The assessment of inhibitory circuits in FTD have led to conflicting results, possibly due to the wide variability of included patients, with different clinical phenotypes and without the assessment of CSF parameters or genetic contributors.

Finally, rTMS and TBS protocols both have the potential of inducing cortical plasticity, which can be useful in assessing deficient neuromodulation in neurodegenerative disorders, as in AD [74] and PSP [117], but also be a suitable rehabilitative tool to improve cognitive performance [124-129].

Future approaches with single-pulse and paired-pulse TMS will surely benefit from the integration of different stimulation paradigms in diagnostic algorithms, aiding in a more efficient differential diagnosis even at the single-subject level. While single TMS sessions currently carry a low specificity, a multi-paradigm approach can support the clinical diagnosis, predict progression and possibly identify at risk patients, providing the footprints of specific pathophysiological processes that affects motor and non-motor areas in the various form of dementia.

The future advances in technological development will further increase the potential of these techniques in accurately predicting the underlying neurodegenerative disorder, as recent studies have highlighted. Indeed, increased spatial sensitivity of the stimulation [130] and the development of more sophisticated paradigms, such as triple- [131] or quadro-pulse [132] stimulation techniques, will aid in detecting preclinical changes in brain connectivity.

Combined with other techniques, as EEG [133,134] and fMRI [135,136], TMS co-registration studies will be key in tracking temporal dynamics and of brain functional and effective connectivity, possibly clarifying some essential issues underlying brain physiology [137]. Future work with the application of these techniques promises to provide valuable advances in our understanding of the pathophysiology of a wide range of neurodegenerative disorders.

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