Chapter 2

Transcranial Magnetic Stimulation and Cognitive Impairment

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Abstract

With transcranial magnetic stimulation (TMS), the motor system in neuropsychiatric disorders has extensively been investigated, and effects of certain pharmacological agents have been monitored. The most consistent finding in neuropsychiatric disorders is a significant reduction of short-latency afferent inhibition (SAI). SAI provides a reliable biomarker of cortical cholinergic dysfunction in neuropsychiatric disorders. Cortical hyperexcitability and asymptomatic motor cortex functional reorganization in the early stages of neuropsychiatric disorders have been demonstrated by TMS. Together with high-density EEG TMS and paired-associative stimulation, TMS showed impaired cortical plasticity and functional connectivity across different neural networks in neuropsychiatric disorders. Neuromodulatory techniques, especially as repetitive TMS (rTMS), hold promise as a therapeutic tool for cognitive rehabilitation because rTMS can enhance cognitive functions in neuropsychiatric disorders.

Keywords: repetitive transcranial magnetic stimulation, cognitive impairment, cortical plasticity, neuromodulation, neurorehabilitation

1. Introduction

Transcranial magnetic stimulation (TMS) allows non-invasive investigation and modulation of brain cortical excitability and brain function [1]. Alternating magnetic fields induce cortically electric currents in specific brain regions. Cortical excitability may be increased or decreased by different stimulation parameters, and the induced changes may be transient or long lasting. Different changes in behavior can be induced with regard to the stimulated region, the stimulation parameters, and the physiology of the stimulated cortical tissue. These effects can be enhancement or can interfer with cognitive functions [2, 3].

The chapter reviews studies reporting about applications of TMS in neuropsychiatric disorders. Most reports have applied TMS to characterize important neurophysiologic and pathophysiologic aspects of neurodegenerative diseases. Several studies using TMS have demonstrated abnormalities in cortical excitability, plasticity and functional connectivity between the motor cortex and other cortical regions. Other studies aimed to evaluate and monitor the effects of certain pharmacological agents.

Long-term neuromodulatory effects applying repetitive TMS (rTMS) can be induced with promising therapeutic potential in neuropsychiatric disorders. These applications can improve our understanding of brain plasticity mechanisms, the basis for the development of new therapeutic strategies in neuropsychiatric disorders.

2. TMS parameters in clinical application

2.1. Central motor conduction time

The so-called central motor conduction time (CMCT) can be calculated by subtraction of the peripheral conduction time from spinal cord to muscles from the conduction time of responses evoked by cortical stimulation. Demyelination of motor pathways increases CMCT, while low amplitude MEPs with little delay or absence of responses are rather suggestive of neuronal or axonal loss [4, 5].

The amplitude of the MEP reflects the integrity of the corticospinal tract and the excitability of motor cortex and spinal level, as well as the conduction along the peripheral motor pathway to the muscles [4, 5].

TMS also allows cortical mapping procedures, with single TMS pulses applied on several scalp positions overlying the motor cortex, exploring the site of maximal excitability (hotspot) and the "center of gravity" of motor cortical output [6].

2.2. Motor threshold

The resting motor threshold (RMT) is by definition the minimum stimulus intensity that produces a motor evoked potential (MEP) greater than 50 μV in 50% out of 10 trials at the completely relaxed tested muscle. RMT provides information about a central core of neurons in the muscle representation in the motor cortex, and reflects both neuronal membrane excitability [7–9] and non-N-methyl-D-aspartate (NMDA) receptors' [8, 9] glutamatergic neurotransmission. The minimum stimulus intensity that produces a MEP (about 200 μV in 50% of 10 trials) during isometric contraction of the tested muscle at about 10% maximum defines the active motor threshold (AMT). AMT provides a measure of corticospinal excitability with greater dependence on the spinal segmental level excitability [4, 5].

2.3. Short-latency afferent inhibition

Short-latency afferent inhibition (SAI) refers to the suppression of the amplitude of a MEP produced by a conditioning afferent electrical stimulus applied to the median nerve at the wrist approximately 20 ms prior to the TMS pulse to the hand area of the contralateral motor cortex [10]

SAI reflects the integrity of central cholinergic neural circuits. It is reduced or absent by the muscarinic antagonist scopolamine in healthy subjects [11]. SAI may also be dependent on the integrity of circuits linking sensory input and motor output [12]. Cholinergic transmission underlies also the neuromodulation of other neurotransmitters.

2.4. Cortical silent period, paired pulse intracortical inhibition and facilitation

Single-pulse TMS delivered during voluntary muscle contraction produces a period of EMG suppression known as the cortical silent period (cSP). TMS can also investigate the intracortical facilitatory and inhibitory mechanisms that influence motor cortical output. Paired pulse TMS techniques involve paired-stimuli based on a conditioning-test paradigm [13]. Stimulation parameters such as the intensity of the conditioning stimulus (CS) and test stimulus (TS) together with the time between the two stimuli (interstimulus interval, ISI) determine interactions between stimuli. When the conditioning stimulus is below and the test stimulus is above the MT, the conditioning stimulus decreases the MEP to the test stimulus at interstimulus intervals from 1 to 5 ms (short-latency intracortical inhibition, SICI), while the conditioning stimulus induces a facilitation of the response to the test stimulus at interstimulus intervals from 6 to 20 ms (intracortical facilitation, ICF).

Short latency intracortical inhibition reflects to a large extent $GABA_A$-mediated intracortical inhibitory synaptic activity [14]. The early part of the silent period originates from spinal inhibition, while the later part is caused by a long-lasting cortical inhibition mediated by $GABA_B$ primarily in the motor cortex [15]. The intracortical facilitation with interstimulus intervals from 6 to 20 ms reflects motorcortical excitatory neurotransmission primarily mediated by NMDA receptors [15].

2.5. Cortical connectivity and plasticity measures

Combined measures of EEG and TMS (EEG) [16–18] can provide real-time information on cortical connectivity and distributed network dynamics.

Several other TMS techniques are currently used to modulate noninvasively the excitability of the cerebral cortex. Cortical responses to rTMS and paired-associative stimulation (PAS) provide information about different aspects of cortical plasticity [4, 15, 19]. TMS can influence brain function if delivered repetitively. RTMS is a technique that delivers single TMS pulses in trains with a constant frequency and intensity for a given time. Depending on the stimulation parameters, particularly the frequency of stimulation, cortical excitability can be modulated and rendered facilitated or suppresses. The modulation induced by rTMS can induce significant and long-lasting changes in focal and non-focal neural plasticity. Generally, low-frequency rTMS (stimulus rates of 1 Hz or less) induces inhibitory effects on motor cortical excitability allowing creation of a reversible 'virtual lesion' [20], while high-frequency rTMS (5–20 Hz) usually promotes an increase in cortical excitability [21, 22].

PAS involves repeated pairs of electrical stimulation of a peripheral nerve (usually the median nerve) followed by TMS applied over the contralateral hand area of the motor cortex [23]. PAS induces a lasting increase in corticospinal excitability, which can be considered a marker of motor cortical plasticity, with long-term plasticity-like mechanisms thought to play a major role [23].

3. Cortical excitability, connectivity and plasticity

3.1. Motor threshold

Most of the studies found significantly reduced RMT in neuropsychiatric disorders as compared with healthy subjects [24–36], while other reports have found a tendency toward a reduced RMT without statistical significance [37–44]. One study noted no difference in RMT between patients with Alzheimer disease (AD) and controls [45], while [46] found increased RMT in AD patients. It can be hypothesized that, in the early stages, mechanisms related to RMT are preserved [45], or that RMT changes reflect functional damage of cortical motor neurons. As the disease progresses, the decrease in RMT might be compensatory to the loss of motor cortex neurons [36, 39]. In a combined TMS-MRI study [47], it was reported recently that motor cortex excitability did not correlate with the cortical thickness in AD subjects. It can be hypothesized that a protective mechanism of hyperexcitability on the sensorimotor cortex may counteract the loss of cortical volume. This protective mechanism was not found in the patients with mild cognitive impairment (MCI). Lahr et al. [48] could show in MCI patients with the TMS technique of paired-associative stimulation (PAS) that there is no difference in synaptic long-term potentiation (LTP)-like plasticity between MCI patients and healthy controls [48]. Another study with transcranial magnetic stimulation addressed mild cognitive impairment in the elderly [49]. About 10 Hz rTMS everyday enhanced memory in the elderly MCI patients after 10 sessions. Thus, rTMS might be effective in cognitive therapy for MCI patients. In a recent study, Nardone et al. [50] found a normal short-latency afferent inhibition (SAI) in 20 subjects with subjective memory impairment [50]. An abnormal SAI was reported in amnestic multiple domain mild cognitive impairment patients. Therefore, SAI holds promise to be a useful biomarker for differentiating individuals with subjective memory complaints those in whom cholinergic degeneration has occurred.

There are a few studies that have assessed AMT in AD patients; only two found significant decreases in AMT when compared with healthy subjects [31, 36]. Therefore, the excitability of spinal projections seems to be relatively preserved during early course AD.

The increased excitability to TMS in AD patients may be the functional correlate of an abnormal glutamatergic system. This hypothesis has been supported by a study demonstrating an altered response to rTMS in AD patients [32].

In contrast with AD patients, patients with dementia with Lewy bodies (DLB) present a normal excitability to single-pulse TMS [29, 51]. This finding suggests that the glutamatergic system is not involved in DLB patients. However, cortical excitability to visual stimuli of lower visual areas (V1–3) as measured by TMS appears to be normal in DLB. TMS-determined phosphene threshold and fMRI-related visual activation shows a positive relationship in controls but a negative one in DLB that suggests a loss of inhibition in the visual system in DLB, which may predispose individuals to visual dysfunction and visual hallucinations [52].

Patients with vascular dementia (VD) have decreased RMT [29, 53]. This increased excitability could represent a functional consequence of the vascular lesions. RMT was recently found to be significantly lower in patients with subcortical ischemic VD, but not in patients with

subcortical ischemic disease without dementia [54]. In a study of Guerra et al. [55], there is evidence for common compensatory mechanisms in subcortical ischemic vascular dementia as it is known from Alzheimer's disease [55] supporting the idea that cortical hyperexcitability can promote cortical plasticity. These results indicate that motor cortex hyperexcitability is a common finding in different dementing illnesses, subcortical or cortical in origin.

3.2. Motor evoked potential amplitude and central motor conduction time

Most studies found no significant differences in MEP amplitude between patients with AD and healthy subjects [25, 27, 31–33, 38, 45, 46], while significant increases in MEP amplitude in AD patients were detected in fewer studies [24, 26, 36]. Interestingly, the center of gravity of motor cortical output shows a frontal and medial shift in patients with AD, without changes in the hot-spot location [39]. This finding may indicate functional reorganization, likely including the dysregulation of the inhibitory frontal centers [39].

MEP amplitude was found to be larger in patients with subcortical ischemic VD with dementia than in patients with subcortical ischemic disease without dementia [54].

None of the studies that examined CMCT in AD [24, 26, 27, 40–42, 46] found statistically significant differences between patients and healthy age-matched subjects. These results confirm that the integrity of the corticospinal tract is not compromised at least in mild to moderate stages of AD.

In contrast, Di Lazzaro et al. [30] found that cortical excitability to single-pulse TMS was impaired in 5 out 20 patients with frontotemporal dementia (FTD). In three patients, MEPs were absent, and a very small MEP was obtained only at maximum stimulator output in two patients. In agreement with these results, patients with FDT are more likely than patients with AD to have motor abnormalities. This finding suggests that TMS may reveal subclinical central motor pathways involvement in patients with FTD. Paired pulse TMS applying the parameters SICI, ICF and SAI can also distinguish AD from FTD with a sensitivity of 91.8% and specificity of 88.6% [56]. AD patients show an impairment of SAI, while FTD shows a remarkable dysfunction of SICI and ICF parameter.

3.3. Cortical silent period, intracortical inhibition and facilitation

A significant reduction of SICI was found by some authors [35, 40, 42, 45], but most studies did not find differences in SICI between AD patients and control subjects [27–29, 31, 36, 37, 41]. In a study, the amount of disinhibition was found to correlate with the severity of AD [40]. Most studies by [25, 27, 32, 40], but not all [24, 46] studies failed to find any significant differences in the cSP duration between AD patients and healthy controls. Taken together, these findings do not support impairments in GABAergic inhibitory circuits in AD. On the other hand, dysfunction of GABAergic circuits has not been demonstrated, and the GABA system seems to be relatively spared in AD [57].

Di Lazzaro et al. found an impairment of SICI in 16% of patients with VD [29]. One study showed a decrease in cortical benzodiazepine receptors in patients with VD due to leukoaraiosis [58],

thus the abnormality of SICI in some VD patients might be related to the disruption of inhibitory GABAergic circuits. However, a study provides evidence of functional changes also in excitatory cortical circuits in patients with subcortical ischemic vascular disease and cognitive impairment (but no dementia) [59].

Alberici et al. [37] found that patients with FTD were comparable with healthy subjects and AD patients for SICI and ICF. In contrast, patients with corticobasal degeneration (CBD) presented significantly reduced SICI at ISI 3 ms, the selective impairment of intracortical inhibition in CBD may help in distinguishing among the FTD clinical spectrum.

None of the previous studies has found significant changes in ICF in patients with AD as compared to healthy controls [27, 35–37, 40–42, 45]. These findings seem to point to a normal NMDA receptor-dependent glutamate excitatory activity in AD, as tested by this cortical excitability measure. However, other studies suggest that abnormalities of glutamatergic neurotransmission might play an important role in AD. The glutamatergic hypothesis of AD has been proposed as an auxiliary mechanism to the cholinergic hypothesis [39] and this may be due to an imbalance between the non-NMDA and NMDA neurotransmission [39, 60–63].

3.4. Short-latency afferent inhibition

The most consistent finding of abnormal cortical excitability in AD patients regards SAI. In fact, all studies reported significant reductions of SAI in patients with AD as compared to healthy individuals [27, 29–31, 34, 41, 42, 44, 60, 64, 65]. SAI was also found to be negatively correlated with performance in abstract thinking [29, 31] and long-term memory [29]. SAI testing may be a useful marker of central cholinergic dysfunction even in early stages of AD [66], while it was found to be not significantly reduced in subjects with MCI [44]. However, in this study the diagnosis of MCI was based on criteria proposed by Petersen in 1999 instead of the revised ones [67] and the relationships to the different MCI subtypes was not defined. In a more recent study, a reduced SAI was found in amnestic MCI-multiple domain patients, while SAI was not significantly different in amnestic MCI-single domain patients and in non-amnestic MCI patients [68].

SAI is significantly reduced also in adults with Down Syndrome (DS) and Alzheimer-type dementia [51] the values correlated with the patient's age and the score on Dementia Scale for DS. This technique may thus represent an additional tool for the diagnosis of Alzheimer-type dementia in subjects with DS.

Nardone et al. [51] described this putative marker of cholinergic activity in patients with DLB and showed a clear tendency toward a reduced SAI. These authors performed SAI testing without randomization of different conditions and the diagnosis of DLB was based on criteria proposed in 1996 instead of the revised ones [69]. Di Lazzaro et al. [29] examined 10 patients with a clinical diagnosis of DLB according to the NINCDS-ADRDA criteria [69] and found a significantly reduced SAI in these patients. Interestingly, SAI correlates with hallucinations in DLB patients and with euphoric manic state and disinhibition in AD patients [70]. SAI investigation may also be useful in the distinction between DLB and Parkinson's disease (PD), because SAI is normal or even enhanced in PD [12, 71].

SAI was evaluated in 20 patients with FTD and compared data with those from 20 patients with AD and 20 control subjects [30]. SAI was normal in FTD, whereas it has been reduced in AD. SAI may thus represent an additional tool to discriminate FTD from AD. These findings are consistent with post-mortem studies showing central cholinergic deficits in AD [72–74] but not in FTD [75].

A reduced SAI has been found in patients with VD, but not to the same extent as AD. Nardone et al. [66] reported that SAI responses in patients with subcortical ischemic VD varied widely, ranging from normal to markedly reduced values. In another TMS study, significant SAI abnormalities were disclosed in 3 out of 12 patients with VD [29]; SAI was strongly correlated with neuropsychological measures of long-term memory and other cognitive functions. In patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the amount of SAI was found to be significantly smaller than in normal subjects [76]. This finding supports the hypothesis of a central cholinergic system impairment in CADASIL. Interestingly, Mesulam [77] demonstrated that pure white matter infarcts, similar to those seen in subcortical VD, can cause cortical cholinergic denervation.

It should be considered that AD and VD are not mutually exclusive conditions; VD patients with SAI abnormalities could have concomitant neuropathological changes of AD and thus represent the percentage of patients with a mixed form of dementia.

In contrast to AD where the major features of the cholinergic neuropathology show few interindividual variations, VD may show considerable interindividual variation in the location of subcortical infarcts and, therefore, in the distribution and magnitude of the resultant cortical cholinergic deficits. In contrast to AD, where there are a few interindividual variations in the pattern and extent of the cholinergic neuropathology, VD may show considerable interindividual variation in the location of subcortical infarcts and, therefore, in the distribution and magnitude of the resultant cortical cholinergic deficit.

3.5. Cortical plasticity and functional connectivity

Some studies have examined non-invasively motor cortical plasticity and functional connectivity in AD. Inghilleri et al. [32] investigated the effects of modulation of cortical motor areas induced by suprathreshold high-frequency (5 Hz) rTMS. Whereas in control subjects 5 Hz-rTMS elicited normal MEPs that progressively increased in size, in AD patients the amplitude of MEPs progressively decreased during the training. These results suggest an altered cortical plasticity in excitatory motor cortical circuits in AD. Conversely, 5 Hz rTMS induced an increase in cSP in both groups, thus indicating a normal plasticity of the cortical inhibitory circuits. Battaglia et al. [38] studied LTP-like plasticity of the motor cortex in AD patients and healthy subjects by employing PAS with interval between peripheral nerve stimulation and TMS set at 25 ms (PAS25); they also performed biochemical analyses in brain slices of amyloid precursor protein (APP)/presenilin-1 (PS1) mice, an AD animal model. PAS-induced plasticity has been significantly reduced in AD patients; moreover, 4–4.5-month-old APP/PS1 mice exhibited deficits of NMDA receptor-dependent neocortical and hippocampal long-term potentiation (LTP), and a marked alteration of NMDA receptor activity.

Julkunen and co-workers [33] have investigated functional connectivity between the motor cortex and other cortical regions. Fifty single TMS pulses 3 s apart were delivered to the motor cortex to evaluate spreading of navigated TMS-evoked EEG responses throughout the brain. Significant motor cortical differences from averaged left and right hemispheres in AD patients were observed. Using real-time integration of TMS and EEG, the authors also demonstrated prominent changes in cortical connectivity. The TMS-evoked response at 30–50 ms decreased significantly over multiple brain regions in patients with AD compared to both healthy elders and subjects with MCI. In particular, a significant reduction has been seen in the ipsilateral parietal cortex and contralateral fronto-central areas. In addition, a significant decrease in the N100 amplitude in the MCI subjects when compared with the control subjects has been found. In a subsequent study, Julkunen et al. [78] found that the TMS-EEG response P30 amplitude correlated with cognitive dysfunction and showed high specificity and sensitivity in identifying healthy individuals from MCI or AD patients.

4. Therapeutic interventions

4.1. Neuromodulatory techniques

RTMS is capable of modulating cortical excitability and inducing lasting effects [79, 80]; both have been shown to have potential therapeutic efficacy in cognitive neuroscience [81]. RTMS has been proven to influence cortical excitability and the metabolic activity of neurons. TDCS is another simple and powerful tool to modulate brain activity, which delivers constant low-intensity current (below the perceptual threshold, 1–2 mA) over the scalp via two large electrodes. The resulting constant electrical field penetrates the skull and influences neuronal function.

rTMS can be applied as continuous trains of low-frequency (1 Hz) or bursts of higher frequency (≥ 5 Hz) rTMS [81]. In general, low-frequency rTMS reduces, and high-frequency rTMS enhance excitability in the targeted cortical region.

The physiologic impact of both neuromodulatory techniques involves synaptic plasticity, specifically LTP and LTD.

4.2. Repetitive transcranial magnetic stimulation

Three studies have dealt with rTMS effects on naming and language performance in AD patients. In two crossover, sham-controlled, single-session studies [82, 83], rTMS was applied to the dorsolateral prefrontal cortex (DLPFC) during the execution of naming tasks. In the first study, a significantly improved accuracy in action naming, but not in object naming, was observed after high-frequency rTMS of both the left or right DLPFC [82]. In the second study [83], the results of the previous study were obtained only in patients with mild AD (Mini-Mental-State-Examination (MMSE) ≥ 17/30), while in patients with moderate to severe AD (MMSE <17/30) both action and object naming were facilitated after rTMS over both left and right DLPFC. In a later study, Cotelli et al. [84] investigated whether the application of high-frequency rTMS to the left DLPFC may lead to a facilitation of language production and/or comprehension in patients with moderate AD. Ten patients were assigned to one of two

groups in which they received either 4-week real rTMS or 2 weeks of sham rTMS followed by 2 weeks of real rTMS stimulation. No significant effects were found on naming performance, while a significant effect was detected on auditory sentence comprehension after 2 weeks of real rTMS sessions. Two additional weeks of daily rTMS sessions resulted in no further improvements, while a significant beneficial effect on auditory sentence comprehension was still observed 8 weeks after the end of the rTMS intervention. An important finding was the absence of any effects on memory and executive functions.

Rektorova et al. [85] examined whether one session of high-frequency rTMS applied over the left DLPFC or over the left motor cortex (MC) would induce any evaluable cognitive changes in seven patients with cerebrovascular disease and MCI. Patients improved in the Stroop interference results after stimulation of the DLPFC but not MC, and in the digit symbols subtest of the Wechsler adult intelligence scale-revised regardless of the stimulation site.

Recently, Cotelli et al. [84] found that rTMS of the left parietal cortex increased accuracy in an association memory task in a patient with amnestic MCI, and the improvement was maintained for 24 weeks.

In another study, Ahmed et al. [86] aimed to compare the long-term effects of high- versus low-frequency rTMS, applied over the DLPFC of both hemispheres, on cortical excitability and cognitive function of AD patients. All patients received one session daily for five consecutive days. The high-frequency rTMS group improved significantly more than the low-frequency and sham groups in all assessed rating scales (MMSE, Instrumental Daily Living Activity Scale and the Geriatric Depression Scale). The improvement was still significant 24 weeks after stimulation began.

Since cognitive training (COG) is known to improve cognitive functions in AD, Bentwich et al. [87] aimed to obtain a synergistic effect of rTMS interlaced with COG (rTMS-COG). Eight patients with mild or moderate probable AD were subjected to daily rTMS-COG sessions (5/week) for 6 weeks, followed by a maintenance phase (2/week) for additional 3 months. Broca's and Wernicke's areas, right and left DLPFC, right and left parietal somatosensory association cortex were stimulated, and COG tasks were developed to fit these brain regions. Alzheimer Disease Assessment Scale (ADAS)-Cognitive and Clinical Global Impression of Change improved significantly after both 6 weeks and 4.5 months of treatment. MMSE, the ADAS-Activities of Daily Living, and the Hamilton Depression Scale improved, but without statistically significant differences. In a recent single case study [88], a patient with initial AD was treated by rTMS over the left DLPFC for 10 stimulation sessions over 2 weeks. Cognitive improvements occurred especially in tests of episodic memory and speed processing, and were still evident 1 month after the last stimulation. In a recent study, Rabey and Dobronevsky could prove that rTMS combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease [89].

5. Discussion

This chapter intended to review the most relevant studies using non-invasive brain stimulation in dementias. A number of studies showed that several TMS techniques might represent a useful additional tool for the functional evaluation of patients with dementia. Among the

studies focusing on motor cortical excitability measures, a particularly consistent and important finding is the significant reduction of SAI in AD patients. Abnormal SAI has also been reported in DLB [29] a form of dementia that responds to cholinergic medications [90]. In contrast, SAI was found to be normal in FTD [30], a non-cholinergic form of dementia. Therefore, SAI testing can be used as a non-invasive test for the assessment of cholinergic pathways in patients with dementia and may represent a useful additional tool in the differential diagnosis between the cholinergic and the non-cholinergic forms of dementia. Furthermore, TMS can thus be used to monitor AD progression and response to treatment [64]. It remains relatively unclear, how early in the course of the disease neurochemical and neuropathological alterations occur. However, neurobiological changes should be examined earlier in the disease process, when presumably they are more relevant for the pathogenesis of AD. Therefore, the findings that SAI abnormalities can be observed in patients with early diagnosis of AD [41] and even in patients with amnestic MCI-multiple domain may have potential diagnostic and therapeutic implications. Identification of SAI abnormalities that occur early in the course of the disease will allow earlier treatment with cholinergic drugs, and may be useful in identifying MCI individuals at increased risk of conversion to AD.

The second most frequent cause of dementia following AD is VD. It was suggested that cholinergic mechanisms play a role also in the pathogenesis of VD; however, the role of the cholinergic system in the development of cognitive impairment is still under discussion in VD, also because previous studies failed to found significant SAI abnormalities in most VD patients.

Interestingly, the cumulative effect of micro bleeds (MBs) on cognition appears to be independent of coexisting ischemic cerebrovascular disease, in particular of the severity of ischemic subcortical VD as assessed by magnetic resonance imaging (MRI) white matter changes [68]. $T2^*$-weighted gradient echo-MRI may thus be a helpful adjunct to standard MRI in clarifying the mechanism of cognitive impairment in patients with cerebrovascular risk factors. Anyway, TMS studies in patients with VD and other dementias have some limitations. First, only post-mortem histology allows confirmation of the precise nature of dementia. Moreover, a simple visual evaluation of MRI was employed and not more advanced neuroimaging techniques, such as voxel-based morphometry, that could contribute to the identification of different forms of dementia.

The combination of TMS and EEG also enables the exploration of neural plasticity and connectivity across different neural networks. Encouraging findings, showing impaired cortical plasticity and functional connectivity between motor and non-motor brain regions in AD, have been obtained. This method may provide a novel tool for examining the degree and progression of dementia.

Overall, several issues should be more carefully addressed in future studies. The impact of TMS depends on the distance between targeted cortex and scalp, as the magnetic field decreases with distance [91]. Since regional cortical thinning has been observed in AD [92], brain atrophy can substantially alter the effect of TMS [81]. Volumetric studies of white matter volume and cortical thinning should thus be included in future studies in order to ameliorate the interpretation of TMS results in patients with cerebral atrophy and dementing illnesses.

On the other hand, the motor cortex does not seem the best cortical area to assess in AD patients, especially in the earlier stages of the disease. In fact, neuropathologic and neuroimaging

studies suggest that non-motor cortical regions, for example, temporo-parietal and frontal association cortices, are profoundly and early affected in AD.

It should be noted that most of the TMS findings show considerable variability between studies. In addition to TMS methodological issues, age at disease onset and duration of disease, genetic factors may also represent a possible cause for such variability. It has been demonstrated that the Val66Met nucleotide polymorphism of the brain derivate neurotrophic factor (BDNF) gene differentially modulates brain plasticity and the response to transcranial stimulation [93]. In addition, the presence of Apolipoprotein E (*APOE*) and its ε4 allele is known to distinctively modulate the clinical phenotype of AD, as revealed by functional neuroimaging [94]. Therefore, the presence of BDNF-Val66Met polymorphism and of the *APOE*-ε4 may influence cortical excitability and plasticity as assessed by TMS. Moreover, it has been reported [95] that levels of total tau (t-Tau) detected in CSF of AD patients mediates abnormal excitatory activity, as measured with 1 Hz rTMS; CSF t-Tau may thus impact mechanisms of cortical plasticity.

The novel techniques of non-invasive neurostimulation have begun to be used to improve cognitive performances in AD. rTMS appears to be safe in patients with AD, even if long-term risks have not always been thoroughly evaluated. For all future studies a careful experimental design is needed and patient selection aspects, stimulation parameters, as well as clinical, cognitive and behavioral assessment tools should be considered. In fact, cognitive decline is not homogeneous across patients with AD and pathological features might affect neural networks differently. Of great importance would also be a careful choice of uniform and validate outcome measures, also to enable comparison across studies. Therefore, appropriately powered studies with more comprehensive outcome measures and sound blinding procedures are needed to confirm the effectiveness of rTMS in patients with dementia. On the other hand, the assumption that cortical plasticity enhancement is needed for the improvement of the cognitive status of patients with AD may be incorrect [96]. Even if TMS studies point to cortical hyperexcitability in AD, the employed techniques aimed at increasing cortical excitability. For this reason, the cortical physiology should be appropriately tested before and after therapeutic brain stimulation. In addition, high-frequency rTMS may not lead to an enhanced cortical excitability in AD. Indeed, rTMS effects are dependent on the baseline cortical activation state at the time of stimulation [97].

Finally, multiple-target stimulation protocols are necessary in order to overcome the widespread cognitive impairment in AD, especially in the more advanced stages of the disease [96].

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