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Chapter 31

Alzheimer disease and neuroplasticity

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Abstract

Alzheimer's disease (AD) is considered the most harmful form of dementia in the elderly population. At present, there are no effective treatments and this is likely due to the incomplete understanding of the pathophysiology. Recent data indicate that synaptic dysfunction could be a central element of AD pathophysiology. It was found that a synaptic breakdown is an early event that heralds neuronal degeneration. Transcranial magnetic stimulation (TMS) has been recently introduced as a novel approach to identify the early signatures of synaptic dysfunction characterizing AD pathophysiology. In this chapter, we review the new neurophysiologic signatures of AD that have been emphasized by TMS studies. We show how TMS measurement of neuroplasticity identified long-term potentiation (LTP)-like cortical plasticity as a key element of AD synaptic dysfunction. These measurements are useful to increase the accuracy of differential diagnosis, predict disease progression, and anticipate response to therapy. Moreover, enhancing neuroplasticity holds as a promising therapeutic approach to improve cognition in AD. In recent years, studies showed treatments with multiple sessions of rTMS can influence cognition in people with neurodegenerative diseases. In the second part of this chapter, we also consider novel therapeutic approaches based on the clinical use of rTMS.

INTRODUCTION

Alzheimer's disease (AD) is one of the most damaging forms of dementia, representing an emerging issue due to the increasing aging of the population. AD is currently contemplated as one of the most severe medical, economic, and social difficulties challenging our society and it is foreseen to become even more problematic over the next decades. Regrettably, there are no actual treatments. The approved treatments for AD are based on drugs acting on the cholinergic and glutamatergic systems, whose clinical efficacy is overall tiny. Since the 1990s, these symptomatic therapies have been shown to induce some improvement of cognition. The most frequently prescribed treatments for AD are Acetylcholinesterase Inhibitors (AchEIs) and memantine. These therapies may offer transient improvement of some symptoms (for a few months in most cases), but do not have any impact in slowing down the progressive decline of everyday activities, communication, and social behavior (Howard et al., 2012). In addition, the current managements are not effective for everybody; it is estimated that only around half of the patients benefit from these treatments.

Recently, diagnostic criteria of early AD have been implemented based on clinical presentation and biomarkers' profiles. Recent consensus pointed to the importance to determine the presence of beta-amyloid and tau-related pathology. These abnormalities may be detected in cerebrospinal fluid (CSF) sampling or with Positron Emission Tomography (PET) imaging (Dubois et al., 2016). Nonetheless, the clinical course of AD is greatly variable mainly due to the limited understanding we presently have of its pathophysiology. Critically, the

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mechanisms determining the severity of AD are largely unknown, thus preventing any significant prognostic estimate at the individual patient level. Thus, there is a critical demand to explore other paths that may expand our knowledge on the pathophysiologic changes occurring in AD, especially in the early phases of the disease when the first clinical signs appear or even before.

In this perspective, we review the emerging contribution of transcranial magnetic stimulation (TMS), a non-invasive brain stimulation method that has been used to identify the prominent alterations of neuroplasticity characterizing AD. Moreover, we will consider the application of repetitive TMS (rTMS) as a new promising therapeutic strategy acting on neuroplasticity to slow down the progression of cognitive decline.

SYNAPTIC DYSFUNCTION IN AD

The AD brain is characterized microscopically by the combined presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly insoluble, densely packed filaments. The soluble building blocks of these structures are amyloid-β (Aβ) peptides for plaques and tau for tangles. Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein, whereas tau is a brain-specific, axon-enriched, and microtubule-associated protein. These pathologic processes likely start many years before the onset of cognitive impairment. However, the first signs of cognitive damage appear only when a substantial synaptic loss has occurred in vulnerable brain regions (Jack et al., 2013).

Alterations of Aβ peptides and tau proteins can be detected in vivo by measuring their levels in the cerebrospinal fluid (CSF). CSF concentrations of beta-amyloid 1–42, total tau (t-tau), and phosphorylated tau (p-tau) proteins are nowadays clinically useful tools for AD diagnosis and phenotyping. These biomarkers may also predict disease progression. For instance, AD patients presenting at the time of diagnosis with high levels of CSF t-tau and p-tau are likely to face a worse disease course (Cho et al., 2016). Recent evidence revealed that the gathering of tau pathology is highly associated with functional and structural weakening of AD brains (Wallin et al., 2010). Moreover, it has been recognized that the assembly of tau in "tangles" correlates with patients' level of cognitive worsening, while beta-amyloid requires the presence of tau proteins to develop its harmfulness. Thus, the progressive neuronal and synaptic loss mirrors the increasing interplay of different pathologic substrates in AD and, therefore, may provide the best surrogate to track disease progression. Moreover, synaptic dysfunction is a widespread initial and noticeable pathologic feature of AD that has been found to precede neuronal loss in several brain areas. In animal models of AD, earlier investigations have mainly focused on the direct toxic role of beta-amyloid in AD-related synaptic damages. Recently, a clearer role of tau has been established (Yin et al., 2016). In particular, it was found that tau overexpression can induce synaptic degeneration even in the absence of neurofibrillary tangles. This synaptic dysfunction has been directly associated with the onset of cognitive impairment in patients with AD (Scheff et al., 2007).

NEUROPLASTICITY IN AD

Recent work supports the hypothesis that loss of synaptic density likely precedes neuronal degeneration, suggesting that impairment of synaptic plasticity mechanisms may play a key role in AD pathogenesis (Jack et al., 2013). In various efforts to find a link between progressive cognitive impairment and brain pathologic alterations, a strong relationship has been identified between the loss of synaptic density and the level of cognitive impairment in AD. As a result, impaired synaptic transmission due to toxic oligomeric species (Selkoe, 2013) may predict disease severity more accurately than neuronal failure that occurs at the later stages of the disease. This is supported by studies in animal models showing that Aβ peptides and tau proteins interfere with neuronal synaptic plasticity (Palop and Mucke, 2010). Specifically, Aβ peptides and tau proteins influence the expression of hippocampal long-term potentiation (LTP), a synaptic correlate of memory and learning (Selkoe, 2002).

These altered mechanisms of neuroplasticity have been linked to various types of alterations, including spine shrinkage, neuronal network disarrangement, and cell death (Lasagna-Reeves et al., 2016), suggesting that synaptic dysfunction may be a key driver of AD-related cognitive decline.

Despite this promising evidence, it is not currently possible to quantify synaptic function or dysfunction directly, in vivo, in AD patients. Various in vivo imaging techniques such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) (Mosconi et al., 2008), functional magnetic resonance imaging (fMRI) (Brickman et al., 2009), and electroencephalography (EEG) have emerged as potential strategies to detect biomarkers for synaptic dysfunction and network connectivity in AD (Cook and Leuchter, 1996). However, FDG-PET and fMRI provide only an indirect estimation of synaptic dysfunction due to their low temporal resolution. In other words, these techniques cannot track synaptic activity at the physiologic time scale in which neuronal interactions occur (i.e., in the range of milliseconds). Rather, imaging methods infer altered synaptic activity as a consequence of slow and subtle changes

in metabolic parameters, such as blood oxygen level-dependent contrast imaging (BOLD) used in fMRI. Unfortunately, these techniques provide measures that, besides being very far from real-time synaptic activity, cannot be used for population comparative studies and are difficult to interpret because of the possible presence of blood flow alterations. While cutting-edge work is currently advancing imaging techniques conducted in experimental research, there is a lack of translation of these methodologies into clinical practice. Most imaging biomarkers have not been validated in unselected patient cohorts, and participants in large AD studies are not representative of the general population. These techniques require special facilities and expertise and are additionally hindered by the lack of standardization in data acquisition and analytic methods between different centers. Finally, most new imaging modalities are still too expensive to be considered cost-effective in non-specialized centers.

TMS TO MEASURE NEUROPLASTICITY IN AD

TMS techniques allow researchers to evaluate in real-time modifications of brain electric activity induced by stimulation both in healthy and pathologic conditions (see Chapters 5 and 7). Briefly, this form of noninvasive brain stimulation is produced by passing a brief electric current through a coil-of-wire, generating a brief, high-intensity magnetic field. When a sufficiently strong magnetic field is applied to the brain, it can induce an electric current in the brain that triggers the depolarization of cortical neurons. Interestingly, when applied repeatedly (i.e., rTMS), stimulation induces progressive changes in brain activity. These techniques have been extensively used for both research and clinical applications (Fitzgerald and Daskalakis, 2012). TMS may represent a valid approach to overcome the limitations of imaging techniques to track synaptic dysfunction in incipient dementia (Cantone et al., 2014; Di Lorenzo et al., 2016; Koch et al., 2016).

Depending on the selected protocol, key physiologic aspects of synaptic activity can be evaluated at both local and global levels. For instance, TMS can be used to assess: (1) the properties of local networks mediated by specific neurotransmitters (Ziemann, 2011); (2) the build-up of plasticity-related phenomena of specific brain areas (Huang et al., 2005); (3) the ongoing oscillatory activity of a specific area or across brain networks (Rosanova et al., 2009); (4) causal relationships between stimulation and relative changes in brain function and performance (Spampinato and Celnik, 2020) by combining measurements of network-based activity (Fox et al., 2012).

Paired-pulse TMS protocols applied over the primary motor cortex can assess the activity of different intracortical circuits such as short intracortical inhibition (SICI) and short afferent inhibition (SAI), which respectively probe GABAergic and cholinergic neurotransmission (Di Lazzaro and Rothwell, 2014; Benussi et al., 2017) (see also Chapters 5 and 13). SAI is reduced in AD patients and the administration of AchEIs, which enhances acetylcholine activity in the synaptic cleft, normalizes SAI responses (Di Lazzaro et al., 2004). This finding is in agreement with the reported nicotine-induced SAI increases in healthy non-smoking subjects (Grundey et al., 2013) and supports the notion that SAI is an expression of inhibitory neurons that are different from those controlling SICI. On the other hand, delivering trains of TMS pulses on the cortex at particular frequencies induces long-lasting excitatory or inhibitory after-effects resembling LTP and long-term depression (LTD) described in animals (see Chapter 5). Since synaptic loss is the strongest correlate of cognitive decline in AD (Klyubin et al., 2008), repetitive stimulation can have two interesting applications in patients with AD: (1) to assess the impairment of cortical synaptic plasticity; (2) to slow cognitive decline as a therapeutic option.

Finally, the integration of TMS with EEG (TMS-EEG) is an emerging strategy that allows to directly probe local and widespread cortical dynamics through the recording of TMS-evoked potentials (Miniussi and Thut, 2010). TMS-EEG also can be used to investigate brain oscillatory activity both within a specific brain area and between anatomically distinct regions. This is particularly relevant and important when considering AD as a disconnection syndrome, often involving erratic brain network activity. As such, TMS-EEG can yield indices of rTMS therapeutic efficacy and its impact on brain networks (enhancing specific brain oscillations, "modulating" functional connectivity between brain regions).

TMS-BASED BIOMARKERS IN AD

Several groups have proposed to use TMS as a strategy to differentiate among the different forms of dementia. For example, with TMS approaches to measure GABAergic and cholinergic neurotransmission, a study showed that it is possible to differentiate AD from frontotemporal dementia (FTD) and normal aging (Benussi et al., 2017). Specifically, SAI was impaired in patients with AD but not in patients with FTD, while SICI, a marker of GABA activity, as well as intracortical facilitation, a marker of glutamatergic neurotransmission, were impaired only in patients with FTD (Benussi et al., 2017). These results are in line with observations of cholinergic deficiency in AD and abnormal glutamatergic and GABAergic neurotransmission in FTD. Therefore,

the evaluation of intracortical mechanisms with TMS could provide some diagnostic value for neurodegenerative diseases, also because TMS-based methods are easy to implement and are inexpensive. Nevertheless, multicenter clinical trials are needed to validate these measures also taking into account that FTD and AD may have overlapping features, such as the possible presence of amyloid positivity or cholinergic deficits in FTD, and glutamatergic overexpression in AD (Benussi et al., 2018).

As described in the previous chapters (see Chapters 5 and 7), rTMS can be used not only to investigate cortical plasticity mechanisms (e.g., LTP) but also to induce plasticity changes in both patients and normal subjects. As such, rTMS represents a valuable tool to identify and track synaptic impairment in AD patients, since it is well known that hippocampal LTP synaptic dysfunction and abnormal neuroplasticity are prominent AD features already at the early stages of the disease. Interestingly, hippocampal plasticity deficits in AD animal models are paralleled by plasticity deficits in the motor cortex (Battaglia et al., 2007). Moreover, internal models (based on memory and updating mechanisms linked to motor cortex function) that are used to program reaching movements are already impaired in the early stages of AD in absence of overt apraxia (Ghilardi et al., 1999, 2000). Therefore, testing the motor cortex may be used to assess plasticity in AD (Koch et al., 2012).

Mild cognitive impairment (MCI) and AD patients show impairment of motor cortical plasticity with different TMS-based protocols (Di Lorenzo et al., 2020). Interestingly, Di Lorenzo and colleagues demonstrated that both MCI and prodromal AD patients that progressed to dementia after 36 months had weaker LTP-like plasticity at the time of first evaluation. These data indicate that impaired LTP-like cortical plasticity is a pertinent pathophysiologic mechanism underlying MCI and AD, and importantly, may represent a biomarker of AD and dementia prognosis. In support of this notion, the patients with more altered cortical plasticity had a more severe cognitive decline at 18-month follow-up and higher levels of CSF t-tau proteins (Di Lorenzo et al., 2016). Interestingly, these associations were found independently of patient age and age of disease onset, suggesting that disruption of cortical LTP-like plasticity is a central mechanism of AD.

The deficiency of LTP-like cortical plasticity was also associated with impaired verbal memory, but not with other cognitive functions, an effect that was not dependent on other biomarkers, demographic information, and clinical factors (Di Lorenzo et al., 2019). An important implication of these results is that LTP-like cortical plasticity may be the most effective neurophysiologic measure in predicting cognitive decline in AD patients. The authors of Motta et al. (2018) set to investigate this hypothesis by comparing LTP-like cortical plasticity and SAI as viable biomarkers of disease progression in a large sample size of patients ($n = 60$) that were followed for 18 months. The results showed that cortical plasticity was better at predicting disease severity and progression than SAI, confirming that LTP-like plasticity is a valuable biomarker for assessing synaptic impairment in AD.

Beyond the diagnostic value of rTMS in AD, it also important to highlight the link between impaired LTP-like cortical plasticity and cognitive decline. For example, the likelihood of accelerated cognitive decline is increased with the greater impairment of LTP-like cortical plasticity. Importantly, this notion suggests that the level of cortical plasticity evaluated at the early stages of the disease can make reliable predictions regarding disease progression. This concept is supported by recent work of our group demonstrating a strong correlation between cognitive decline and synaptic loss (Motta et al., 2018), which suggests that synaptic degeneration is a key mechanism in dementia. The level of LTP-like cortical plasticity impairment was also linked with higher t-tau but not 1–42 Aβ CSF levels. Although Aβ peptides can aggregate to form several soluble oligomers that may induce direct detrimental effects on neuronal transmission (see Chapter 28), previous work has also failed to detect a correlation between Aβ 1–42 fragments detected in the CSF and cortical plasticity. Additionally, patients with high tau CSF levels had opposite responses to an rTMS protocol that normally induces LTP (Koch et al., 2016). Subsequent analysis found that the degree of tau levels was linked with LTD-like cortical plasticity (i.e., reversal of LTP) and disease progression. In other words, these results suggest that more hostile tau pathology is associated with prominent LTD-like mechanisms and more rapid cognitive decline.

Synaptic dysfunction is also likely to be influenced by genetic factors. For example, a strong association between Apolipoprotein E (APOE) polymorphisms and cortical plasticity exists. This is because APOE regulates both beta-amyloid clearance/aggregation and tau-related microtubule stabilization, which are known to alter mechanisms of synaptic plasticity. A recent study from our group showed that the presence of APOE polymorphisms implies different mechanisms of CSF tau-related dysfunction in AD patients (Koch et al., 2017). In this study, the levels of CSF tau were found to correlate with the amount of impaired cortical plasticity, while a similar association between CSF tau and more aggressive disease progression was found in AD patients carrying the APOE4 genotype but not APOE3. Of note, only patients with the APOE4 genotype that displayed high levels of CSF tau showed apoptosis in

astrocytes. Taken together, these findings reveal that CSF tau is linked to reduced cortical plasticity, cognitive decline, and astrocyte survival in patients displaying specifically the APOE4 genotype, establishing an important role for APOE4 in worsening tau pathology (Koch et al., 2017).

Finally, the integration of TMS and EEG has thus far been scarcely used in the field of dementia, with only a very limited number of studies using TMS-EEG studies investigate cortical correlates of cognitive impairment in AD patients. In one study, TMS-EEG has been able to link cortical activity changes with cognitive decline, while also showing specificity and sensitivity in identifying healthy subjects from those with cognitive impairment (Ferreri et al., 2016). It should be noted, however, that the potential of TMS-EEG in tracking longitudinally disease progression was not investigated. In the context of AD, we recently showed that TMS-EEG protocols provide the possibility to directly measure cortical functional activity in cognitive related areas such as the dorsolateral prefrontal cortex (DLPFC) or the posterior parietal cortex (PPC) extending the potential role of TMS biomarkers in assessing the effects of therapies on cortical activity outside the primary motor cortex (Koch et al., 2018). The detection of novel TMS-EEG markers of synaptic dysfunction (i.e., cortical excitability, connectivity, and oscillation) across brain regions may also provide additional predictive biomarkers of response to therapies in AD.

TMS-BASED THERAPEUTICS IN AD

Currently, conventional care for AD is based on cholinergic and glutamatergic drugs even though these treatments have limited efficacy and often cause adverse side effects. Therefore, novel non-pharmaceutic therapies must be implemented. Repetitive non-invasive brain stimulation represents a particularly promising strategy to slow down cognitive decline and the appearance of behavioral disorders in AD. Indeed, rTMS applied to patients with mood disorders and depression can influence cognitive processes, also proving to be safe and painless (Guse et al., 2010). It is important to note that exposing individuals to multiple rTMS sessions over an extensive period (i.e., several weeks) will likely have longer-lasting effects on the modulation of plasticity and behavior. From a neurobiological point of view, rTMS may lead to substantial clinical improvements by promoting changes in synaptic plasticity, which is the most important biologic mechanism underlying learning and memory processes. In particular, LTP is likely the best target since it is linked to cognitive function (Di Lorenzo et al., 2019). Indeed, LTP-like cortical plasticity is impaired already during MCI (Di Lorenzo et al., 2020) and in the early stages of AD and such a plasticity alteration is associated with verbal memory impairment (Motta et al., 2018). Therefore, a potential strategy could entail the use of high-frequency rTMS to enhance LTP-like cortical plasticity at the early AD stages to slow down disease progression. A combination of TMS-EEG and fMRI could then be used to ascertain whether or not rTMS induced changes at both local and global levels.

Most rTMS studies have investigated the effects of relatively short time treatments (i.e., maximum lasting 2 weeks); however, there is a growing agreement that longer interventional periods may be more effective. Indeed, the review of TMS safety and efficacy studies suggests that long-term and maintenance rTMS treatments in the early stages of AD may induce a slower decline of cognitive functions and a reduction of disease progression rate (Lefaucheur et al., 2014). Another important point is the best target of stimulation: recent investigations have indicated that stimulating the prefrontal cortex may be the best area for improvement of cognitive functions (Cotelli et al., 2006; Ferrucci et al., 2008; Turriziani et al., 2012; Rutherford et al., 2015). In addition to this region, studies in healthy individuals suggest that stimulation of the right and left DLPFC, Broca and Wernicke, and the right and left parietal somatosensory association cortex should be performed during cognitive tasks to further boost TMS effects (Buckner et al., 2008). Prominent neuropathologic abnormalities (i.e., β-amyloid plaques and neurofibrillary tangles) in the early stages of AD are present in the posterior cortical regions, including the precuneus (PC), the posterior cingulate, the retrosplenial, and lateral PPC. Moreover, erratic functional connectivity between medio-frontal and posterior cingulate regions suggests the presence of alterations in the default mode network in both amnestic MCI and overt AD (Gili et al., 2011). Since PC is a key node of the default mode network and animal tracing studies have shown reciprocal cortico-cortical connections with the posterior cingulate cortex (Pandya and Seltzer, 1982), targeting PC with rTMS can be viable for treating AD. Moreover, studies in AD patients have shown reduced cortical thickness surrounding the PC, which is often followed by abnormally decreased functional connectivity during memory tasks. Interestingly, the engagement of PC activity is critical for episodic memory retrieval (Lundstrom et al., 2005), which is often impaired already in the early stages of AD. Thus, interventions like rTMS over the PC may represent an ideal strategy to slow down disease progression rate and counteract memory decline in AD.

This hypothesis is supported by work performed in healthy subjects demonstrating that rTMS over the PPC and PC can enhance short and long-term memory processes (Bonnì et al., 2015). Based on these results,

we recently ascertained whether 20 Hz rTMS over the PC increased long-term memory in patients with AD. We found that stimulation in patients improved episodic memory and modulated the connectivity between parietal, frontal, and temporal areas. These results provide the first evidence that targeting PC with noninvasive stimulation may be an efficacious strategy to improve cognitive dysfunction in AD. It should be noted that, while these results are promising, the effects were evaluated over a short temporal window of 2 weeks. Future work will determine whether a longer period of such a treatment, that is from 6 to 12 months, substantially modifies the clinical progression of AD.

CONCLUSIONS

TMS holds great promise in understanding and improving the mechanisms of synaptic dysfunction in AD. The recent findings demonstrating TMS as a reliable diagnostic tool for AD, coupled with the possibility to integrate it with imaging tools such as fMRI and EEG, can undoubtedly help to advance our knowledge about disease progression and response to therapy. Implementing rTMS protocols over clinically relevant areas could indeed aid the treatment of cognitive functions in patients with mild dementia. Importantly, it is possible that long-term treatments spanning over several months could eventually slow down cognitive decline in AD.

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