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LETTER

Neurophysiological biomarkers of Alzheimer's disease: In vivo evaluation of synaptic dysfunction

The revised criteria for diagnosis and staging of Alzheimer's disease (AD)[1] update the 2018 Research Framework and reaffirm the concept of AD as a primary biological entity. These new criteria focus on biomarkers that represent distinct pathological processes, measurable in living individuals using neuroimaging and biofluid assays to track disease course. Specifically, the framework proposes three categories: core biomarkers of AD neuropathologic change, non-specific biomarkers of AD pathogenesis that are also involved in other brain diseases, and biomarkers of common non-AD co-pathologies.

The pathological changes in AD begin years before the manifestation of clinical symptoms[2] that emerge when brain damage surpasses an individually determined threshold. This latter is influenced by the individual cognitive reserve and brain resilience to abnormal protein deposition.

Despite the substantial advances outlined in these criteria, a significant gap remains between the biochemical and the structural changes driving AD pathogenesis and the corresponding dysfunction of neural networks which is correlated with cognitive impariment. Recent studies indicate that this gap can, at least partially, be filled by techniques that allow for the in vivo functional evaluation of cortical circuit excitability and plasticity. Over the past two decades, non-invasive neurophysiological techniques, namely transcranial magnetic stimulation (TMS) and electroencephalography (EEG), have been used as biomarkers of synaptic dysfunction and seem promising for evaluating the N (injury, dysfunction, or degeneration of neuropil) category.

In these updated criteria, the role of synaptic loss and dysfunction in neurodegeneration is highlighted, along with possible evaluation tools including positron emission tomography imaging, fluid biomarkers, and EEG. We would like to suggest that TMS may be an integral part of these tools, as TMS-based measures have achieved a significant level of maturity, offering insights into neuroplasticity and cortical connections at the level of specific neurotransmitters (Figure 1). These measures are becoming increasingly valuable for the characterization and differential diagnosis of dementia.[3]

Notably, some researchers consider AD a "synaptopathy," because synaptic dysfunction, driven primarily by amyloid—especially amyloid beta oligomers—and tau deposition, is detected in the early stage of the disease, preceding neurodegeneration and atrophy in the neocortex.[4]

In support of this notion there is evidence that synaptic dysfunction correlates more closely with clinical symptoms than with pathological burden[5] and that altered synaptic function plays a key role in the clinical symptom heterogeneity of AD. Indeed, it is well documented that patients with similar levels of pathological burden can exhibit different degrees of cognitive impairment. This variability is thought to arise from individual compensatory mechanisms to brain damage, such as neural networks remodeling and plasticity changes, which, unsurprisingly, occur at the synaptic level.

In this context, TMS might also be useful as a tool for monitoring disease progression. In the early stages of AD, the neural network disruption, the subsequent excitation/inhibition imbalance in the neocortex, and the increase of cortical excitability can be evidenced by the reduction of motor thresholds.[6] As AD advances, various neurotransmitter circuits undergo alterations and these changes can be monitored through TMS protocols. For instance, deficit in central cholinergic circuit activity can be assessed in the AD early stage using a paired-pulse TMS protocol called short-latency afferent inhibition (SAI).[7] Notably, administration of anticholinesterase inhibitors, L-dopa, or dopamine agonists restore SAI.[7] Also, GABAA activity, tested by the paired-pulse TMS protocol short-interval intracortical inhibition (SICI), is reduced in AD patients with longer disease duration,[8] while there is an increase of glutamatergic activity, as tested by the intracortical facilitation (ICF) protocol, even though data regarding the latter are more debated.[6,7] These measures might also assist in the differential diagnosis of dementia, as each form of dementia exhibits a distinct neurophysiological signature.[6] Deficits in synaptic plasticity, including impaired long-term potentiation (LTP) and enhanced long-term depression (LTD, particularly in the hippocampus) have also been shown, mostly in mouse models, to play a critical role in AD.[9] These synaptic abnormalities are associated with cognitive deficits and may underlie the epileptiform activity often observed in patients.[9] Repetitive TMS (rTMS) protocols have indeed provided evidence of impaired LTP-like plasticity in the human motor cortex and rTMS has been shown to improve cognitive performance in AD patients.[10]

In real-world settings, predicting the progression of neurodegeneration, starting from the subjective complaint of cognitive impairment (CI) to mild CI and dementia, continues to be a challenge.

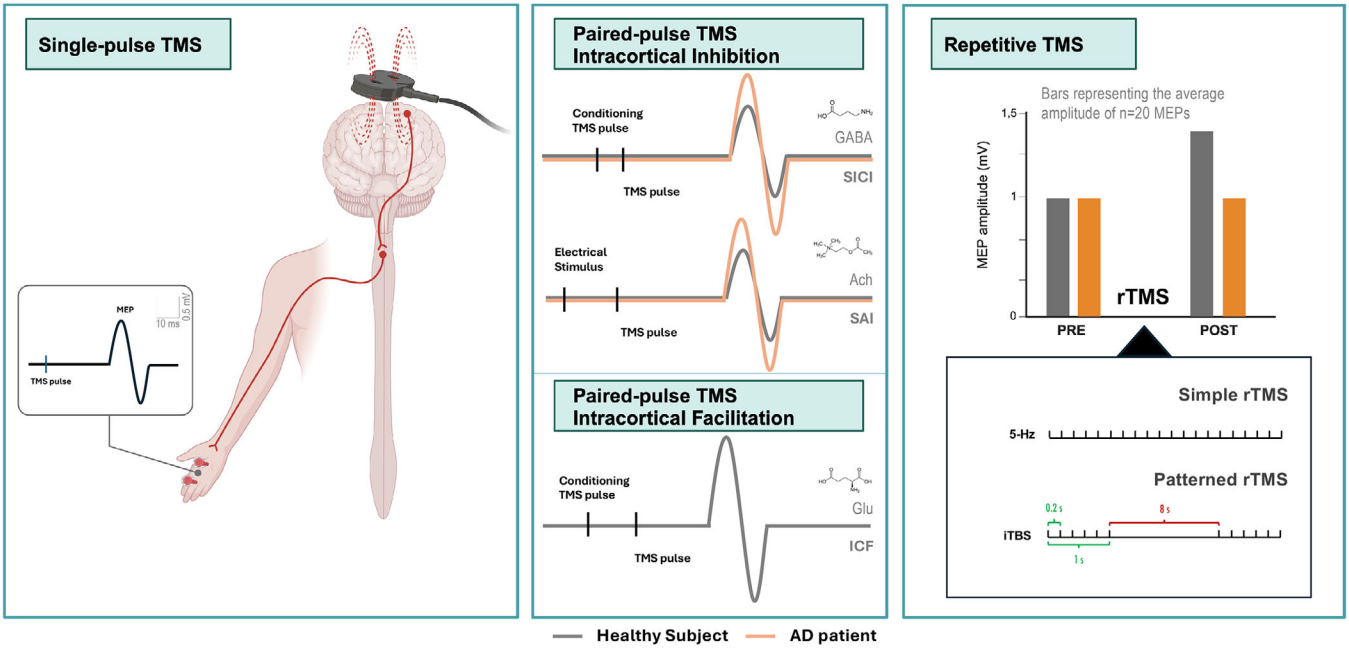

FIGURE 1 Graphical representation of TMS functioning and potential application for AD. TMS is a non-invasive brain stimulation technique that uses brief, high-intensity magnetic fields to alter cortical excitability. TMS works by delivering magnetic pulses through an electromagnetic coil placed on the scalp, inducing electrical currents that modulate neuronal activity in targeted brain regions. The electrical response from the target muscle opposite the stimulated area, called MEP, is then recorded after a single TMS pulse (left panel: Single Pulse TMS). Peak-to-peak MEP amplitude is used as the main readout for TMS. Paired pulse TMS (ppTMS) protocols involve administering two stimuli to selectively activate inhibitory/excitatory cortical circuits (central panel: Paired pulse TMS). The first pulse, known as the conditioning pulse, influences the functioning of the neural circuits, while the second pulse, the test pulse, measures the resulting changes in cortical excitability. In particular, a subthreshold conditioning stimulus followed by a suprathreshold pulse (test stimulus) with an ISI of 1 to 5 ms causes inhibition of the MEP (i.e., a reduction of MEP amplitude), a protocol known as SICI. Conversely, a longer ISI of 10 to 25 ms (ICF) leads to an increase of MEP amplitude. SAI is another paired-pulse protocol, in which electrical stimulation of a peripheral nerve (conditioning stimulus) inhibits the response to a subsequent TMS pulse on the motor cortex. The administration of multiple TMS pulses in a short period—known as repetititive TMS (rTMS)—induces neuroplasticity phenomena, resulting in long-lasting changes of cortical excitability. As an example (right panel: Repetitive TMS), two excitatory rTMS protocols are shown: (1) high-frequency rTMS (where TMS pulses are given at 5 Hz), and (2) iTBS, a patterned rTMS protocol involving short trains of stimuli at 50 Hz repeated at intervals of 200 ms for 2 seconds, with 8 second no-stimulation intervals. The divergent effects of ppTMS and rTMS on MEP amplitude in healthy subjects and people with AD are shown as lines of different color, except for ICF in AD for which no definitive data are available. AD, Alzheimer's disease; ICF, intracortical facilitation; ISI, interstimulus interval; iTBS, intermittent theta burst stimulation; MEP, motor-evoked potential; ppTMS, paired pulse transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; SAI, short-latency afferent inhibition; SICI, short interval cortical inhibition; TMS, transcranial magnetic stimulation. Created with Biorender.com

Additionally, no biomarkers exist that can reflect the effects of therapeutic interventions in real time, as structural pathological changes take time to reverse. Neurophysiological tools offer significant potential as monitoring instruments due to their excellent time resolution, broad availability, and cost effectiveness.

We are entering a new era in the management of dementia, in which, thanks to a better understanding and greater accessibility of biomarkers, the diagnostic process has become more objective. These biomarkers allow for a precise characterization of the pathological profile of the individual affected by AD. In this context, multimodal assessment, which provides valuable information for a better-informed diagnosis and staging of AD, could be further strengthened by the inclusion of neurophysiological tools like TMS and EEG.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the study.

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CONFLICT OF INTEREST STATEMENT

All authors have no disclosures to report. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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