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Improving autobiographical memory in Alzheimer's disease by transcranial alternating current stimulation

Lucie Bréchet[1,2,4], Christoph M Michel[3,4], Daniel L Schacter[5] and Alvaro Pascual-Leone[1,2,6]

We review the latest evidence from animal models, studies in humans using electrophysiology, experimental memory paradigms, and non-invasive brain stimulation (NIBS), in the form of transcranial alternating current stimulation (tACS), suggesting that the altered activity in networks that contribute to the autobiographical memory (ABM) deficits may be modifiable. ABM involves a specific brain network of interacting regions that store and retrieve life experiences. Deficits in ABM are early symptoms in patients with Alzheimer's disease (AD), and serve as relevant predictors of disease progression. The possibility to modify the neural substrates of ABM opens exciting avenues for the development of therapeutic approaches. Beyond a summary of the causal role of brain oscillations in ABM, we propose a new approach of modulating brain oscillations using personalized tACS with the possibility of reducing ABM deficits. We suggest that human experimental studies using cognitive tasks, EEG, and tACS can have future translational clinical implications.

Addresses
[1] Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife, Boston, MA, USA
[2] Department of Neurology, Harvard Medical School, Boston, MA, USA
[3] Functional Brain Mapping Laboratory, Fundamental Neuroscience Dept., University Geneva, Switzerland
[4] Center for Biomedical Imaging (CIBM), Lausanne, Geneva, Switzerland
[5] Department of Psychology, Harvard University, Cambridge, MA, USA
[6] Guttmann Brain Health Institute, Institut Guttman de Neurorehabilitació, Barcelona, Spain

Corresponding author:
Pascual-Leone, Alvaro (apleone@hsl.harvard.edu)

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Autobiographical memory impairment in dementia

The subjective sense of re-experiencing personal past events in their naturalistic contexts is a crucial feature of episodic autobiographical memory (EAM) [1] (for a recent review, see Ref. [2]). However, with age, the ability to retrieve one's life's past episodes and to imagine or to plan one's future declines, and autobiographical memory (ABM) becomes general knowledge-based or semanticized (SAM) [3–5]. In other words, we remember a given event from our past not because we re-experience it, but because we recall the stories and facts we have been told about it. Of course, EAM and SAM are associated with different behavioral and cognitive features and are supported by distinct brain substrates and processes [2]. For example, deficits in EAM associate with a faded sense of self and impaired identity, and play a central role in the cognitive deterioration of patients with Alzheimer's disease (AD), the most common form of dementia [6]. Overall, deficits in ABM are early and very debilitating symptoms in patients with AD [7] and relevant predictors of disease progression [8].

Recent studies in AD mouse models, clinical neurology, experimental psychology, cognitive neuroscience, and non-invasive brain stimulation converge to the idea that altered activity in large-scale networks contributes to the ABM deficits. Brain areas involved in ABM largely overlap with the core memory network, comprising medial temporal lobe structures, temporal cortices, medial prefrontal cortex, and the posterior parietal regions [9–11]. Neuroimaging evidence shows that AD is related to progressive neurodegeneration in these regions [12]. However, identifying the brain network supporting ABM is essential but not sufficient to understand the neural mechanisms associated with ABM and accounting for its decline in dementia. Instead, we argue that it is necessary to consider the spatiotemporal signatures of brain activity associated with ABM and their changes caused by the pathological processes associated with aging and dementia. To that end, we first discuss the oscillatory brain entrainment in the AD mouse model and the altered oscillatory rhythmic activity in AD patients that contribute to the ABM-related deficits. We then describe recent experimental memory studies, which examined age-related and AD-related brain changes in ABM. Finally, we highlight that recent advances in non-invasive brain stimulation (NIBS) show promising and beneficial effects on memory and cognition for older adults (for recent reviews, see Refs. [13–16,17•]) and focus particularly on transcranial alternating current stimulation (tACS), which may modify ABM network abnormalities.

Brain oscillatory entrainment may benefit AD pathology

AD is characterized by a progressive loss of memory accompanied by complex pathophysiology that includes amyloid-beta and tau protein accumulation, microglia dysfunction, neurodegeneration, and altered oscillatory network activity [18]. However, even before the accumulation of Aβ and p-tau, studies provide evidence that Aβ oligomers cause synapse-specific dysfunctions in parvalbumin-positive (PV+) and somatostatin-positive (SST+) interneurons leading to a dysregulation of theta and gamma oscillations. Loss of gamma activity has been linked to alterations in the mechanisms of brain plasticity [19–21], an early finding in AD thought to also be related to the synaptic toxicity of Aβ oligomers [22,23]. Interestingly, a consistent finding in individuals with AD is a relative attenuation and dysregulation of gamma frequency [24–26], and a shift from faster (including gamma) to slower (including theta) brain activity [27], which may represent an early consequence of the underlying pathology. Indeed, disrupted theta and gamma oscillatory activity is reflective of altered functional and structural brain integrity [28] and heralds p-tau and Aβ accumulation, memory deficits, and cognitive decline in AD [29].

A recent seminal study in a mouse model of AD (5XFAD) found that optogenetic modulation of PV+ and SST+ interneurons restores hippocampal network 40 Hz gamma oscillations and synaptic plasticity [30]. Similar results could be induced by multisensory stimulation [31•]. Remarkably, induction of gamma oscillations via optogenetic activation or multisensory stimulation also modified inflammatory brain processes via activation of microglia and resulted in clearance of Aβ and p-tau deposition [30] and consequential cognitive benefits [31•]. Induction of gamma activity in presymptomatic AD mice even prevented subsequent neurodegeneration and behavioral deficits. This suggests that the induction of gamma oscillations may represent a novel and powerful therapeutic approach for AD. A translation of this work to humans is feasible and promising (for more details, see [17•]. It has been shown that in humans transcranial Alternating Current Stimulation (tACS) can safely and selectively enhance gamma or theta oscillations in specific brain regions [32]. Others have also shown that modulation of brain oscillations in humans with other forms of transcranial Electric Stimulation (tES) is possible and may alter mechanisms of brain plasticity [33] and memory functions [34,35,36•,37–41].

Altered oscillatory rhythmic activity contribute to AD-related memory dysfunction

Clinically, AD is diagnosed based on neurocognitive exams and detection of specific symptoms, including memory deficit, naming difficulties, visuospatial problems, and others. However, the onset of the disease, including pathological brain changes and abnormalities in the memory network, begins years before the manifestation of typical symptoms [42]. Therefore, early biomarkers are needed to identify AD earlier and thus target patients who could benefit from disease-modifying treatments [43]. Electroencephalography (EEG), as a direct measure of neuronal synchrony, has been advocated as a candidate biomarker for AD, since numerous studies have provided validated evidence for changes in event-related as well as spontaneous brain rhythms in AD [44]. During the resting-state EEG (rsEEG), participants are not required to perform any task, therefore the acquisition of spontaneous brain activity during the absence of any external stimulus seems ideal, particularly for older individuals with mild cognitive impairment (MCI) or AD. Among the typical effects of AD on rsEEG belongs slowing of the power spectrum from high-frequency (alpha, beta, gamma) to low-frequency, decrease of the complexity of the brain electrical activity, and decrease in neuronal synchronization, expressed by a reduction in connectivity between cortical brain regions [24,45,46]. The latter effect, however, has not been confirmed in studies on older participants with subjective memory complaints [47]. Interestingly, some studies have shown an increase in synchrony, which is thought to be a compensatory mechanism [48]. When measured with fMRI, the default mode network (i.e. a set of brain regions widely overlapping with the core memory network) becomes most active during inwardly oriented mental activity (e.g., introspection, mind wandering, wakeful rest, imagination and recall) and becomes de-activated during externally oriented tasks. It has been shown that this network is less suppressed and poorly modulated by task demands in AD participants [49]. Recently, rsEEG microstates have been shown to serve as potential functional markers of early disruption of neurocognitive networks in AD participants [50].

In an analysis focused on the cognitive neuroscience of aging, Campbell and Schacter [51] identify a number of potential issues with the interpretation of resting-state networks. These include the fact that regions within a resting state network are often disconnected in different cognitive functional networks. In addition, regions disconnected in a resting state network become connected in cognitive functional networks. Furthermore, a particular region within resting state network may have multiple roles in distinct cognitive functional networks. Finally, the function of a region cannot be based on its role during rest, because it varies depending on the participant's performance. On the other hand, while event-related studies during task performance with EEG or fMRI offer the opportunity to examine the effects of AD on specific brain circuits, these recordings are not ideal for most AD patients, such that even simple memory tasks may cause increased anxiety. In a recent study, Brechet *et al.* [52] examined the spatiotemporal dynamics of brain activity during the episodes of instructed thoughts with both

high-resolution 7-T fMRI and high-density EEG, by instructing healthy participants to direct their thoughts to episodic autobiographical memories without any explicit task. As one of the fundamental goals of cognitive neuroscience of aging is to understand why some individuals experience faster cognitive decline than others [6], we argue that resting-state studies should be complemented with cognitive, task-related studies in order to achieve better understanding of the aging.

Among the most robust effects of AD on rsEEG are an increase of low-frequency and a decrease of high-frequency oscillations in frontal and posterior brain areas, respectively [27]. However, changes in frequency power do not directly indicate modulations of functional neuronal connectivity in large-scale networks, which is one of the main features of AD, as indicated by fMRI studies [53]. Neuronal communication and functional integration in large-scale networks are promoted by phase synchrony, particularly in the gamma (40 Hz) frequency range [54]. It has been suggested that phase synchrony is the mechanism that links the distributed memory representations underlying autobiographical memories [55,56]. Functional connectivity through phase synchrony can be measured by spectral EEG coherence and related measures [57]. Studies using such measures indeed showed a reduction in functional connectivity between different electrode sites in AD patients [24,45]. However, these effects are difficult to interpret due to signal dependencies induced by volume conduction [57]. Recent advances in high-density EEG recordings and source imaging methods allow us to analyze functional connectivity between the different nodes of specific large-scale networks [58] and dissociate the contribution of various brain networks [59]. Evidence shows that such methods could lead to promising biomarkers for AD [60].

How age-related and AD-related brain changes impact autobiographical memory

The recollection of mental states associated with past events requires binding across multiple brain areas. Fuentemilla *et al.* [61] examined the role of neural synchrony of large-scale networks in healthy participants versus a participant with severely deficient autobiographical memory (SDAM). The participants were asked to make audio-recordings describing EAM or general semantic knowledge over a period of 2–7 months. These recordings were then replayed to the participants while measuring their brain activity using MEG. The authors observed neural synchrony at the gamma frequency range in response to the EAM, but not to the general semantic knowledge in the healthy participants, while the increase in large-scale neural synchrony was absent in the SDAM participant. The increase in gamma synchrony was associated with a distributed network comprising frontal, temporal, and parietal brain regions. While the loss of EAM is a core feature of dementia and AD, surprisingly little is known about the progression of EAM deficits over time. Therefore, Irish *et al.* [12] conducted a longitudinal study to explore the effects of cortical atrophy on recent and remote ABMs in AD and frontotemporal dementia (FTD) participants versus healthy older controls. They found that participants with AD or FTD showed significant EAM impairments when compared to the healthy controls, and suggested that over time, memory undergoes a shift towards SAM retrieval in AD participants, as their one-year follow-up results showed that the decrease in memory performance was correlated with cortical thinning in lateral temporal regions.

Traditionally, EAM studies rely on questionnaires or interviews and investigate EAM retrieval using cue words. Plancher *et al.* [62] pointed out that most neuropsychological assessments of EAM (e.g., Wechsler Adult Intelligence Scale, WAIS) are far from the personal, self-related events that AD participants experience in everyday life. The authors tested EAM in a more ecologically valid way by using virtual reality (VR) environments and examining whether environmental factors that may affect encoding, such as active or passive exploration, influence EAM performance in pathological aging. Importantly, Plancher *et al.* [62] emphasized that classical neuropsychological studies would benefit from a multi-component approach to assess EAM, including virtual reality and active encoding of self-referential information. For example, St Jacques *et al.* [63] tested age-related changes in the quality of memory reactivation for naturalistic events during a guided museum tour and showed a reduction in subsequent memories in older adults compared to the young. Furthermore, the authors found reactivation enabled memories to be selectively enhanced or distorted via updating, and as such, their results support the dynamic and flexible nature of ABMs, which could be ideally tested in a real-life like situations. Brechet *et al.* [64] demonstrated higher recognition memory accuracy in healthy participants following a delay in memories from the first-person perspective (1PP) for realistic events encoded in VR environments that included the participant's body. Indeed, egocentric remembering is thought to be crucial for later re-experiencing of the memories [65]. Using an immersive virtual reality system, Brechet *et al.* [66•] were able to directly manipulate the presence or absence of one's body, which seems to prevent a loss of initially irrelevant past events. These findings provide further evidence that personally meaningful memories of our past are not fixed, but may be strengthened by later events, and that body-related integration is vital for the successful recall of episodic memories.

To summarize, these data show that the neural synchrony of a distributed network, including frontal, temporal, and parietal brain regions, is critical for the prevention of memory loss. Furthermore, the substrate of ABM might be flexible and modifiable, which opens exciting avenues

for the development of new targeted, therapeutic approaches of ABM deficits in AD patients. Future studies should explore whether personal photographs of familiar places and people or the use of virtual reality technology could enhance EAM memories of AD patients even further. Crucially, developing a more self-relevant, virtual assessment of EAM and training tools that are flexible and adaptable to the individual's cognitive profiles would be beneficial for the healthy aging population as well as MCI and AD patients.

Transcranial alternating current stimulation (tACS) to modify the autobiographical memory network abnormalities

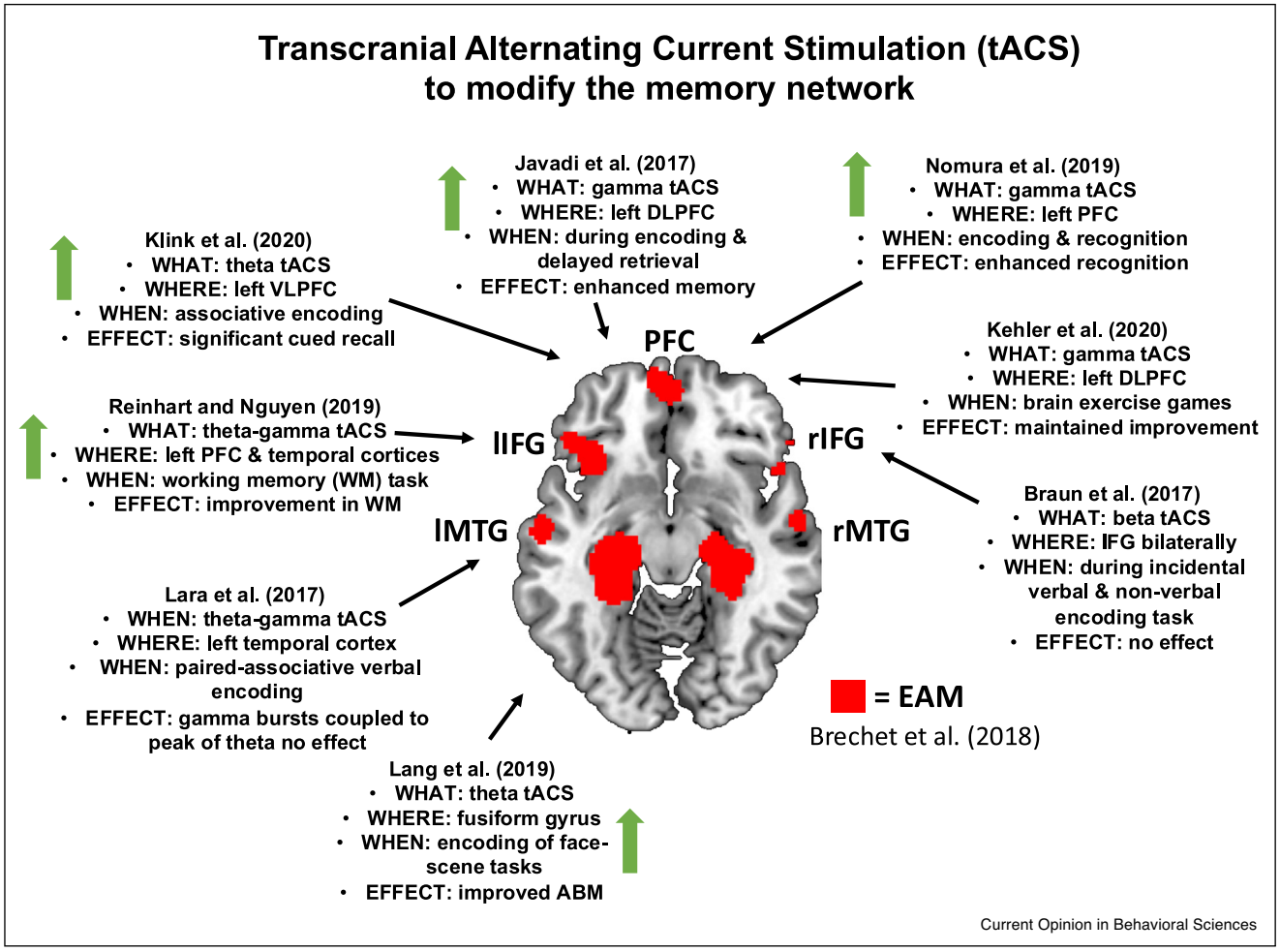
Accumulating evidence in aging research suggests that cognitive decline is associated with alterations in the anatomical and functional connectivity of large-scale brain networks. In fact, cognitive decline indicates the presence of pathology and should not be considered an obligatory consequence of aging *per se* [67]. The decrease in neural interactions and communication within and between large-scale networks might be related to the weakening of physiological mechanisms that rely on phase synchronization. Could fading memories be re-charged back as are batteries? Could modulation of brain oscillations strengthen underlying brain mechanisms and thus enable easier retrieval of memories? Non-invasive brain stimulation (NIBS) studies, particularly when combined with electrophysiological measurements of functional connectivity, show that weakened physiological mechanisms may be reversible. Specifically, tACS allows modulating neural oscillations in a frequency-specific manner accompanied by an induction of behavioral effects that can outlast the application of the stimulation itself.

While studies investigating theta tACS in young, healthy participants show promising improvement in working memory tasks, the effects of tACS in older adults and testing the modifications in episodic memory are still mostly missing. Figure 1 provides a summary of the available literature on memory modulations using tACS. Thus far, the efficacy of targeting gamma oscillations using tACS in aging has been sparse. In particular, we are not aware of any published study that investigated the effects of gamma-tACS on autobiographical memory in aging. Therefore, we here included studies testing the effects of tACS on healthy young participants during different types of memory tasks, such as working memory, episodic memory, and paired-associate memory. Different effects of NIBS are expected as the brain oscillatory activity undergoes aging-related changes. Past studies showed varying results concerning the stimulation in young and older participants. Therefore, even though most of the discussed tACS studies did not test older adults or did not focus on autobiographical memory, we see the value of including these studies in the present review as they may suggest specific contributions for future comparisons between young versus older populations.

Javadi *et al.* [68] applied gamma tACS to the left dorsolateral prefrontal cortex (DLPFC) of healthy young participants during encoding and delayed retrieval in an episodic memory task and found that the memory performance was significantly enhanced when the same gamma frequency was applied both at encoding and retrieval, but not when the tACS frequencies differed. Braun *et al.* [69] used beta tACS bilaterally over the inferior frontal gyrus (IFG) while participants were performing an incidental verbal and non-verbal encoding task. Following two distractor tasks, participants were tested on recognition of the previously encoded words and faces. The stimulation did not modulate the formation of episodic memories, and the authors concluded that tACS in the beta frequency is not suitable for modulations of episodic memory formation. Lara *et al.* [70] applied cross-frequency theta-gamma tACS in the left temporal cortex during a paired-associate memory encoding task in healthy young adults. The learned word lists were re-tested either 10 min or 24 h after the encoding. Gamma bursts coupled to the through of theta tACS induced significant memory impairment, while gamma bursts associated with the peak of theta tACS had no significant effect.

Lang *et al.* [71] demonstrated that theta tACS applied to the fusiform gyrus during the encoding of the face-scene task resulted in improved ABM performance. Nomura *et al.* [72] found that gamma tACS over the left PFC applied during encoding and recognition enhanced episodic memory in healthy young adults. Reinhart and Nguyen [36•] showed that theta tACS applied in phase over the left prefrontal and temporal cortices improved working memory in older adults with an effect of 50 min post-stimulation. Klink *et al.* [73] tested the impact of theta tACS over the left ventrolateral prefrontal cortex (VLPFC) during memory encoding of 30 face-occupation pairs in healthy older adults. Participants were tested on cued recall and recognition tasks after 20 min of the retention period and 24 h later. Overall, tACS did not significantly improve memory performance. However, an interaction of age and stimulation showed a significant effect on the cued recall task so that only the oldest participants benefited from tACS. In a pilot study of Kehler *et al.* [74], the authors examined whether 30 min daily sessions of 40 Hz tACS over the left dorsolateral prefrontal cortex, paired with brain exercises for 4 consecutive weeks, would improve cognitive functions in participants with MCI or mild to moderate dementia. The study showed that the older adults who received tACS, compared to those who did not receive tACS, maintained their memory improvement at a one month follow-up assessment. In an ongoing clinical trial, Xing *et al.* [75] are currently evaluating the efficacy and safety of one hour daily sessions of 40 Hz gamma using three electrodes over the forehead and the mastoid area for three weeks in AD patients. Furthermore, this study examines the amyloid deposits using PET, the neural activity using EEG and simultaneous EEG-fMRI as well as structural MRI to

Figure 1



Summary of published studies on modulation of memory with transcranial alternating current stimulation (tACS).
The most investigated stimulation target sites to try to modify the memory network are shown together with description of i.) what frequency was used for the stimulation, ii.) where was the stimulation was applied, iii.) when was the stimulation was performed and iv.) what was the effect of tACS on memory. VLPFC: ventrolateral prefrontal cortex; WM: working memory; DLPFC: dorsolateral prefrontal cortex; PFC: prefrontal cortex; AG: angular gyrus; ABM: autobiographical memory. The figure is adapted from a recent meta-analysis on episodic autobiographical memory [80].

evaluate the possible changes in brain volume and the integrity of white matter. The recruitment for this trial is planned to be completed in 2021. The main appeal of the potential of tACS is that it can take into account the exact rhythms that are critical for normal brain functioning. Traditional pharmacological treatments, as well as other forms of NIBS, cannot target the same rhythms. Nonetheless, the precise neural mechanisms that are important for cognitive processing in healthy individuals, and how these processes are impaired in individuals with cognitive impairment, are still not fully understood.

Future directions

Several further steps are needed to fully explore the effectiveness of tACS in modulating ABM. These include the development of new technologies that may help to further increase the precision of tACS targeting, and allowing for individualized stimulation patterns defined by mean of modelling of the induced electrical field based on structural MRI scans and functional imaging results using EEG and fMRI. More accurate, individualized montages may proof crucial when targeting abnormal protein (amyloid or tau) deposition in AD patients and stimulating the relevant brain rhythms to modify memory and cognition. Increasing knowledge about brain connectivity with high-density EEG and functional connectivity measures will enable more precise and multiple-target stimulation, including subcortical regions, as recently demonstrated by Seeber *et al.* [76•]. The use of temporal interference (TI) stimulation approaches may allow to

selectively and directly target deep brain structures such as the hippocampal formation [77]. Gaining information about the large-scale brain networks' dynamics over the lifespan, and characterizing the relevant frequencies and phases of brain oscillations associated with memory processes are critical pre-requisites for future tACS studies. Effective targeting of the relevant abnormal spatio-temporal brain signatures will benefit from recent advances in modelling enabling multiple-site tACS stimulation [78] and the possibility to track intricate connectivity patterns both within and between network dynamics. Such approaches should also consider coupling tACS with appropriate behavioral and cognitive tasks, and implementing close-loop control systems to define the tACS dose by the neurophysiologic impact as determined by real-time EEG measurements.

Going forward, NIBS could enable researchers to design more efficient and targeted applications of patient-tailored home-based tACS, with a training program to train a caregiver to deliver daily sessions of tACS that can be remotely monitored by a study team. In one of the first longitudinal case studies, Clements-Cortes *et al.* [79] reported maintained cognition in one 89 year old female with AD throughout three years of daily rhythmic sensory 40 Hz stimulation. These data are encouraging as a therapeutic potential of non-invasive brain stimulation in humans. Carefully designed and appropriately powered and controlled studies are however needed to fully evaluate the promise of such approaches.

Conflict of interest statement

Dr. A. Pascual-Leone is a co-founder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Neuroelectrics, Magstim Inc., Nexstim, Cognito, and MedRhythms; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging.

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