Toward noninvasive brain stimulation 2.0 in Alzheimer's disease

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Declaration of interest

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Toward noninvasive brain stimulation 2.0 in Alzheimer's disease

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Abstract

Noninvasive brain stimulation techniques (NiBS) have gathered substantial interest in the study of dementia, considered their possible role in help defining diagnostic biomarkers of altered neural activity for early disease detection and monitoring of its pathophysiological course, as well as for their therapeutic potential of boosting residual cognitive functions. Nevertheless, current approaches suffer from some limitations. In this study, we review and discuss experimental NiBS applications that might help improve the efficacy of future NiBS uses in Alzheimer's Disease (AD), including perturbation-based biomarkers for early diagnosis and disease tracking, solutions to enhance synchronization of oscillatory electroencephalographic activity across brain networks, enhancement of sleep-related memory consolidation, image-guided stimulation for connectome control, protocols targeting interneuron pathology and protein clearance, and finally hybrid-brain models for in-silico modeling of AD pathology and personalized target selection. The present work aims to stress the importance of multidisciplinary, translational, model-driven interventions for precision medicine approaches in AD.

Keywords

Alzheimer's disease; Noninvasive brain stimulation; Transcranial magnetic stimulation; Transcranial electrical stimulation; Precision medicine

1. Precision medicine in Alzheimer's disease

In high- and middle-income countries, life expectancy has increased, with the older age population outnumbering previous census reports. As people age, however, the incidence of neurodegenerative diseases also rises, with 6.2 million people being affected by Alzheimer's Disease (AD) in the United States alone in 2021, an estimate expected to increase in the forthcoming years (Alzheimer's Association, 2021). The biggest challenges in AD are represented by its complex, multifactorial nature, where the non-linear pathophysiological interaction between multiple genetic, biological and environmental factors accounts for high inter-individual variability of pathophysiological and clinical dynamics. The variable course of AD requires implementing new strategies based on early detection, prediction and individualized intervention to fully meet the criteria of precision medicine (Hampel et al., 2019b). Precision medicine is an emerging translational science paradigm that aims at optimizing the effectiveness of disease prevention and therapy by considering an individual's specific "clinical-biological make-up", integrating multi-dimensional data (e.g. (epi-) genetic, interactomes, cellular, and large-scale networks systems) with medical and psychosocial information (Hampel et al., 2018b). The ultimate goal is hereby the individualization and personalization of interventional care.

In recent years, noninvasive brain stimulation (NiBS) has gathered substantial public and scientific interest, considered its potential application throughout multidisciplinary frameworks spanning over brain physiology, cognitive neuroscience and network sciences (e.g. connectomics). In this article, we discuss opinions on opportunities and caveats of the use of NiBS in AD (or probable AD in studies not reporting appropriate proteinopathy testing via lumbar puncture or positron emission tomography) from a precision medicine-

oriented perspective. Building upon prior literature studies, we will discuss different new conceptual frameworks for the use of NiBS in personalized targeting for diagnosis, disease tracking, and mechanistic understanding of AD pathophysiology. Although a wide range of NiBS approaches exist, the present work aims at covering the two most frequently applied transcranial methods, that are transcranial magnetic stimulation (TMS) and low-intensity transcranial electrical stimulation (tES).

2. Noninvasive brain stimulation approaches in Alzheimer's disease: towards precision medicine

NiBS can be useful in understanding brain network pathophysiology, expanding on traditional recording techniques of spontaneous or evoked electroencephalographic or magnetoencephalographic activity. Indeed, NiBS offers the opportunity to directly interact with brain functioning in a noninvasive, safe and painless way, with a good time resolution and relatively high spatial precision.

In the clinical domain, TMS is the most widely used technique of noninvasive modulation of state and activities of specific brain circuits (Farzan et al., 2016). TMS consists of delivering short (up to 300μs) magnetic pulses of high intensity (up to 2.5 Teslas) by a copper-wired coil applied to the scalp. According to Faraday's law of electromagnetic induction, these magnetic pulses are capable of inducing electrical currents in the superficial layers of the cortex (Hallett, 2000). These currents cause direct axonal excitation or trans-synaptic activation of neurons, depending on the excitability properties of the neural structure and their orientation in the induced electric field. Neuronal activations by TMS can be used to characterize functioning or dysfunctioning of various brain networks for improving pathophysiological understanding or for diagnostic purpose. In this regard, TMS methods, mostly based on conditioned TMS techniques, have been successfully used in investigating molecular and neurotransmitter dysfunctions characterizing the AD pathology (Di Lazzaro et al., 2002; Mimura et al., 2021; Nardone et al., 2008, 2015a) and highlighting biomarkers for the differential diagnosis between AD and other forms of dementia (e.g. Frontotemporal Dementia – FTD) (see Section 2.5) (Benussi et al., 2020; Koch et al., 2020; Nardone et al., 2014; Ni and Chen, 2015; Vucic and Kiernan, 2017). Furthermore, these results pave the way to more therapeutic applications for boosting individual cognitive performance through the targeting of various brain regions and functions (Hsu et al., 2015; Nardone et al., 2015b; X. Wang et al., 2020; Zhao et al., 2017). Indeed, depending on the pattern (tonic or phasic) and frequency (repetitive TMS- rTMS at high, ≥ 5 Hz or low, < 5 Hz frequencies) of stimulation, the number of pulses, or the metaplasticity of the affected brain networks, either facilitatory or inhibitory effects can be achieved by TMS that outlast the period of stimulation. An overview of the protocols and results of the main randomized, multisession, sham-controlled trials of TMS in AD is available in Table 1.

On the other hand, low-intensity transcranial Electric Stimulation (tES) makes use of surface electrodes of different polarities (anodal or cathodal) to deliver electrical currents through the intact scalp and thus modulate neuronal or axonal membrane's polarization (depolarization or hyperpolarization below spike threshold). Electrodes are placed in

sponges soaked into saline solution or other conductive means and, depending on the intensity and duration of stimulation, act in increasing (anodal- atDCS) or decreasing (cathodal- ctDCS) the likelihood of neurons to fire thus, differently from TMS, which directly induces neural firing (Paulus, 2011). The modality of the delivered electrical current differentiates 3 forms of tES: transcranial Direct Current stimulation (tDCS), transcranial Alternating Current Stimulation (tACS) and a subform of tACS, transcranial Random Noise Stimulation (tRNS), where a low oscillatory current is applied with random variations in its frequency and intensity (Antal and Herrmann, 2016). The majority of studies on tES in AD have been conducted using tDCS. Little evidence has so far been collected in regard of tACS in addressing gamma oscillatory activity in AD based on evidence from animal models (Brechet et al., 2021; Dhaynaut et al., 2020; Iaccarino et al., 2016), whereas no study has so far employed tRNS in AD. An overview of the protocols and results of the main randomized, multisession, sham-controlled trials of tDCS in AD is available in Table 2.

Throughout TMS and tES studies, cortical regions are traditionally chosen as stimulation targets based on two principles: i) they occupy superficial cortical layers that can be easily accessed by the stimulation and ii) they have a role in naming, memory or spatial orientation, as those are among the first cognitive deficits to emerge in the course of AD pathology (Fig. 1).

Evidence-based safety and therapeutic guidelines have recently been defined based on the multiple studies assessing TMS and tES clinical effects (Antal et al., 2017; Lefaucheur et al., 2020). Both approaches have reported promising results in the amelioration of AD cognitive symptomatology (Ahmed et al., 2012; Bystad et al., 2016; Devi et al., 2014; Khedr et al., 2019b; Saxena and Pal, 2021; X. Wang et al., 2020), although continuous exploration is needed (Buss et al., 2019). Indeed, a major limitation across TMS and tES studies lies in the difficulty of comparing their efficacy due to the high variability observed across study protocols (Buss et al., 2019; Teselink et al., 2021). In particular, protocols' characteristics vary greatly in terms of stimulation parameters (such as frequency, number of pulses, duration of stimulation), number of sessions, the presence and duration of follow-ups periods, the area(s) being stimulated and their number (one or multiple stimulation targets), as well as the presence or not of concomitant cognitive training. For this reason, recent meta-analytic work has focused on various subgroup analyses in trying to determine which combination of parameters have the highest success in promoting cognitive enhancement in AD patients (Chou et al., 2020; Chu et al., 2021; Wang et al., 2021; X. Wang et al., 2020). In TMS studies, for example, a higher improvement rate has been observed in studies where multiple sites were targeted in combination with cognitive training and when stimulation interventions were administered in mild-to-moderate, rather than advanced, stages of AD (X. Wang et al., 2020).

Thus, current results on the use of NiBS in AD are encouraging, but there is still the need to better characterize the long-term benefits of stimulation (Teselink et al., 2021). In addition, other factors might have an impact on the strength, duration and consistency of the observed results. First of all, study designs have mostly focused on group-level "one-fits-all" stimulation protocols to target cognitive deficits in AD, failing to capitalize on the individual variability underlying brain functional and structural connectome organization. Secondly, an

important issue is the timing of the stimulation according to the brain state. It is usual to have expectations on NiBS optimization according to spatial determinants (cortical site of stimulation determined as hubs/nodes of brain networks, use of image-guided navigation or targeting). However, temporal determinants are at least as important. Finally, most stimulation protocols suffer from limited application exposure, as patients necessarily have to be stimulated in hospital settings with a large burden for them as well as their caregivers, thus limiting exposure to a maximum of few weeks or months of compliance. In the following paragraphs, we will review and discuss innovative stimulation scenarios and possible potential solutions to these shortcomings.

2.1. A possible role of gamma frequencies in protein clearance and neuroinflammation

The gamma frequency electroencephalography (EEG) band reflects a spectrum of oscillations (usually between 35 and 100 Hz or higher) resulting from the continuous interplay between excitatory and inhibitory brain networks (Chinnakkaruppan and Tsai, 2020). Given that an increase in gamma frequency expression in EEG activity is observed throughout the hippocampi and neocortex during task execution, it has been hypothesized that gamma oscillations are relevant for the integration of sensory information across distant brain regions, subserving an important role especially for attention and memory-related processes (Babiloni et al., 2009; Chinnakkaruppan and Tsai, 2020). For this reason, the study of gamma activity has recently gathered substantial interest in AD, where these cognitive processes are readily disrupted. In healthy subjects, increased gamma activity during the encoding phase (200–300 ms after stimulus onset) is predictive of subsequent memory retrieval (Gruber et al., 2004), and it further differentiates between good and bad memory performers (Kaiser et al., 2008). In older adults, the amount of gamma desynchronization in mid-frontal areas correlates with performance in working memory measures differently in mild cognitive impairment (MCI) – an intermediate stage between healthy elderly and AD – and healthy elderly (Park et al., 2012). In language processing, gamma desynchronization has been suggested to underlie the synchronous activity between and within cortical areas and to represent a measure of neural activation (ihara et al., 2003). In this study, the greater gamma desynchronization observed in healthy elderly compared to MCI was also interpreted as evidence of the fact that the control group required fewer neural resources during a short term memory task compared to MCI (Park et al., 2012). Furthermore, changes in the gamma fractal dimension (a measure of complexity) have been detected in the MCI stage as predictors of cognitive worsening at a working memory task after 1 year, such as that lower variability and higher complexity of the gamma rhythms were observed in individuals who worsened, compared to those who maintained a stable state (Missonnier et al., 2010). Based on this evidence, the feasibility of modulating gamma activity noninvasively to act on cognitive processes appears desirable. This can be achieved through a variety of approaches, including stimulation of auditory, visual, and somatosensory modalities (Fan et al., 2020; Martorell et al., 2019; McDermott et al., 2018), with more recent efforts focusing on NiBS approaches.

According to the Interneuron Gamma Network (ING) hypothesis, the mechanism underlying gamma oscillations involves synchronous inhibitory postsynaptic potentials of GABAergic interneurons (Chinnakkaruppan and Tsai, 2020). In a mouse model of AD, low magnetic

field stimulation in the gamma band improved cognitive function and long term potentiation (LTP) of synaptic transmission in the hippocampus (Zhen et al., 2017). An accelerated amyloid-β plaque clearance and increased microglia activation in the visual cortex was found to result from optogenetically driven interneurons to oscillate in the gamma band (40 Hz) (Iaccarino et al., 2016). In the context of human NiBS, a possible solution to entrain neural oscillation in a frequency-specific manner is represented by transcranial Alternating Current Stimulation (tACS). In one study, tACS applied in the gamma band over the motor and dorsolateral (DLPFC)/dorsomedial (DMPFC) prefrontal cortices partially improved cognitive performance in the majority of MCI subjects, but not in AD (Naro et al., 2016). At 2 years follow-up, the MCI subgroup who failed to respond to tACS had converted into AD (Naro et al., 2016). As this evidence remains highly preliminary, ongoing clinical trials are further exploring the impact of protracted daily exposure to gamma-tACS, which will be optimized to target individual amyloid-β maps in mild-to-moderate AD patients [NCT03880240].

Gamma induction could have a relevant potential for targeting neuroinflammation mechanisms. In this regard, experimental models indicate that externally induced gamma oscillations might play a neuroprotective role (Chinnakkaruppan and Tsai, 2020). Furthermore, gamma induction has been suggested to possibly decrease the risk of epileptic discharges in AD by selectively promoting the activity of task-positive regions and reducing overall levels of hyper-synchrony across networks (Palop and Mucke, 2016). In few studies, the feasibility of externally inducing gamma activity in healthy humans has been proven (McDermott et al., 2018), together with its link with memory processes (Gruber et al., 2004; Kaiser et al., 2008; Park et al., 2012; Vaz et al., 2020). As its effects on abnormal protein clearance and increased microglia appears supported by animal models (Iaccarino et al., 2016), the use of gamma induction through brain stimulation could be of interest in future AD human clinical trials. Nevertheless, alterations in the power spectra of the aging brain are not limited to alterations in the gamma frequency band, but rather span over multiple oscillatory dynamics, as discussed next.

2.2. Synchronization of oscillatory networks and modulation of brain states

A potential neurophysiological biomarker of aging is the progressive quantitative reduction of spectral power in beta and alpha EEG bands, in favor of a more preponderant slower theta and delta EEG activity (Jafari et al., 2020; Jeong, 2004). This high-to-low-frequency ratio is also significantly more decreased in clinically diagnosed AD patients compared to healthy subjects, while MCI subjects remain in between (Jeong, 2004). In addition to the frequency domain, the spatial domain (connectivity and coupling between distant brain structures) also plays a major role. Indeed, proficient cognitive functioning requires the continuous exchange and integration of information across different cortical regions, not necessarily in physical proximity or via direct structural connections. Hence, the coupling of EEG activity within more than one frequency band (i.e., cross-frequency coupling) is required. For instance, alpha/beta rhythms in deep layers regulate the superficial layer gamma bands as a crucial mechanism of working memory (Bastos et al., 2018), beta-gamma interactions have been reported during motor imagery and unexpected reward in learning (De Lange et al., 2008; Wang et al., 2019) and alpha-beta-gamma synchronous activity is

recorded during mental arithmetic tasks (Palva et al., 2005). In addition, the gamma-theta coupling is involved in speech perception, whereby gamma oscillations work in integrating the speech auditory stream at the phonemic timescale, whereas theta oscillations signal syllable boundaries and in turn orchestrate gamma activity (Giraud and Poeppel, 2012). Gamma-theta coupling is also associated with memory encoding and retrieval processes mediated by the entorhinal cortex and hippocampal structures (Mormann et al., 2005; Schack et al., 2002; Vivekananda et al., 2021). The latter, in particular, has driven research interest toward the exploration of coupling of oscillations as a marker of memory decline in aging (Jafari et al., 2020; Park et al., 2011). Indeed, in healthy older adults, preserved theta-gamma coupling over parietal sites has been associated with higher accuracy and better delayed recall at multiple memory tasks (Park et al., 2011). In contrast, the progressive increase of theta frequencies over gamma oscillations was reported in MCI to dementia progression (Moretti et al., 2011; Musaeus et al., 2020). The loss of long-range connections observed during aging is considered responsible for the gradual uncoupling of the gamma-theta bands; furthermore, the increase in the gamma-theta ratio appears to be associated with the progressive atrophy of the amygdala-hippocampal axis, possibly reflecting an early limbic involvement that might account for the behavioral disturbances seen in dementia (Moretti et al., 2011, 2009). According to the authors, the reduction in the amygdala volume is mostly associated with the increase in the theta expression, whereas the loss of inhibitory mechanisms (mainly GABA-mediated) due to the atrophy of the hippocampus could determine the decrease in the gamma expression instead (Moretti et al., 2009). More recently, in a mouse model, early stage AD was also found to be associated with a reduced synchronization of hippocampal gamma-theta oscillations, which could however be largely restored following 14 days of repetitive TMS (S. Wang et al., 2020). Since hippocampal neural alterations precede the emergence of overt cognitive deficits, the authors suggest the modulation of early hippocampal oscillatory alterations (theta and gamma) might be crucial in prodromal AD stages (S. Wang et al., 2020). Based on these premises, we might assume that enhancing physiological synchrony of gamma-theta oscillations could be beneficial, possibly facilitating memory processes in aging. In line with this assumption, a recent study has shown how 25 min of cross-frequency coupling tACS stimulation over the left prefrontal/temporal cortices was successful in ameliorating working memory performance in older adults, with sustained effects up to 50 min after the end of the stimulation (Reinhart and Nguyen, 2019). Although evidence for a performance improving effect following enhancement of cross-frequency coupling through tACS is still very preliminary, the underlying rationale encourages more in-depth studies. Furthermore, recent evidence has proven the feasibility and safety of the delivery of stimulation via multiple electrodes, whose montage can be individualized based on neuroimaging and electrophysiological data (see Section 2.4). Multifocal tACS would ease the selective targeting of multiple frequency bands in multiple different brain regions, thus better matching oscillatory brain dynamics at the network level (Fig. 2a).

More precise entrainment of brain oscillations has further motivated the development of closed-loop EEG-NiBS protocols for more precise targeting of brain states. A brain state can be defined as a momentum of brain functioning representative of an underlying set of processes sustaining a specific function (e.g., working memory, motor imagery), whose

occurrence can be detected within tens of millisecond precision through EEG recording. In this sense, NiBS interventions can be seen as acting by momentarily inducing an alteration in brain state trajectories toward a desired direction/state, with the feasibility and likelihood of such drift depending upon the brain state present at the time of stimulation (Zrenner et al., 2016). Closed-loop approaches make use of predictive algorithms to gather information on “past and present” brain activity and subsequently guide the targeting of upcoming neural events, thus tuning future stimulation timing and properties (Jones et al., 2018). Therefore, they can be particularly informative in choosing a target that might have a greater potential of inducing the desired effect (Zrenner et al., 2016). A closed-loop system could be used to track specific EEG features of the AD brain, for example to (i) identify spontaneous burst of gamma activity to reinforce such activity via tACS in the same frequency band, or (ii) to precisely predict the phase of a theta oscillation to deliver a burst of gamma and thus induce cross-frequency coupling during a memory task (see Fig. 2a). This form of state-dependent stimulation of ongoing EEG oscillations in real time (i.e., with the precision of a few milliseconds) has been recently accomplished for the sensorimotor μ-rhythm. It was demonstrated that the negative vs positive peak of the μ-rhythm represent states of high vs low corticospinal excitability (presumably reflecting different underlying networks), and that repetitive stimulation with gamma-bursts (100 Hz triplets) selectively applied at the high-excitability state (negative peak) resulted in LTP-like corticospinal excitability alteration, whereas no such effect emerged when stimulation was applied at the low-excitability state (positive peak) or at a random phase of the μ-rhythm (Zrenner et al., 2018).

Moreover, closed-loop stimulation has been used to readily target certain features of sleep-related brain activity playing a meaningful role in memory consolidation (Jones et al., 2018), as discussed in the following paragraph.

2.3. Modulation of sleep patterns

Sleep represents a critical state for the aging brain, especially when considering its link with formation, deposition and clearance of amyloid-β plaques and memory consolidation mechanisms (Lucey and Bateman, 2014; Uddin et al., 2020). A variety of sleep-related disturbances may represent critical hallmarks of aging and predictors of dementia conversion, including diminished time spent in deep sleep stages, increased number of awakenings, excessive daytime sleepiness, decrease in slow-wave oscillatory activity and overall disrupted circadian rhythms (for a review see Romanella et al., 2020). Several efforts are therefore being made in the use of NiBS for the investigation of sleep mechanisms and their possible restoration (Brunetti et al., 2020; De Gennaro et al., 2017; Gorgoni et al., 2016). Particular attention was paid to modulation of slow-wave activity (SWA) characterizing deep stages of non-REM sleep. According to the synaptic homeostasis hypothesis, SWA mechanisms act in restoring synaptic activity levels, specifically re-establishing a medium level of synaptic strengths, which are increased during daytime (Tononi and Cirelli, 2006). This synaptic down-regulation can be reliably disclosed by similar fluctuations observed in TMS-derived measures of cortical excitability. For instance, increased cortical excitability was reported following sleep deprivation, as evidenced from lower TMS intensities needed to elicit comparable baseline motor-evoked potential amplitudes before a paired-associative stimulation paradigm (Kuhn et al., 2016).

SWA homeostasis is meaningfully linked with multiple cognitive processes too, such as memory consolidation. Causal evidence of such a link comes from studies applying slow oscillatory (0.75 Hz) transcranial direct current stimulation (so-tDCS) on the scalp of healthy young individuals during sleep, in which a positive correlation between the increase of endogenous SWA and improvement of memory performance the following morning was found (Romanella et al., 2020). Such a link in young individuals has prompted so-tDCS studies in healthy elderly and MCI participants, but with conflicting results: some studies reported increased SWA without memory improvement, others showed meaningful associations even when so-tDCS over the bilateral frontal cortices was limited to daytime naps (Romanella et al., 2020). The first attempt in the MCI population has also shown some promising results, whereby so-tDCS increased SWA and spindle synchronization compared to sham stimulation, leading to improved visual memory performance the following morning (Ladenbauer et al., 2017). A possible explanation for the controversial results in studies targeting SWA is that most of these approaches rely on open-loop paradigms, that mostly failed to precisely target the highly time-varying endogenous activity of these events (Jones et al., 2018). This issue has been addressed by a study specifically testing the induced cognitive effects of a whole night closed-loop tACS stimulation selectively entraining SWA, showing that in healthy young individuals, this protocol leads to a selective improvement of long-term memory (Jones et al., 2018). Considering the biomarker validity of sleep alterations in aging, their link with cognition and their further predictive power for conversion into dementia, tACS specifically applied to entrain SWA might represent a promising, still largely unexplored, approach in at risk and pathological MCI/AD populations (Romanella et al., 2020), for which dedicated clinical trials are now being carried out (NCT03112902).

As previously introduced, gamma-theta coupling plays a relevant role in memory processing in the awake state, but its role in REM sleep has also been postulated: the increase of gamma-theta synchronicity during sleep might underlie offline consolidation processes (Boyce et al., 2016), thus representing a second target of interest for future NiBS applications during sleep. A particularly appealing, yet challenging, approach concerns the use of home-based therapies, whereby individuals will have the opportunity to bring home tES devices and receive remotely controlled tDCS or tACS stimulation outside the hospital settings, and in a more comfortable domestic environment, but still under remote medical supervision and with licensed medical devices. Indeed, the most significant burden of current NiBS therapies is the prolonged commitment required by patients and study partners to daily travel to hospital settings and the several hours necessary to carry out a whole stimulation protocol. A possible advantage of home-based therapies might be better patients' compliance to longer and even more personalized therapies taking in consideration individual daily habits (Sabbagh et al., 2020). Furthermore, therapies can be continued even during a pandemic (Bikson et al., 2020).

2.4. Network control theory for connectome stimulation in dementia

The core pathological hallmarks of AD (i.e., abnormal brain Aβ42 and phospho-tau protein accumulation, hypometabolism and atrophy) follow specific spreading patterns that tend to overlap with the topographical organization of resting-state networks (Buckner, 2005;

Palop and Mucke, 2016). Networks arise from the coupled neuronal activity of distant regions of the brain, whose positive and negative associations underlie different brain states including cognitive functioning. On the other hand, disruption of their conjoined activity occurs in many diseases, including dementia. Of all brain networks, the Default Mode Network (DMN) has been historically associated with the core organization of brain activity when the individual is at rest, but it also plays a significant role in memory retrieval, mental imagery, and internal speech (Spreng et al., 2016). DMN has been closely linked with AD pathological course, as the disaggregation between its posterior nodes occurs prior to any amyloid-β plaque formation and deposition, further triggering a cascade of network failures that accompanies disease progression (Jones et al., 2016). Such posterior disaggregation, paralleled by changes in the alpha-EEG oscillatory activity, is followed by an increased activity between posterior and frontal regions that further accounts for the "connectivity overload" responsible for the subsequent structural and functional connectome disruption, as well as of the resulting cognitive impairment (Jones et al., 2016). Aberrant neural activity and breakdown of DMN connectivity have been reported to occur in the early stages of the disease, including preclinical stages; moreover, robust evidence indicates that amyloid deposition occurs very early in the DMN and that the precuneus is one of the DMN regions earliest affected by Aβ accumulation (Palmqvist et al., 2017; Schultz et al., 2017). Pathological changes in connectivity have been reported in other networks too, with a decrease in connectivity between Dorsal Attention (DAN), Executive Control (ECN), and Sensorimotor (SMN) networks characterizing patients' clinical progression (Brier et al., 2012; Soman et al., 2020). Network disruptions are highly specific not only in the AD clinical-biological continuum, but also across the entire spectrum of neurodegenerative dementias. For instance, markers based on the balance between DMN and the Salience network (SN) allow high discrimination accuracy between AD and FTD (respectively showing decreased DMN and increased SN activity in AD, with a specular pattern observed in FTD) via both static (Zhou et al., 2010) and dynamic connectivity analysis (Moguilner et al., 2021).

Although networks alterations in AD are by now broadly accepted in the neuroscientific community, only a limited amount of studies has directly tried to target them using NiBS. For instance, targeting of the DMN has been achieved through stimulation of the precuneus, resulting in enhanced memory performance through the modulation of its connectivity to parietal and frontal sites, accompanied by an increase in high-frequency brain oscillatory activity (Koch et al., 2018). Although results are very preliminary, several efforts are currently under test for the systematic use of network modulation approaches (Rossini et al., 2019). First of all, we need to develop multifocal stimulation devices for the concurrent targeting of multiple, distant cortical sites. A first step in this direction has been taken by means of multifocal network-targeted tDCS, which has shown favorable results in stimulating motor network activity compared to traditional bipolar montages targeting the motor cortex (Fischer et al., 2017; Mencarelli et al., 2020). Furthermore, current efforts are now being directed in individualizing such montages based on multimodal neuroimaging data which can be used to determine the exact location, number and intensity of current of each electrode necessary to engage an entire network of interest rather than a single

brain region (Ruffini et al., 2014). A more in-depth description of the recent advances of biophysical modeling is provided in the next paragraph.

Another field of study that might be useful in guiding network-guided stimulation approaches in AD is represented by the mathematical study of networks' organization and structure, as by means of *graph theory* and *network control theory* approaches (Karrer et al., 2020; Liu et al., 2011). The former deals with the topological properties of graph construction that might ease information transfer in a network, whereas the latter deals with the theory behind network controllability and state-to-state transfer, with both having multiple implications for NiBS approaches in AD (Fig. 2c). The study of nodes properties from a mathematical perspective can be informative, for instance, to identify the likelihood of a region to have a central role in network functioning, or of the amount of energy required to steer the system in a desired state and further inform on input-output energy costs. Most importantly, those principles might be applied to favor the transition of brain states, for example from a baseline resting state to an active cognitive process (e.g. memory encoding state), or again to boost network *resilience* against external "perturbation" (as defined by any transient or sustained event able to change brain structure and/or function, e.g. brain atrophy, local buildup of proteins, hypometabolism) (Fig. 2c) (Hampel et al., 2019a). Importantly, network-theory derived targets differ from traditional stimulation sites as they account for intrinsic topological properties of the individual brain and make use of informed models to predict response outputs. *In silico* models have already proven the theoretical success of using control theory to detect the role of nodes in brain controllability (Betzel et al., 2016; Gu et al., 2015; Karrer et al., 2020) and possibly act on them to interact with pathological neural elements (e.g. AD-related EEG activity changes) (Sanchez-Rodriguez et al., 2018). However, causal validation in humans of those theoretical frameworks is still missing. As per today, NiBS might represent the most promising, noninvasive approach to test such theoretical predictions in a causal manner.

2.5. Perturbation based biomarkers, plasticity and individual resilience to pathology

As NiBS techniques provide a unique (causal) window into the mechanisms of brain functioning, their usefulness in providing a snapshot of brain states throughout the disease course and along the clinical-biological continuum is being discussed, considering their possible usefulness to (i) discern between healthy and pathological states and possibly identify states "prodromal-to-dementia"; (ii) help in the differential diagnosis across dementia types; (iii) monitor for progression of pathological brain states (Koch et al., 2020). The terminology of *perturbation-based biomarkers* has therefore been recently introduced to account for these potentials (Fig. 2b), representing the combination of NiBS with neuroimaging/electrophysiology in an effort to capture an instantaneous brain response to external magnetic/electrical perturbation.

As per TMS-derived biomarkers, cortical excitability studies using paired-pulse paradigms are particularly promising. When delivering a subthreshold (below RMT) conditioning stimulus, followed by a suprathreshold (above RMT) test stimulus using the same coil over the same cortical site, it produces a change in test motor evoked potential (MEP) size. When the inter-stimulus-interval (ISI) between the two pulses is short (2–6 ms), a

reduction of the test MEP size is observed, due to the GABA-A-mediated phenomenon of short-interval intracortical Inhibition (SICI). When the interval is around 6–12 ms, glutamatergic facilitatory effects are observed, corresponding to the phenomenon of intracortical facilitation (ICF) (Liepert et al., 1997). A different form of paired-pulse paradigm consists of delivering an electric stimulation to the median nerve at the wrist shortly (20 ms) before a suprathreshold TMS test pulse over the contralateral motor hand area (Mariorenzi et al., 1991). The conditioning peripheral stimulation produces a reduction of test MEP amplitude, named short-latency afferent inhibition (SAI), possibly mediated by cholinergic brain pathways. Since the cholinergic system is the earliest and most extensively disrupted neurochemical system in AD, in association with the loss of hippocampal projection during early stages of AD (Hampel et al., 2018a), SAI assessment is particularly appealing. Moreover, SAI is decreased by cholinergic receptors blockades (Di Lazzaro et al., 2000) and it is restored by acetylcholinesterase inhibitors (Di Lazzaro et al., 2005) and dopaminergic drugs in AD patients (Koch et al., 2014; Martorana and Koch, 2014), with a possible use for the control of pharmacological interventions. Recent evidences suggest reduced SAI, and possibly SICI, with normal ICF in AD patients, whereas FTD patients are characterized by normal SAI and reduced SICI and ICF (Benussi et al., 2020, 2017). The ability of TMS measures to detect cholinergic alterations can be useful in increasing AD diagnostic sensitivity (Benussi et al., 2018).

A second easily accessible biomarker is represented by NiBS-derived measures of plasticity, particularly relevant since the AD brain is characterized by altered plasticity mechanisms, especially LTP. Intermittent theta burst stimulation (TBS) protocols have been used in trying to restore the cortical excitability balance with sustained effects for up to one hour. These after-effects are thought to reflect influences on the strength of glutamatergic synapses via NMDA receptors, AMPA receptors and calcium channel effects (Huang et al., 2007). LTP-like cortical plasticity impairment may be specifically related to memory deficits, even when demographic and clinical factors are taken into account (Di Lorenzo et al., 2019). Furthermore, LTP-like cortical plasticity impairment is associated with tau but not 1–42 Aβ cerebrospinal fluid (CSF) levels (Koch et al., 2016). The presence of APOE polymorphisms implies different changes in AD patients: CSF tau levels are linked to cortical plasticity, cognitive decline and astrocytes survival only when associated with the APOE4 genotype (Koch et al., 2017). Furthermore, experimental animal models have shown that even before any brain deposition, soluble Aβ oligomers specifically block mechanisms of cortical plasticity and synaptic viability, such as hippocampal LTP (Shankar et al., 2008), which is regarded as an electrophysiological correlate of learning and memory (Palop and Mucke, 2010). As such, LTP-like cortical plasticity appears to be a promising biomarker able to identify AD patients and further predict their cognitive decline (Motta et al., 2018).

Finally, perturbation-based biomarkers can be derived from the concomitant use of TMS and EEG to track the interactions of brain areas during sensory processing, cognition or motor control and, moreover, to evaluate neurological disorders, such as AD, characterized by altered connectivity. Few studies already showed that cortical stimulation in AD patients was associated with alteration in TMS-induced activity over several brain areas compared with healthy controls, suggesting a potential role of TMS-EEG as a neurophysiological marker for diagnosis and early identification of MCI and AD (Hallett et al., 2017). TMS-

EEG co-registration demonstrated that in mild AD patients without motor symptoms, the sensorimotor system is strongly hyperexcitable and deeply rearranged with the recruitment of additional neural sources (Hallett et al., 2017). Furthermore, the combined use of TMS-EEG allows detecting plastic and oscillatory alterations outside the traditionally investigated motor strip. This could allow for multimodal biomarkers to be possibly derived from other resting-state networks, such as the DMN, whose progressive disaggregation is an already established biomarker of AD progression (see previous paragraph). The principle of leveraging the perturbation of complex systems/networks as a mean to access more specific features of these systems, as compared to passive recording, is not new, and has shown clinical relevance in the case, for instance, of disorders of consciousness, where the perturbational complexity index of the response to single pulse TMS as recorded via EEG is able to discriminate consciousness levels (i.e. vegetative state, minimally conscious state, etc.) with higher accuracy than other neuroimaging or neurophysiological markers (Casarotto et al., 2016). The use of TMS-EEG as potential biomarker has greatly benefitted from studies evaluating the use of drugs to characterize the exact molecular changes that are reflected by the EEG potentials evoked by TMS (Darmani and Ziemann, 2019). Knowledge of the pharmaco-physiological mechanisms of brain excitability assessed via TMS-EEG could greatly promote the use of this technique in disorders marked by pathological brain network connectivity and excitability changes, such as AD (Darmani and Ziemann, 2019).

Perturbation-based biomarkers might represent, therefore, useful and repeatable indexes for clinical follow-up. Most importantly, they represent a snapshot of a patient's pathophysiological stage, which might not be completely reflected by clinical manifestations, especially in the prodromal phases. In fact, it is now fully accepted that neurodegenerative mechanisms work in the darkness for many years (even decades) before symptoms appear; the reason for this is the presence and amount of a "neural reserve" (silent synapses and circuits), which can be progressively recruited via neuroplastic phenomena to vicariate functions of lost synapses and circuits. Indeed, the individual threshold of brain resilience to incipient pathophysiological alterations relates to both genetic and environmental factors, which can be explained as the interaction between the amount of Brain (Katzman, 1993) and Cognitive (Stern, 2009) Reserve levels. As a result, highly resilient patients might present only relatively mild cognitive deficits with respect to their underlying neural degeneration and thus either fail to report to a neurologist until more advanced stages of the disease, or be misdiagnosed based on neuropsychological measures alone, in the absence of appropriate neurophysiological/neuroimaging data. Furthermore, disease progression for patients with higher levels of reserve appears to be initially slower, but once they reach the critical level, their clinical decay occurs faster (Hall et al., 2007).

In this regard, the individual level of cortical plasticity and excitability might represent biomarkers of resilience (Menardi et al., 2018). This suggests the possibility of using NiBS interventions to act on them (Passow et al., 2017). For example, possible interventions might involve prolonged exposure to brain and cognitive stimulation protocols capable of favoring plasticity mechanisms and network strengthening as a first step in promoting healthy brain maintenance and in counteracting, or at least delaying, cognitive decay (Nyberg et al., 2012).

Future longitudinal studies looking at the feasibility of such interventions are needed.

2.6. Hybrid-brain models for precision targeting and adaptive therapy

The use of advanced computational models enables what may be called *Brain Stimulation 3.0,* as a further improvement over NiBS approaches informed by imaging or electrophysiology. In the case of tES, for instance, montage optimization in tES 2.0 is defined today from the knowledge of the underlying physio-electrical properties of the individual neural tissues, and subject-specific electrical field (E-field) models are derived from the geometric reconstruction of the head and parametrization of tissue conductivity (Fig. 3b and c). More specifically, tissue segmentation into multiple layers, including skull, scalp, CSF, grey, and white matter components is accomplished starting from the individual MRI (Fig. 3b). Each of the separate tissue masks is then used to create geometric surfaces made of small finite elements, such as triangles and tetrahedral. Representations of the electrodes are further embedded in the model to derive an accurate estimation of the induced E-field from a priori knowledge on the electrical properties of tissues and of the amount of current injected in each electrode (Miranda et al., 2013). For visualization purposes, the E-field can be represented on the individual cortical surface in the form of a vector representing the magnitude and the direction. In this sense, prior studies have pointed out that the most informative component might be the one normal to the cortical surface as it is understood to exert the maximum effect on the pyramidal cells, known to have a perpendicular orientation with respect to the cortical surface (Ruffini et al., 2014). Based on this work, E-field models are used by optimization algorithms to design targeted electrode montages. The starting point is represented by a given target E-field value in one or more cortical regions, for which the algorithm determines the optimal number, position and current intensity of a finite number of electrodes necessary to reproduce a close match of the desired E-field (Ruffini et al., 2014). This use of personalized cortical montages is of major importance as it considers individual variations in cortical morphology, even more relevant in pathological settings characterized by drastic neural rearrangements. These models have hence the advantage to achieve accurate estimates of the amount of current reaching the cortex during a stimulation protocol, and, more importantly, the associated electric field (the causal mechanistic element) and its impact on a specific class of neurons (e.g., differentiating the impact over pyramidal neurons and inhibitory interneurons).

Nevertheless, the tES 2.0 approach still has shortcomings in several ways. First, the specification of the targeting problem is based on simple assumptions of what needs to be done (e.g., inhibit or excite a given cortical region) and how to achieve it (e.g., that a cortically inward E-field is excitatory) and ignores important complexities of brain functions, which resemble a dynamical, complex, plastic network. Both specifications, the desired effects and how an externally applied electric field can achieve them, cannot be attained without a *physico-physiological model* of the brain. Because of this, tES 3.0 relies on so-called *hybrid brain models* (HBMs) (Ruffini et al., 2018). Hybrid models allow integrating physical and physiological data to generate more personalized models that represent both the passive physics of currents and fields in the head and brain, and also the physiological circuitry as it responds to them (for a similar solution see the The Virtual Brain simulator (Sanz Leon et al., 2013)).

HBMs are networks where the nodes are represented by Neural Mass Models (NMM). This is a valuable approach to construct such models as NMMs are able to capture both micro elements, ranging from dendritic and postsynaptic potentials, to larger scale neural interactions (Fig. 3d), and represent the brain in a computationally tractable manner. NMMs are then treated as nodes of a network where, depending on the desired level of specificity, they can represent single cortical columns or whole brain regions, their links (edges) either being that of structural fibers (e.g. white matter cortical tracts) or derived from correlational/effective functional coupling measures (Sanchez-Todo et al., 2018). Activity of the coupled NMM nodes can then be used to mimic real electrophysiological data (e.g., EEG time courses), as well as the effects of drugs on neural ensembles. Hebbian mechanisms can be implemented in the models as well, allowing the prediction of changes in neural plasticity induced by brain stimulation (Sanz Leon et al., 2013). Through the use of continuous data assimilation (e.g., EEG), personal brain models can be updated and therapy adapted. In this regard, recent evidence has been gathered on the use of closed-loop paradigms in deep brain stimulation studies in Parkinson's Disease and Major Depressive Disorder (Scangos et al., 2021; Zhu et al., 2021). Across studies, the stimulation parameters were continuously adjusted based on the incoming oscillatory activity of interest via either detection or supervising control algorithms (Scangos et al., 2021; Zhu et al., 2021), which were designed based on biophysical models of the cortex-basal ganglia-thalamus network (Zhu et al., 2021). All such applications fall in the framework of *adaptive therapeutics*, where stimulation trajectories are continuously adapted as a function of the undergoing brain changes (e.g. occurring concomitant fluctuations), which in turn might be driven by the concurrent effect of administered drug therapies or other plastic changes induced by the stimulation itself. In the past few years, computational connectomics applied to deep brain stimulation studies has also been useful in detailing structural and functional connectivity changes following prolonged exposure to stimulation and to detect meaningful shifts in patients' brain dynamics toward a healthier regime (Saenger et al., 2017). Similarly, whole-brain computational models have been employed to detect Hebbian-like changes in the structural projections of the subthalamic nucleus, with functional consequences in one rare case study (van Hartevelt et al., 2015). As for what concerns noninvasive stimulation scenarios, realistic, individualized, head-models have been recently used to determine the optimal cortical distribution of multiple stimulating electrodes in order to deliver inhibitory currents targeting the epileptic foci and reduce seizures rates in adult and pediatric populations (Kaye et al., 2021). A practical example of the use of NMMs can also be found in the study of epileptiform activity, where NMMs have been used for the modeling of interictal spikes and burst, focal and generalized seizures and their propagation (Wendling et al., 2016). Their implementation has helped highlighting the usefulness of computational models in integrating knowledge of the brain system via its mathematical representation, to investigate "potentially important parameters, either related to neurons, to network of neurons or to networks of networks" (Wendling et al., 2016). In regard of brain stimulation, NMMs have been used in an animal model to understand the physiological mechanisms by which tDCS interacts with the brain endogenous rhythms (Molaee-Ardekani et al., 2013). In this study, NMMs representing subpopulations of pyramidal cells and inhibitory interneurons were employed to model the evoked activity of tDCS during air-puff stimulation of rabbits' whiskers, representing the first successful attempt in using

complex models to reveal the mechanisms beyond the interaction between the brain and an exogenous stimulation (Molaee-Ardekani et al., 2013). In AD, hybrid models could be employed to specifically target populations of neurons and their interaction, such as GABA-ergic parvalbumin (PV) inhibitory interneurons and pyramidal neurons, whose dysfunction appears to underlie the above-mentioned reduction in gamma band expression, with consequent drastic effects on cognition (Chinnakkaruppan and Tsai, 2020).

Even though HBM definitely constitutes the most far-fetching of the applications proposed in this perspective, their implications for the development of personalized, adaptive therapies in AD and related dementias cannot be overstated. Future studies addressing highly realistic, multi-layers models of the complex system dynamics underlying stimulation scenarios are needed to guide advancement in the field.

3. A translational framework and roadmap for NiBS in AD

Early in the pathophysiological course of AD, changes of the excitation/inhibition balance due to altered interneuronal responses and synaptic transmission occur that can be detected through TMS-derived measures of cortical excitability. The use of combined TMS-EEG might help to expand the detection of cortical alterations beyond the motor cortex and possibly stimulate residual plasticity mechanisms (Fig. 4a–c, 1st row). Pathological shifts in brain oscillations -namely of the networks underlying EEG rhythms-also characterize the course of AD, with a decrease in the expression of high frequency bands, in favor of slower oscillations. Future studies should test the use of tACS to promote healthy brain patterns (e.g. through the increase of alpha activity) (Fig. 4a–c, 2nd row). In addition, tACS delivered at the gamma frequency is now being tested as a potential intervention to act on neuroinflammatory processes, which further represent a key step in the pathological course of AD (Fig. 4a–c, 3rd row). As the patterns of brain atrophy and proteinopathy appear to occur along known neural networks (e.g., DMN), future interventions might make use of knowledge on the brain topological organization for the building-up of guided interventions addressing altered network dynamics (Fig. 4a–c, 4th row). Finally, NiBS can be used to enhance the receptivity of the brain by means of priming or synergistic methods, where NiBS interventions are combined with dedicated cognitive tasks (Sabbagh et al., 2019). Future interventions might further expand on the use of such methodologies during particularly receptive brain states, such as those observed during sleep (Fig. 4d).

In conclusion, comprehensive care plans should be constructed, aiming at improving the patients' quality of life, considering the individual starting point and promoting the choice of stimulation paradigms that best suit patients' profiles, possibly augmenting individual resilience in face of the pathology (Fig. 4d).

4. Conclusions

Conceptually new NiBS approaches are now under the lens of ongoing trials, aiming at system-scaled interventions capable of integrating the multi-level biological and neurophysiological complexity of AD. Such innovative therapeutic approaches are supported by high spatiotemporal resolution, adaptive tuning based on ongoing plastic changes,

and individualized protocols. Our view on present and future NiBS opportunities in AD aims to primarily stress the importance of multidisciplinary, translational, model-driven interventions to further increase the potential of brain stimulation as a possible methodology for direct and individualized patient care that can be considered a still unmet need in AD.

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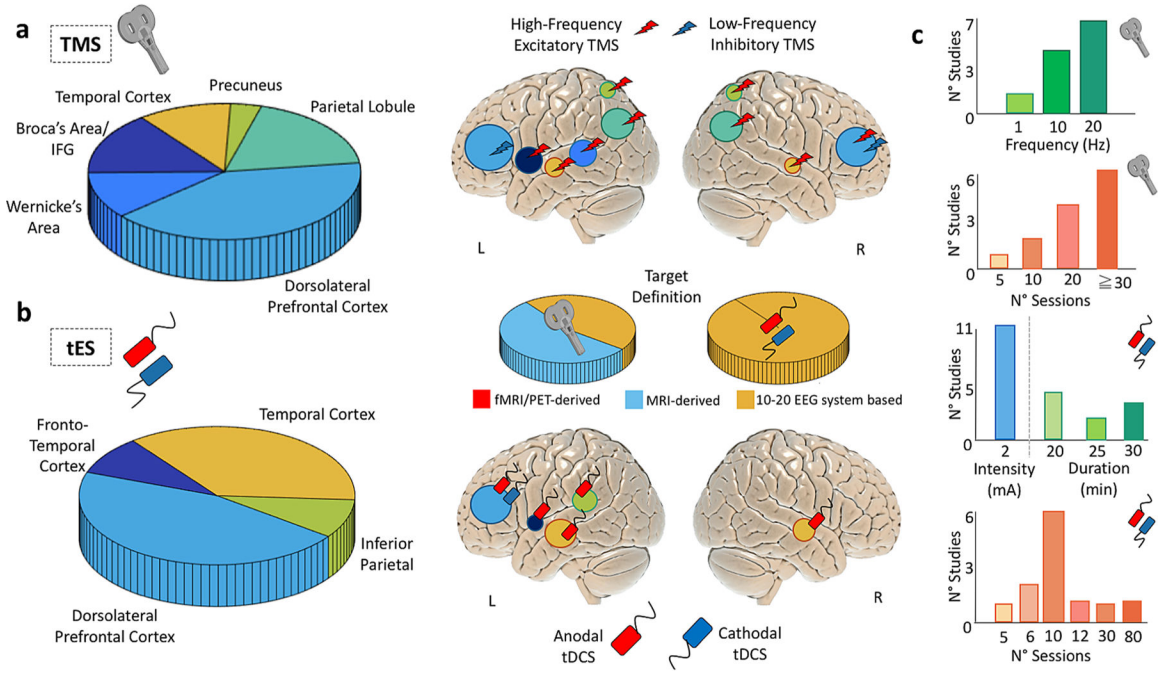

Fig. 1.

Past and Present NiBS Applications in AD. Traditional stimulation targets in AD therapeutic studies have been mostly represented by superficial cortical regions whose dysfunctions are responsible for early cognitive symptoms (language, memory, orientation deficits) that generally bring the individual under clinical attention. The most common stimulation sites in TMS (a) and tES (b) multi-session, sham-controlled studies of the past 10 years are presented in form of pie charts as well as on brain surfaces. The size of the dots is proportional to the number of studies targeting each region. Most TMS studies have administered high-frequency stimulation protocols (patterned 5–20 Hz stimulation), whereas few tES studies have compared the effects of anodal and cathodal stimulation targeting the same area. Overall, few studies used neuronavigated MRI-based stimulation protocols and no studies have leveraged functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to guide target selection. (c) Details on the parameters of stimulation and overall number of sessions across studies are also reported for TMS and tES.

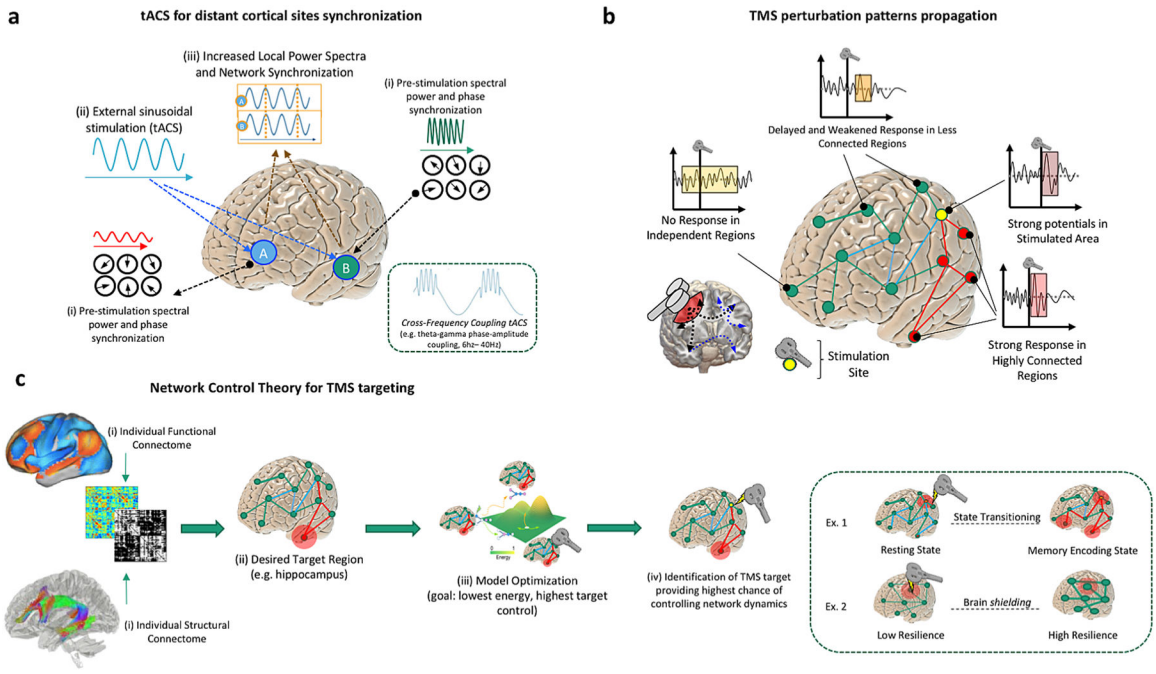

Fig. 2.

NiBS Precision Medicine Approaches. Novel therapeutic opportunities cover a range of approaches for targeting AD pathological hallmarks. (a) tACS mechanisms of action for the synchronization of oscillatory activity across distant cortical sites, which could be applied to re-tune aberrant cross-frequency ratios (e. g., decrease alpha/beta over theta/delta ratio), as well as to promote oscillatory frequencies with a possible role in the reduction of proteinopathy and neuroinflammation (e.g. gamma band). Adaptive protocols could make use of the incoming information regarding the occurring neural changes for the continuous fine-tuning of stimulation parameters. This can be achieved online during continuous EEG monitoring (as for closed-loop protocols), or offline via repeated neuroimaging data collection, necessary to monitor changes in brain properties (e.g., connectivity, perfusion) and thus adjust stimulation protocols. (b) The cortical response to a TMS pulse can be used as a biomarker for the identification of abnormal (e.g., increased or decreased) brain functions when compared to age-matched populations. Furthermore, TMS-EEG can be a direct marker of stimulation spreading, probing major communications pathways in the brain and further highlighting possible aberrant trajectories or compensatory recruitment. (c) Brain network graphs can be used to guide NiBS via network control theory principles. The study of individual topological properties of nodes and the patterns of information flow can be informative for the identification of the most suitable cortical targets to correct deviant pathological trajectories affecting brain networks (e.g., the DMN) and secondarily affect deep structures not directly targetable (e.g., the hippocampi). Furthermore, the control of brain states might favor the transition between them, for example promoting the switch to a particular cognitive state, or even promoting resilience states toward higher network robustness to external perturbations.

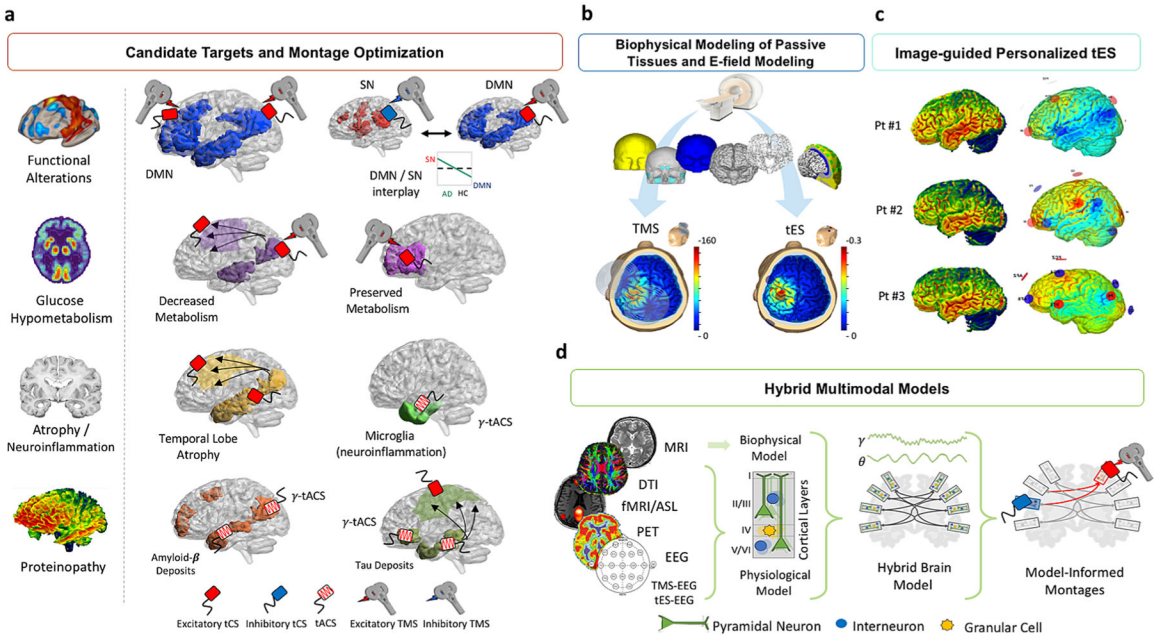

Fig. 3.

Therapeutic Targets and Personalized Montages. (a) Numerous targets of interest exist that might guide future interventions. NiBS might be used to boost diminished activity in affected networks (e.g., DMN) or to decrease the hyperactivity in others (e.g., SN), favoring a return to inter-network balancing similar to healthy controls. Excitatory protocols might also be employed to increase the metabolism in affected areas or to sustain the metabolism in preserved areas. The notion on the spreading routes of the pathology might indeed encourage preventive interventions, whereby excitatory protocols might help sustaining neural functions in regions yet-to-be affected. Similarly, atrophic regions might still represent a NiBS target for sustenance of spared neural mechanisms, as well as a prevention for future atrophy. Finally, tACS might be employed for the targeting of neuroinflammation and proteinopathies, with important implications in the quest for amyloid-β plaques reduction and PV+ interneurons targeting. (b) The heterogeneity of AD pathology further requires targeting to be achieved through highly personalized montages that consider individual brain morphology and tissue characteristics (atrophy, CSF, etc.). (c) Highly personalized solutions can be achieved based for instance on amyloid deposition. (d) An even greater level of personalization could be achieved through the implementation of hybrid models, which further allow optimization towards targeting of specific neuronal populations, such as PV+ inhibitory interneurons and pyramidal neurons.

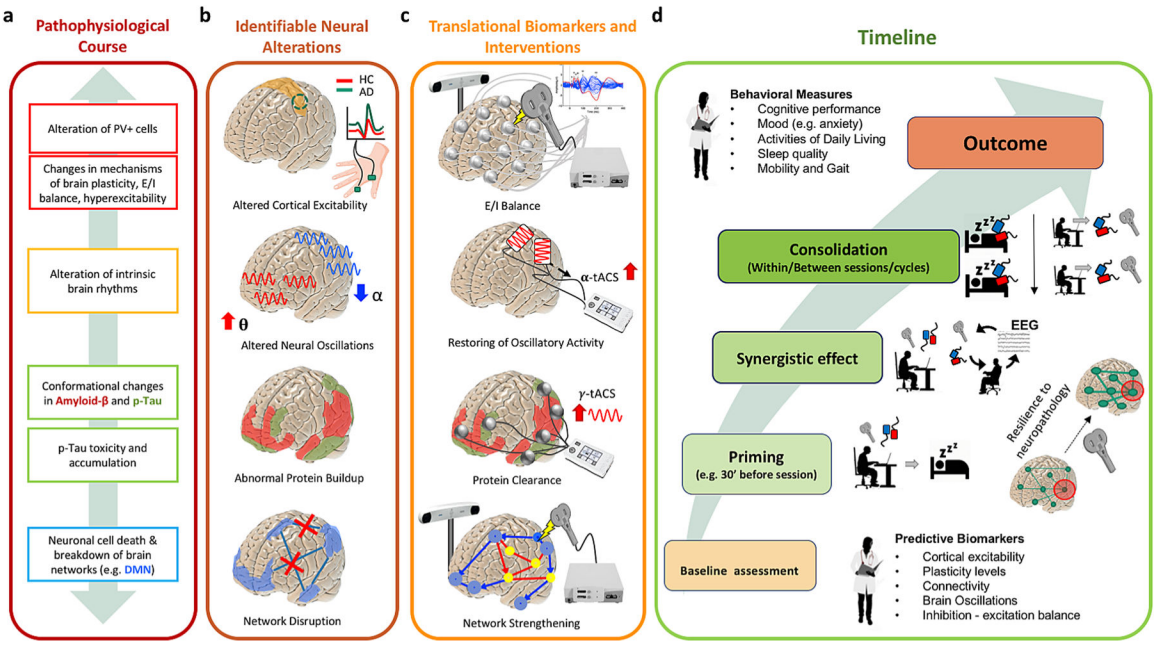

Fig. 4.

Pathophysiological Framework and Opportunities. Known pathophysiological alterations characterizing the AD course are briefly summarized (a) together with their main neural correlates (b). Proposed NiBS biomarkers and interventions associated with each of the pathophysiological alterations are suggested (c) ranging from the use of combined TMS-EEG as a biomarker of disease stage and progression, to frequency-specific tACS to restore altered intrinsic brain rhythms and abnormal protein accumulation, up to the study of brain networks dynamics and their modulation. In an ideal interventional timeline, NiBS biomarkers assessed at baseline could guide the tuning of the protocol based on the individual profile, including daily habits, to opt between different interventional plans (priming, synergistically combined with other training/activities, or as consolidation between cycles of activities). For the same reason, clinical outcomes should be directed toward the impact that NiBS interventions might have on the daily life of the individual, aiming toward improved cognition, mood, self-independence and overall greater resilience to the pathology, to guarantee a return/maintenance of a high life quality (d).

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Table 1

rTMS studies in AD: study participants, rTMS protocol and clinical outcome measures.

Year/Authors	AD (n)	rTMS	Real (n)	Sham (n)	Stimulation Site / sessions (n)	Study type	Administered cognitive tests and main findings
(Xingxing et al., 2021)	75 mild to moderate	20 Hz 100% RMT 2000 pulses	37	38	Left DLPFC 30 sessions over 6 weeks	Randomized, sham-controlled	Small but significant improvement at the administered MMSE and ADAG-Cog scales after 6 weeks of treatment.
(Brem et al., 2020)	34 mild to moderate	10 Hz 120% RMT *nr	16	18	Bilateral DLPFC, Left inferior frontal gyrus, left superior temporal gyrus, bilateral inferior parietal lobule. 30 sessions over 6 weeks	Randomized, sham-controlled, multicenter clinical trial	rTMS combined with cognitive training resulted in improvement at the ADAS-Cog in the 4–6 weeks after the end of stimulation.
(Zhang et al., 2019)	30 mild to moderate	10 Hz 100% RMT 1000 pulses	15	15	Left DLPFC and left lateral temporal lobe. 20 sessions over 4 weeks.	Randomized, sham-controlled	After 4 weeks of rTMS combined with cognitive training, patients' scores improved in the ADAS-cog, MMSE, ACE-III, in the subscales of word recall memory in the ADAS-cog, and in the domains of attention, memory, visual–spatial functions in the ACE-III. The improvement was still present at 4 weeks follow-up.
(Turriziani et al., 2019)	14 mild	1 Hz 90% RMT 600 pulses	7	7	Bilateral DLPFC. 10 sessions over 2 weeks.	Randomized, sham-controlled	Patients treated with real rTMS showed an improvement of recognition memory at the end of the two weeks of treatment, that persisted at 1-month follow-up.
(Sabbagh et al., 2019)	109 mild to moderate	10 Hz 110% RMT 1300 pulses	59	50	Broca's area; Wernicke's area; bilateral DLPFC; bilateral IPL. Daily sessions applied across 3 regions for 6 weeks.	Prospective, randomized, double-blind, sham-controlled, multicenter clinical trial	Patients with baseline ADAS-Cog <30 favorably responded to real stimulation with 31.7% participants showing 24-point improvement on ADAS-Cog versus 15.4% in the sham group.
(Koch et al., 2018)	14 prodromal	20 Hz 100% RMT 1600 pulses	14	14	Precuneus. 10 sessions over 2 weeks	Randomized, double-blind, sham-controlled, crossover	36% improvement at delayed recall at RAVLT.
(Zhao et al., 2017)	30 mild to moderate	20 Hz *nr *nr	13	17	P3/P4 and T5/T6 30 sessions over 6 weeks	Prospective, randomized, double-blind, sham-controlled	ADAS-cog, MMSE and WHO_UCLA AVLT scores significantly improved at 6 weeks follow-up compared to baseline. MoCA showed improvement in mild AD patients. Subgroup analysis showed rTMS effects in mild AD patients were superior to those of moderate AD patients.
(Lee et al., 2016)	26 mild to moderate	10 Hz 90–110% RMT 1200 pulses	18	8	Broca's area; Wernicke's area; bilateral DLPFC, bilateral parietal somatosensory associative areas 30 sessions in 6 weeks.	Prospective, randomized, double-blind, sham-controlled	ADAS-cog score significantly improved in patients receiving real stimulation combined with cognitive training both immediately after and at 6 weeks follow-up. MMSE and CGIC scores also improved in the treatment group. Subgroup analysis revealed the effect was superior for the mild group, especially in the domains of memory and language.
(Rutherford et al., 2015)	10 early to advanced	20 Hz 90–100% RMT 2000 pulses	10	10	Bilateral DLPFC. Stage 1: 10 sessions over 2 weeks with 3 additional maintenance sessions over 2 weeks (total 13 sessions); Stage	Stage 1: Double-blind, sham-controlled, crossover study; Stage 2: open-label,	Changes in MOCA scores were statistically significant after 2 weeks of real treatment, with stronger results in participants at the earlier stages of disease. At the 4-week follow-up, no statistically significant change was observed,

Year/Authors	AD (n)	rTMS	Real (n)	Sham (n)	Stimulation Site / sessions (n)	Study type	Administered cognitive tests and main findings
					2: 10 sessions over 2 weeks every 3 months	long-term follow-up.	but still there was a noticeable improvement in all assessed performances.
(Wu et al., 2015)	52 moderate	20 Hz 80% RMT 1200 pulses	26	26	Left DLPFC. 20 sessions over 4 weeks.	Randomized, double-blind, sham-controlled	After 4 weeks of antipsychotic treatment combined with real or sham rTMS treatment, the group receiving real stimulation had significantly greater improvement on the BEHAVE-AD total score and on the ADAS-Cog total score.
(Rabey et al., 2013)	15 mild to moderate	10 Hz 90–110% RMT 1300 pulses	7	8	Broca's area; Wernicke's area; bilateral DLPFC, bilateral parietal somatosensory associative areas. 30 sessions over 6 weeks followed by biweekly sessions for 3 months.	Randomized, double-blind, sham-controlled	Improvement in the average ADAS-cog and CGIC scores after 6 weeks in the group receiving real TMS combined with cognitive training. Improvement remained after 4.5 months of treatment, compared to mild worsening in the group receiving sham stimulation and cognitive treatment. NPI improved non-significantly.
(Ahmed et al., 2012)	45 (32 = mild to moderate, 13 = severe)	20 Hz 90% RMT 2000 pulses; 1 Hz 100% RMT 2000 pulses	20 Hz (n = 15) and 1 Hz (n = 15)	15	Right DLPFC stimulation followed by left DLPFC stimulation. 1 daily session for 5 days	Randomized, sham-controlled	20 Hz rTMS group improved more than the 1 Hz rTMS and sham at the MMSE, IADL, and GDS at all time points after treatment (immediately after, 1 and 3 months after). In the 20 Hz rTMS group, mild/moderate dementia improved in all rating scales, not observed in the severe dementia group instead. In the 1 Hz rTMS group, there was significant improvement in IADL in mild/moderate dementia only, with no significant changes in the other rating scales nor in the sham group.
(Cotelli et al., 2011)	10 moderate	20 Hz 100% RMT 2000 pulses	4 weeks (n = 5) and 2 weeks (n = 5)	2 weeks (n = 5)	DLPFC (Brodmann areas 8/9). Daily session of 5 days for 2/4 weeks	Prospective, randomized, sham-controlled	Significant amelioration on auditory sentence comprehension, with no significant effect on naming performance.

* *nr* = not reported; ACE-III = Adden-brooke's Cognitive Examination III; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive test; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; BDAE = Boston Diagnostic Aphasia Examination; CGIC = Clinical Global Impression of Change; CVSET = Complex Visual Scene Encoding Task; DLPFC = Dorsolateral Prefrontal Cortex; GDS = Geriatric Depression Scale; IADL = Instrumental Activities of Daily Living; IFG = Inferior Frontal Gyrus; IPL = Inferior Parietal Lobule; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test (-A or –B); WHO-UCLA AVLT = World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test.

Table 2

tDCS studies in AD: study participants, tES protocol and clinical outcome measures.

Year/Authors	AD (n)	tDCS	Real (n) (atDCS/ ctDCS)	Sham (n)	Site of Stimulation/ Sessions (n)	Study type	Administered cognitive tests and main findings
(Gangemi et al., 2020)	Study 1: 26 mild Study 2: 18 mild	2 mA, 20 min (2.5 mA/cm^2)	Study 1: 13 atDCS; Study 2: 9 atDCS	Study 1: 13; Study 2: 9	Anode: F7-T3, Cathode:Fp2; Study 1: daily for 10 days, Study 2: daily for 10 days each month, for 8 moths	Randomized, double-blind, sham-controlled	Participants receiving real stimulation maintained the same level of neuropsychological performance (positive effect on temporal and personal orientation, attention, calculation, recall, and in preventing worsening of apraxia symptoms) while the participants in the sham group showed a significant decrease. This was true both for the short and the long-term intervention.
(Im et al., 2019)	18 early	2 mA, 30 min (0.07 mA/ cm^2)	11 atDCS	7	Anode: F3, Cathode: F4; daily for 6 months	Randomized, double-blind, sham-controlled	Improvement in MMSE and BNT, but not in delayed recall. AtDCS marginally prevented executive function decrease.
(Lu et al., 2019)	201 mild	2 mA, 20 min (0.06 mA/ cm^2)	69 atDCS + working memory training 68 atDCS + control training	64 + working memory training	Anode: T3, Cathode: contralateral upper limb; 12 sessions over 4 weeks.	Randomized, double-blind, sham-controlled	tDCS + working memory training showed greater improvement in memory performance after a 4 weeks intervention, and at 8 weeks follow-up. Favorable transfer effects were observed on a broader spectrum of cognitive functions, including attention and language.
(Khedr et al., 2019a)	46 mild to moderate	2 mA, 20 min (0.06 mA/ cm^2)	23 atDCS	21	Anode: bilateral temporal lobe (T3-P3; T4-P4), Cathode: left arm; 10 sessions over 2 weeks.	Randomized, double-blind, sham-controlled	MMSE, clock drawing test, and MoCA significantly improved in the real group. The Cornell depression score improved significantly in real and sham groups. There was a significant increase in serum Aβ 1–42 in the real but not in the sham group. A significant positive correlation between changes of Aβ1–42 and MMMSE and MoCA was observed.
(Inagawa et al., 2019)	19 mild to moderate	2 mA, 20 min (0.06 mA/ cm^2)	19 atDCS	19	Anode: F3, Cathode: Fp2; Twice daily for 5 days	Randomized, double-blind, sham-controlled, crossover design	Patients receiving real tDCS did not show any significant change at the MMSE and ADAS-Cog compared to those receiving sham treatment.
(Roncero et al., 2017)	10 anomic	2 mA, 30 min (0.06 mA/ cm^2)	5 atDCS	5	Anode: left inferior parietal region, Cathode: right fronto-orbital area; 10 sessions per condition	Double-blind, crossover, pilot study	Small increase for untrained picture-naming items and digit span after atDCS, whereas performance decreased after sham. atDCS effects persisted 2 weeks after the end of the protocol.
(Bystad et al., 2016)	25 moderate	2 mA, 30 min (0.06 mA/ cm^2)	12 atDCS	13	Anode: T3, Cathode: Fp2; 6 sessions over 10 days	Randomized, double-blind, sham-controlled	Changes in the CVLT scores were not significantly different between atDCS and sham for recognition, immediate and delayed recall. There were nonsignificant differences in score at the MMSE, clock-drawing test, and TMT-A and B.
(Khedr et al., 2014)	34 mild to moderate	2 mA, 25 min (0.08 mA/ cm^2)	11 atDCS, 12 ctDCS	11	Anode: left DLPFC, Cathode: controlateral supraorbital region; 10 sessions for each stimulation modality.	Randomized, double-blind, sham-controlled	Both atDCS and ctDCS improved MMSE compared to sham, whereas ctDCS improved performance IQ.

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(Suemoto et al., 2014)	40 moderate	2 mA 20 min (0.06 mA/ cm^2)	20 atDCS	20	Anode: left DLPFC, Cathode: controlateral supraorbital region; 6 sessions during 2 weeks.	Randomized, double-blind, sham-controlled	Changes on apathy over time were not different between atDCS and sham.
(Cotelli et al., 2014)	36 mild to moderate	2 mA, 25 min (0.08 mA/ cm^2)	12 atDCS + individualized memory training 12 atDCS + motor training	12 + individualized memory training	Anode: left DLPFC, Cathode: right deltoid muscle. 10 sessions over 2 weeks.	Randomized, double-blind, sham-controlled	Both the atDCS + individualized memory training and the sham + individualized memory training groups had significantly improved performances at 2 weeks compared with the atDCS + motor training group.
(Boggio et al., 2012)	15 mild to moderate	2 mA, 30 min (0.06 mA/ cm^2)	15 atDCS	15	Anode: T3 and T4, Cathode: controlateral deltoid muscle; Daily for 5 days	Sham-controlled, crossover design	Visual recognition memory improved for at least 4 weeks after atDCS. No effect was reported on general cognitive performance nor for visual attention measures.

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive test; BNT = Boston Naming Test; CVLT = California Verbal Learning Test; MMSE = Mini-Mental State Examination; TMT = Trail Making Test; WRT = Word Recognition Test.