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NONINVASIVE BRAIN STIMULATION IN PATHOLOGICAL BRAIN AGING ON EARTH AND SPACE EXPLORATION: FROM PERSONALIZATION TO INNOVATIVE APPLICATIONS.

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1. INTRODUCTION

During the three years of my Ph.D., I studied and investigated different protocols of noninvasive brain stimulation (NIBS) techniques and their underlying mechanisms of action. NIBS defines a wide range of protocols and devices relying on electromagnetic principles to noninvasively influence neural activity through the generation of electrical fields. Over the last two decades, they have been extensively used to investigate the neural basis of many cognitive and sensory-motor domains, as well as potential therapeutic interventions to restore physiological brain activity in psychiatric and neurological diseases. Specifically, I focused on two main classes of NIBS: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). My goal was to identify innovative TMS and tES applications that could be implemented to counteract harmful consequences following pathological aging and neurodegeneration on Earth and in space exploration. To increase NIBS success in these domains, I explored a new personalized approach to optimize stimulation adapting it to brain modifications due to pathological aging, as well as space missions. I start with a brief introduction (**Chapter 1**) to explain the outline of the dissertation.

In **Chapter 2** I present a detailed overview of the technical aspects of the NIBS techniques**,** including different TMS and tES protocols, and their previous applications in the literature. Although NIBS protocols can successfully target single brain regions, multiple studies moved to a network-oriented approach while investigating NIBS efficacy. This framework allows the simultaneous stimulation of different brain areas belonging to the same or different networks, imitating a more natural cortical activation and thus offering a more efficient stimulation. I discuss the advantages of this new targeting approach, along with the safety profiles of both TMS and tES, and their comparison to different techniques of NIBS, such as focused ultrasound.

Then I elaborate on the previous literature identifying domains and cohorts of patients that could most benefit from NIBS interventions. My goal was to familiarize myself not only with modalities on how to improve NIBS efficacy, but also to find innovative applications that could be exploited with better chances to help patients and research investigation. In my opinion, NIBS interventions targeting sleep might represent an excellent opportunity not only to maintain life quality in the healthy aging population, but also to enhance cognitive performance and, when pathology arises, to actively intervene to slow down the clinical symptoms. To investigate potential NIBS applications modulating sleep in pathological aging I first focused on Alzheimer's Disease (AD), and how to intervene in the prognosis and cognitive abilities of AD patients. Sleep changes are considered one of the earliest biomarkers of AD diagnosis. I performed extensive literature and collected up-to-date evidence of the relationship between sleep modifications in healthy aging and the neuropathological cascade responsible for AD clinical symptoms. Furthermore, I provide a critical analysis that explained how sleep abnormalities influence the prognosis of AD pathology, by intensifying Aβ and tau protein accumulation. I then discuss potential NIBS strategies to target sleep disruptions. Specifically, tES may help investigate the neural substrates of sleep, as well as identify sleep-related

pathology biomarkers, and ultimately help patients and healthy elderly individuals to restore sleep quality and cognitive performance. I consider the opportunities and practical challenges of implementing NIBS to modulate sleep in both healthy individuals and AD patients. Interestingly, previous literature published by our group elaborated on a pattern of accelerated brain aging induced by space-flight. Astronauts involved in long-duration space-flight missions are indeed exposed to specific risk factors known to induce severe changes in brain structure and function. Cosmic radiations, specifically, seem to promote the accumulation of amyloid-β in mouse models and trigger neuroinflammation, resulting in the alteration of hippocampal-related cognition. Seen the similarities with neurodegenerative diseases, I explore potential NIBS applications in space missions and suggest Earth-based NIBS protocols to accelerate/consolidate training before missions, as well as identify post-flight biomarkers of brain changes/adaptation and guide recovery. In-flight NIBS could also be implemented to enhance crew performance and psychological well-being, but further validation of mission-specific protocols will be needed. The knowledge I gained on NIBS solutions in neurodegenerative diseases and space missions resulted in three published review papers and a perspective/position manuscript, integrated into one section of the thesis (**Chapter 3**).

Following this theoretical background, the remaining chapters (4, 5, and 6) elaborate on the main goal of the dissertation by actively identifying and testing how to improve NIBS practical applications. However promising, the impact of NIBS can be drastically altered by changes in brain morphology, such as functional and structural cortical modifications triggered by neurodegenerative diseases. Along with a standard inter-individual variability, cortical atrophy typical of AD would result in fundamental differences in electromagnetic field exposure across patients. Ignoring these modifications would raise safety concerns or hinder NIBS efficacy. To overcome these issues, during my second year, I started creating realistic individual 3D computational models of the head and running simulations (with both tES and TMS) to predict the distribution of electric fields. This process would allow the personalization of NIBS treatment and would provide better control of the electric field to achieve greater efficacy in AD patients. Changes in brain morphology are not only induced by pathological brain aging and AD, but also by time spent in deep space, due to many space stressors, such as cosmic radiations and microgravity, as previously introduced. Over the course of my Ph.D., I had the incredible opportunity to have access to neuroimaging data collected on a group of Russian ROSCOSMOS cosmonauts. To test the potential efficacy of NIBS on this special cohort, I ran a computational study testing how morphological changes caused by space-flight would impact the TMS-induced electric field. To overcome individual and space-associated structural differences, I segmented the MRI scans collected on ROSCOSMOS cosmonauts before and after their six-month space-flight, along with data from a control group of non-flying participants. I simulated the electric field generated by TMS over four different brain regions associated with primary cognitive and sensory functions and analyzed differences in Cerebrospinal Fluid (CSF) as well. My results show that cosmonauts showed a significant increase at post-flight in TMS-induced E-field over the primary motor cortex and a decrease in the electric field reaching the angular gyrus as compared to healthy controls. An increase in CSF volume after space-

flight was observed in both groups and it was partially responsible for the differences. Thanks to biophysical modeling and simulations, I then offer a few examples of TMS personalization based on individualized neuroimaging data. **Chapter 4** presents the advantages of using biophysical modeling in studies, and includes a manuscript presenting the findings from the cosmonaut cohort, as well as multiple published studies in AD patients to either identify potential optimal targets for NIBS data collection and/or analyze the results correcting for e-field.

While refining the modalities to optimize and personalize the stimulation, I came across a potential issue in NIBS experimental paradigms. A strong placebo response, often seen in NIBS protocols, could confound the effect induced by the treatment. The reason behind this might be explained by an overlap in the cortical regions targeted in NIBS studies with neural correlates of the placebo effect. As an example, NIBS interventions frequently target the left dorsolateral prefrontal cortex (DLPFC) to treat psychiatric diseases, as well as enable cognitive enhancement. On the other side, several lines of evidence confirmed that this region might be partially responsible for the emergence of placebo response. The presence of the placebo effect is therefore difficult to identify and exclude in clinical trials and research studies employing NIBS techniques. One could argue that active stimulation might, in fact, just activate regions responsible to induce placebo effects per se. Knowing the relevance of this reasoning in planning future neuromodulation studies, I decided to further investigate the exact neural correlates underlying the phenomenon. In the last decade, various single neuroimaging studies examining placebo effects have been published. This offered an opportunity to group the knowledge and further investigate the underlining regions associated with the induction of placebo response. In **Chapter 5**, I, therefore, present the results of two different studies I ran on investigating placebo effects. First, I performed a meta-analysis in healthy volunteers aimed to identify placebo-responsible regions and networks. The findings not only help in further tailoring NIBS studies to take into consideration placebo effects but also offer a new exciting and potential opportunity for NIBS applications. NIBS techniques could manipulate the placebo effect by modulating the activity and excitability of placebo-associated regions. Furthermore, I noticed that large placebo responses have been observed in many NIBS treatment trials to treat depression. To investigate the potential overlap with regions/circuits specifically targeted by depression treatments and what the implications of this overlap would be on measuring efficacy in placebo-controlled clinical trials, I performed a second meta-analysis including both healthy subjects and the patient population. After identifying a common set of brain regions implicated in placebo effects across healthy individuals and patients, I provide evidence that these regions indeed overlap with depression treatment targets. This confirms that NIBS treatments might be modulating the same regions/networks as placebo effects. This finding has critical implications for the optimization of future NIBS protocols in this field to control for placebo effects.

Finally, I applied this knowledge to practical applications. I had the chance to personally design experimental paradigms aimed at testing NIBS protocols. In **Chapter 6** I present in detail three original studies I ideated and was responsible for, with the invaluable help and collaboration of colleagues and

supervisors. The first two studies were planned and run at the Siena Brain Investigation and Neuromodulation Lab (Si-BIN Lab, Siena), where I spent the first half of my Ph.D. As aforementioned, manipulating sleep via NIBS could potentially counteract the detrimental effects of pathological aging. Specifically, both healthy elderly and AD patients present difficulties falling asleep, as measured in an increased and delayed sleep-onset latency (time required to fall asleep). Therefore, my **first study** aimed to induce sleepiness via tES. The goal was to prove the feasibility and efficacy of the tES protocol to actively modulate drowsiness and potentially shorten the time required to fall asleep. Healthy participants came to the Si-BIN Lab after lunch and performed a sleepiness-induced task while laying on a bed in a dark and temperature-controlled room with their eyes closed. After establishing a baseline (first session), they performed the task during a block of 20-minute stimulation. We chose a protocol of transcranial alternating current stimulation (tACS) for its ability to entrain spontaneous brain oscillations, by administering current with a specifically chosen frequency. We included 3 tACS conditions: stimulation in beta frequency (20Hz), in the theta range (6Hz), and sham. Our goal was to stimulate regions functionally connected to some sub-cortical areas responsible for sleep induction, such as preoptic area, suprachiasmatic nucleus, and pineal gland. Thanks to the knowledge developed on biophysical modeling and NIBS personalization, I was able to identify an optimized montage to successfully engage the activity of these structures through a network effect. We collected and analyzed pre- and post-task behavioral and EEG data. Our results showed that theta-tACS induces significant post-stimulation sleepiness on self-report measures such as the Karolinska Sleepiness Scale, with no effects for stimulation in other frequency bands. Reaction times recorded for each stimulus during the task also show significantly increased cognitive slowing/drowsiness during theta-tACS. Analysis of eyes-closed resting-state EEG pre and post theta-tACS showed that this stimulation also induced a sleepiness-associated EEG pattern. Our preliminary findings suggested the feasibility and success of theta-tACS with an optimized montage to induce sleepiness and potentially shorten sleep onset latency. We are now looking to test this protocol on elderly at risk to develop AD (beta-amyloid positive or preclinical) and patients with a current diagnosis of MCI/AD.

During the second year, my colleague Dr. Francesco Neri and I also conceptualized a combination of repetitive TMS (rTMS) and speech therapy to enhance linguistic abilities in patients with dementia. Although the pandemic stopped the data collection of this **second study**, due to the high risk of contracting the virus in the elderly, we were able to collect some preliminary data on two patients with Logopenic Primary Progressive Aphasia (lvPPA). LvPPA is a form of dementia characterized by a slowly progressive cognitive deterioration, firstly affecting language. Speech impairments include difficulties in repetition, phonological errors, anomies, along with sub-optimal language comprehension. We enrolled two 70 and 80yo male lvPPA patients who came to the lab and underwent 10 consecutive days of rTMS to improve linguistic abilities. Excitatory rTMS was real-time guided with a neuro-navigation system, individualized to specifically target the patient's left Broca area. Immediately after each rTMS session, thus capitalizing on its neuromodulatory after-effects, patients underwent one-hour speech therapy with a trained

therapist. Before and after the treatment, we assessed potential improvement in language with a neuropsychological assessment and collected the resting-state functional connectivity (rsFC) changes by functional magnetic resonance imaging (fMRI). Our findings showed that the combined intervention successfully improve linguistic abilities, namely verbal fluency naming, repetition of real words, and forward digit span. In both patients, cognitive improvement was also accompanied by changes in brain activity patterns involving alternative language networks. Although the results are already promising, we look forward to further developing this combined treatment for dementia by optimizing the rTMS protocol to personalize the intervention based on the individual brain morphology.

During the second half of the Ph.D., I moved to Boston to collaborate with the Berenson-Allen Center for Noninvasive Brain Stimulation and the Gordon Center for Medical Imaging, Massachusetts General Hospital, at Harvard Medical School (Boston, MA, USA), under the supervision of Prof. Emiliano Santarnecchi. In Boston, I had the opportunity to work on a study investigating brain resilience employing a combination of TMS and concomitant electroencephalography (EEG) recording (TMS-EEG). This protocol enables a deeper investigation of local reactivity and neural connectivity mechanisms. The EEG can measure brain dynamics in response to a perturbation to neuronal networks caused by a TMS pulse. The goal of this **third study** was to test if exposure to external stimulation, such as TMS, could momentarily modulate brain resilience. First, resilience reflects the ability of a complex system to sustain damage while still maintaining a proficient level of functioning. At the neural level, the brain's resilience to focal lesions or diffuse pathological processes develops as a function of favorable genetic predispositions and exposure to enriched environments. This is particularly relevant in situations where the neuropathology caused by a disease, such as AD, impacts brain networks (e.g. due to beta-amyloid plaques) and therefore results in a loss of connections and functions. Manipulating the activity within specific networks via NIBS could open the opportunity to enhance brain resilience in both healthy cohorts and patients. To test this idea, a group of healthy subjects underwent a single-pulse TMS protocol during targeting two regions belonging to two negatively correlated networks: the Dorsal Attention (DAN) and the Default Mode (DMN) networks. First, we tested for induced changes in network topology using graph theory analysis, followed by the exploration of resilience through an in silico lesioning procedure, testing the ability of the network to resist the progressive removal of its nodes and edges. Results prove that, for both networks tested, the delivery of a TMS pulse changed some resilience indexes, by inducing an immediate significant reduction in the measure of modularity. TMS targeting the DMN was also accompanied by a transient increase in the measures of clustering coefficient and local efficiency. Interestingly, all such TMS-induced changes in topology were significantly correlated with the increased resilience of the brain network in silico to the targeted removal of its edges. Although exploratory, to our knowledge no previous studies tested the possibility to act on the brain wiring to improve its resilience to external perturbation, possibly opening a new research line toward future brain shielding interventions with NIBS.

In the last chapter, I conclude this thesis with a general discussion of the limitations of this work and a summary of the contributions I hopefully provided to the literature. I look forward to the future challenges and opportunities in NIBS research that might provide new treatments to help people.

2. NONINVASIVE BRAIN STIMULATION TECHNIQUES

As aforementioned, NIBS encompasses techniques able to modify brain activity employing controlled, high-resolution transcranial delivery of electric field stimuli. They have been extensively used to investigate the neural basis of many cognitive and sensory-motor domains, as well as potential therapeutic interventions to restore physiological brain activity in psychiatric and neurological diseases. Specifically, two main classes of NIBS are currently applied for clinical and research purposes, TMS and tES (Figure 1). Here, we offer an overview of both techniques, covering their underlying mechanisms of action and the most validated protocols. We will also review the safety and feasibility of NIBS protocols, discussing the advantages and limitations of these techniques over other forms of stimulation.

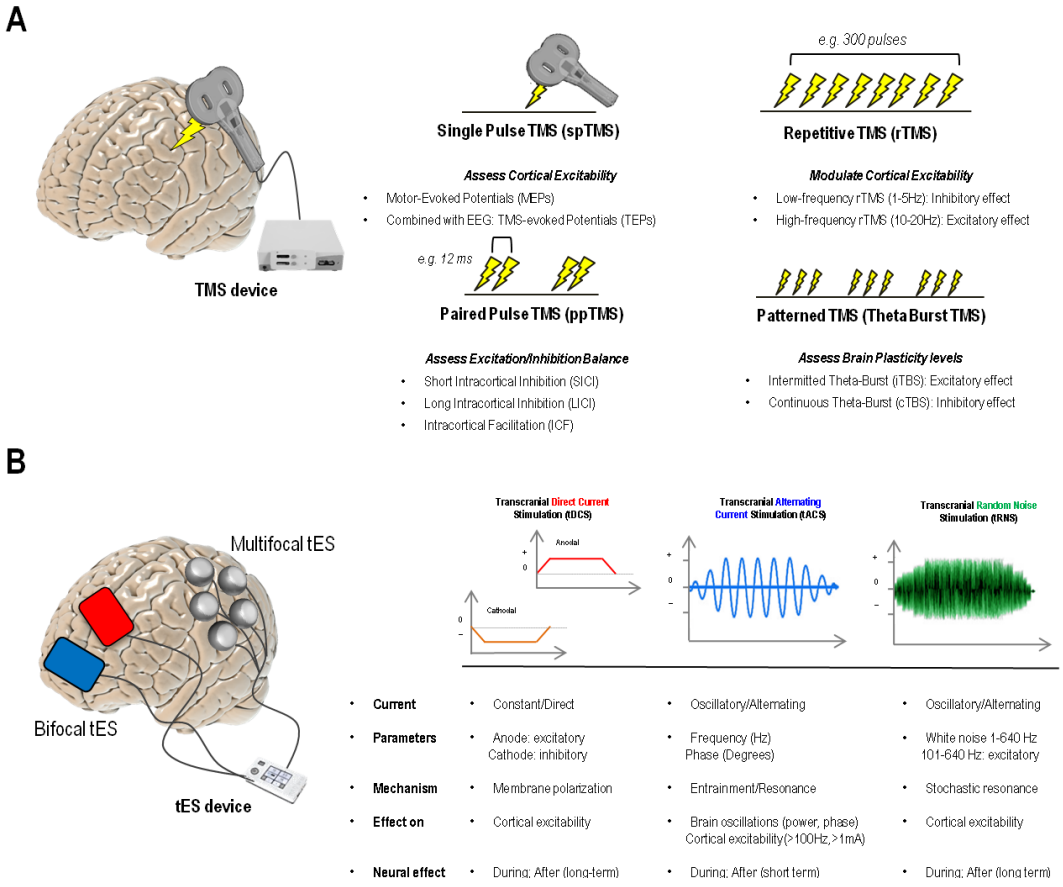


Figure 1. Noninvasive Brain Stimulation Techniques. **Panel A.** Transcranial Magnetic Stimulation (TMS) relies on the electrical current going through a conductive coil, inducing a time-varying focal high magnetic field (~2T) that generates a strong electric field (>100 V/m) directly causing neuronal spiking with a high spatial resolution (~0.5^3 cm of activated brain tissue) (down, left). Different TMS protocols can be implemented by delivering trains of TMS pulses (repetitive TMS- rTMS) or by pairing pulses, inducing various effects including increase/decrease of corticospinal excitability, increase/decrease in cortical plasticity, modulation of brain excitatory/inhibitory balance, and changes in local connectivity and blood flow/perfusion. **Panel B**. Transcranial Electrical Stimulation (tES) requires at least two electrodes (red=anode, blue=cathode), with at least one applied directly on the scalp (up, left). More channels can be added to extensively record EEG and/or perform high-resolution "multifocal" tES. Available protocols include transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). Stimulation protocols differ from one another and allow to induce changes in cortical excitability, as well as more specific effects on brain oscillations, e.g., the α or γ rhythms.

2.1. Transcranial Magnetic Stimulation

TMS is based on Faraday's principle of electromagnetic induction: a pulse of electrical current flows through loops of wire (forming the coil) and generates a time-varying magnetic field that in turn creates an electric field. The induced electric field alters ions' disposition and depolarizes neurons to the point of triggering an action potential. Different electric field strengths and forms can be generated by TMS through the modification of physical and biological parameters, such as magnetic pulse waveform, coil shape, orientation, intensity, frequency, and patterns of stimulation (Rossi et al., 2009a).

When **single-pulse TMS (spTMS)** is applied to the motor cortex (M1), the stimulation activates the corticospinal descending pathways triggering the motor-evoked potentials (MEPs). MEPs can be recorded through electromyographic recordings from contralateral muscles from the stimulation (Rossi et al., 2009). RMT refers to the lowest TMS intensity necessary to evoke an MEP in a target muscle with an amplitude of 50μV with at least a 50% probability (Rossi et al., 2009). RMT reflects the membrane excitability of corticospinal neurons and interneurons projecting onto the M1, as well as the excitability of motor neurons in the spinal cord and neuromuscular junctions (Rossi et al., 2009).

Paired-pulse TMS (ppTMS) protocols consist of 2 successive pulses with an inter-stimulus interval (ISI) ranging from a few milliseconds to hundreds of milliseconds. Both pulses are generally applied over the M1 of the dominant hemisphere. This method is used to explore intracortical networks depending on the intensity and ISI used (Kujirai et al., 1993; Valls-Solé et al., 1992). ISI of a few milliseconds is generally used to investigate short intra-cortical inhibition (SICI) mechanisms that are thought to reflect GABAergic interneurons activity (Rossi et al., 2009). ISIs between 7-20ms is chosen instead for intra-cortical facilitation (ICF) mechanisms, primarily reflecting glutamatergic interneurons activity (Kujirai et al., 1993). TMS pulses delivered over the M1 of both hemispheres can be useful to explore inter-hemispheric inhibition (e.g., transcallosal inhibition; Ferbert et al., 1992).

Contrary to spTMS and ppTMS, **repetitive TMS (rTMS)** can change and modulate cortical activity beyond the stimulation period. The physiological bases of rTMS after-effects have not yet been identified, but the main underlying mechanisms seem to involve long-term potentiation (LTP) and long-term depression (LTD). LTP is defined as an increase in synaptic strength, whereas LTD reflects a decrease (Klomjai et al., 2015). Accordingly, rTMS protocols affect the excitability and neuroplasticity of a stimulated area outlasting TMS duration per se, depending on inter-individual variability (Maeda et al., 2000a) as well as on the stimulation parameters, leading to a decreased cortical excitability when low-frequency rTMS (≤1 Hz) is applied, whereas an increase is seen following high-frequency rTMS (≥5 Hz) protocols. rTMS applications have been mainly used to study cognition, brain-behavior relations, and the pathophysiology of various neurologic and psychiatric disorders. New rTMS approaches involve the application of high-frequency bursts of stimuli at theta frequencies, known as **theta-burst stimulation (TBS).** Stimulus intensity required for TBS is lower compared to other rTMS protocols (Huang et al., 2005) and can be applied in a continuous

(cTBS) or intermittent (iTBS) fashion depending on the purpose: cTBS tends to depress excitability of the M1, while iTBS has the opposite effect (Huang et al., 2005).

While stimulating the scalp, the resulting electrical field produced current density distributions that are asymmetrical in magnitude and direction. Because TMS has a spatial resolution of approximately 0.5-1cm (Thielscher and Kammer, 2002a; Toschi et al., 2008), precise targeting of the area to stimulate is pivotal for the outcome. To finely target areas, especially when a rapid and objective outcome measure cannot be revealed such as for M1 with MEP and MT, navigated brain stimulation (NBS) has been developed. NBS devices consist of infrared camera-detecting trackers placed on a headband worn by the subject and on the coil. Using Magnetic Resonance Imaging (MRI) brain data, NBS can rebuild the subject's head in 3-D and record coil position, ensuring better accuracy in targeting the chosen areas and as well as to have a finer estimation of the strength and direction of TMS-induced electrical field.

2.2. Transcranial Electrical Stimulation

tES applies low transcranial electrical currents (0.5-2mA) that generate weak electric fields to target specific brain areas, allowing for the sub-threshold modulation of firing properties of cortical neurons and ongoing rhythmic brain activity. Various tES protocols can be implemented through different stimulation parameters, such as shape, position, number of electrodes, current waveform, frequency, and duration of stimulation. The electrical current is delivered through two or more surface electrodes placed on the scalp and connected to a current waveform generator. Transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) are the most common protocols (Paulus, 2011).

tDCS. tDCS induces a low-amplitude (0.5-2mA) direct current that modulates brain excitability eliciting neuronal membrane modifications depending on the direction of the generated electric field (Ruffini et al., 2013). Current flows from the anodal electrode to the cathode, creating intracranial electric fields that alter cell membrane depolarization (i.e., increase of excitability) underneath the anode, and hyperpolarization (i.e., decrease of excitability) in the cathode (, with plastic effects. Anodal tDCS over M1 has indeed been shown to increase MEP amplitude, whereas cathodal tDCS decreases it. In particular, tDCS brings the underlying neurons closer or further from their firing threshold (Bikson et al., 2004), leading to an increase in glutamine and glutamate levels and/or decreasing γ-aminobutyric acid (GABA) concentrations. N-methyl-D-aspartate (NMDA) receptor-dependent mechanisms as well as brain-derived neurotrophic factors (BDNF, Fritsch et al., 2010) also play a key role. Although the increased duration and/or intensity of stimulation might be assumed to maximize tES effects, studies have suggested that the dose-response relationship is nonlinear (Batsikadze et al., 2013; Kidgell et al., 2013; Monte-Silva et al., 2013). Jamil and coworkers (2017) have recently investigated tDCS dose-dependency by systematically measuring neuroplastic responses to stimulation. Healthy participants received anodal or cathodal tDCS applied for 15 min to left M1 at different intensities: sham, 0.5, 1.0, 1.5, and 2.0 mA. MEPs elicited by single-pulse TMS were recorded before and at

multiple time points up to 2h following stimulation to quantify M1 plasticity. Results indicated a nonlinear relationship between stimulation intensity and the induced neuroplastic response, for both anodal or cathodal tDCS. Consistent with previous research (Labruna et al., 2016), they found that the facilitatory response seen after 1.0 mA anodal tDCS was greater in participants with higher sensitivity to TMS (i.e., those requiring a lower TMS intensity to elicit MEPs). This relationship is currently assumed to reflect inter-individual differences in anatomical (e.g. skull thickness, cortical morphology) and physiological (e.g. neurotransmitter availability and receptors distribution) factors, that similarly affect NIBS techniques both online (Labruna et al., 2016) and after stimulation (Ridding and Ziemann, 2010). Modifications in synaptic strength are also enabled/hampered by a mechanism of homeostatic plasticity that may cause further variability in efficacy. Synaptic connection is, in fact, facilitated/suppressed depending on the previous amount of network activity. As an example, Monte-Silva and coworkers (2010) found that the efficacy of inhibitory cathodal tDCS could be enhanced when followed by a second session of stimulation during the aftereffects of the first one. On the other hand, the effect was significantly reduced if the second stimulation was applied when the aftereffects of the first session were dissipated (Montesilva et al., 2010). This will furthermore require particular attention when planning multiple sessions of stimulations and testing tDCS efficacy.

tACS. Most aspects of human cognition show corresponding patterns of brain oscillatory activity, determined by the synchronous neuronal firing across different spatial and temporal scales. Therefore, the chance to engage in oscillatory activity, rather than simply increase or decrease activity in a target region as with tDCS, could lead to a more powerful, finer control of brain activity and corresponding behavior. In this regard, tACS has been suggested as the most promising technique to safely and noninvasively modulate brain rhythms. tACS delivers alternating current that continuously shifts between positive and negative electric fields (Tavakoli and Yun, 2017), thus inducing periodic shifts in the transmembrane potential, alternating depolarizing and hyperpolarizing effects, enabling the entrainment of intrinsic brain oscillations due to its sinusoidal waveform. In particular, tACS drives cortical populations to oscillate at the same natural frequency as the one delivered by the stimulation itself, with a greater amplitude as per the resonance phenomenon (Paulus, 2011). As with tDCS, it also allows stimulation over multiple brain regions at the same time, i.e. favoring synchronization or tACS can be applied over a wide frequency range, from 0.75Hz during NREM sleep to enhance declarative memories (Ketz et al., 2018), to γ frequency (40-80Hz) to modulate fluid intelligence (Santarnecchi et al., 2013), problem-solving ability (Santarnecchi et al., 2019), and visuospatial coordination (Santarnecchi et al., 2017). Behavioral effects have been demonstrated at the level of sensorimotor (Feurra et al., 2011, 2013; Santarnecchi et al., 2017), visual (Kanai et al., 2008), somatosensory (Feurra et al., 2011b), and higher-order cognitive domains (Polania et al., 2012; Santarnecchi et al., 2013).

tRNS. Differently, tRNS elicits an increase of cortical excitability with stimulation delivered in the form of random noise, produced through electrical patterns at a random frequency over a broad spectrum (0.1–640Hz; Terney et al., 2008). tRNS can increase or decrease the excitability at different intensity range

(Moliadze et al., 2012). This type of stimulation is thought to induce long-term potentiation of cortical plasticity through different mechanisms, for example through the repeated opening of sodium channels (Terney et al., 2008). Indeed, in a pilot study on tRNS application over the M1, MEPs were inhibited by carbamazepine, a Sodium (Na+) channel blocker (Chaieb et al., 2015). As second hypothesized mechanisms of action, tRNS might act using stochastic resonance (Miniussi et al., 2013), according to which weak signals can be amplified by the addition of noise (McDonnell and Abbott, 2009). In this sense, random noise added to subthreshold neural oscillations in the brain would result in a summation of the two currents strong enough to exceed the threshold. To date, few studies have investigated the effects of tRNS in modifying EEG features, mostly focusing on a simple motor or sensory tasks (Fertonani et al., 2011; Terney et al., 2008). As demonstrated via spTMS, tRNS seems to be the most effective tES technique to increase cortical excitability of the M1 Although the potential applications of tES protocols to modulate cognitive and motor abilities are well-known and replicated, they also require particular attention to factors that may affect the results of stimulation (for a comprehensive review see Krause and Kadosh, 2014). Different studies over the last decade have shown varying results between individuals due to the differences in cortical activity (Krause et al., 2013), tissue composition under the stimulating electrodes (Russell et al., 2013), age (Leach et al., 2019), and gender (Russell et al., 2017). Moreover, the proportion of individuals fail to respond to stimulation altogether (López-Alonso et al., 2014). Besides, the electric field resulted by tES protocol can be significantly altered by various parameters of methodological decisions, such as current intensity (Bastani and Jaberzadeh, 2013), electrode placement (Moliadze et al., 2010), and current phase and frequency in the case of tACS and tRNS (Nakazono et al., 2016).

2.3. Combine TMS and tES with electroencephalography (TMS-EEG and tES-EEG)

The combined use of TMS and EEG enables a deeper investigation of local reactivity and neural connectivity mechanisms. Indeed, TMS can be used to perturb neuronal networks, while EEG can enable the measurement of brain dynamics in response to perturbation (Figure 2). TMS pulse to a specific region is indeed known to evoke activation over secondary interconnected cortical areas. For this reason, TMS-EEG has become of particular interest to study causal communication connections between distant brain regions with a high temporal resolution, providing insights into mechanisms of effective connectivity (Friston et al., 1993; Massimini et al., 2005). When a single TMS pulse is applied over a specific cortical region, the transmission of generated activity can be detected by space-temporal analysis of TMS-evoked potentials (TEPs; Ilmoniemi et al., 1997). Furthermore, time-frequency analysis allows to measure TMS evoked cortical oscillations, highlighting how different cortical areas resonate at specific frequencies in response to perturbation (e.g. alpha in the occipital cortex, beta in the motor cortex), mirroring their dominant (so-called "natural") spontaneous regional oscillatory activity (Rosanova et al., 2009).

Like TMS-EEG, tES can be successfully combined with EEG to provide information about perturbation biomarkers. Specifically, EEG is used to probe the state of the cortical area affected by tES (either the stimulation site itself or an interconnected region) and to evaluate tES-induced connectivity and excitability

modifications within a functional network (Miniussi et al., 2012). By studying Event-Related Potential (ERPs), i.e., time-locked EEG deflections triggered by specific external or internal signals (Buzsáki, 2009), it would be possible to investigate activity modulation induced by tES in specific cortical regions (Miniussi et al., 2012), indexed by changes in amplitude or latency of the ERPs generated by somatosensory, visual or auditory stimuli. tES-EEG assessments during a space mission can help identify potential biomarkers associated with different environments or diseases inducing changes in cortical excitability, phase-coherence, and other connectivity metrics.

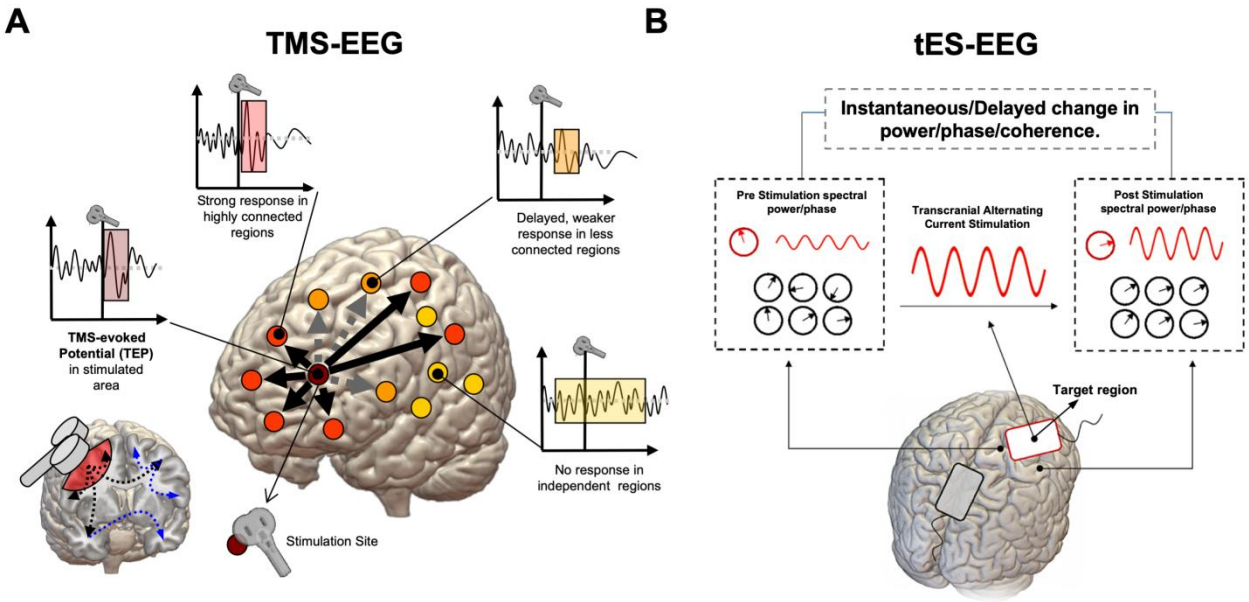


Figure 2. Perturbation-Based Sleep Biomarkers via Combined TMS-EEG and tES-EEG Recording. Brain Stimulation techniques can be combined with electrophysiology, as in the case of simultaneous TMS-EEG and tES-EEG recording. In the case of TMS, a focal magnetic pulse is delivered to a specific brain region using a neuronavigation system (based on an individual's MRI) which allows for precise anatomical targeting of cortical areas at 1-millimeter resolution (**Panel A**). The activity elicited by the pulse is mostly local, with distant effects usually observed for regions structurally or functionally connected to the stimulation site (i.e., orange dots). Both local reactivity and short-long range connectivity can be evaluated, either in terms of TEPs or time-frequency analysis. Indirect connections via third regions are also possible (blue and grey dashed lines), creating a complex topography. Individual response to TMS may differ in terms of the number of regions reacting to the TMS pulse, as well as for the timing of the response: strongly connected regions might show bigger and earlier responses to TMS, while distant or out-of-network regions might show delayed or even no responses. While TMS provides higher spatial resolution, when applied using alternating current, tES allows for frequency-specific modulation of brain electrical activity by supposedly tuning neuronal populations towards an externally induced oscillatory pattern (**Panel B**). The response to tACS can be expressed in terms of spectral power changes during and/or after stimulation, as well as phase-coherence and other connectivity metrics, with the effects being measurable both at the stimulated area as well as in other distant, resonant regions.

2.4. Network Targeting with NIBS

The same approach can be used to target brain functional networks. Brain activity is organized in a set of resting-state functional networks (RSNs) whose synchronized activity span between spatially distinct interconnected regions (Figure 3, Panel A). Functional connectivity (FC) within the networks can be measured via fMRI. RSNs involve areas responsible for both sensory processing as well as for high-order cognition. The most studied networks include the Default Mode Network (DMN), Frontoparietal

Control Network (FPCN), Sensorimotor (SM), Ventral Attention Network (VAN), Anterior Salience Network (AS) (Damoiseaux et al., 2006; Heuvel et al., 2009; Zuo et al., 2010). The DMN is particularly relevant due to its pivotal role in the spontaneous activity of the human brain and because of its vulnerability to modifications due for instance to extreme conditions such as deep space missions.

Although studies have administered stimulation over singular specific derivations (Figure 3, Panel B), new devices enable multisite stimulation of neural networks, engaging interconnected cortical areas as well as entire networks (Dmochowski et al., 2011; Miranda et al., 2013a; Ruffini et al., 2014). To do that, multifocal stimulation using several relatively small electrodes has been used to achieve more focal stimulation of specific cortical targets (Ruffini et al., 2014). This allows a spatially specific protocol that can simultaneously stimulate different areas belonging to the same (e.g. DMN) or different networks. Modulating a whole network associated with brain function may also imitate a more natural cortical activation, therefore offering a more efficient stimulation.

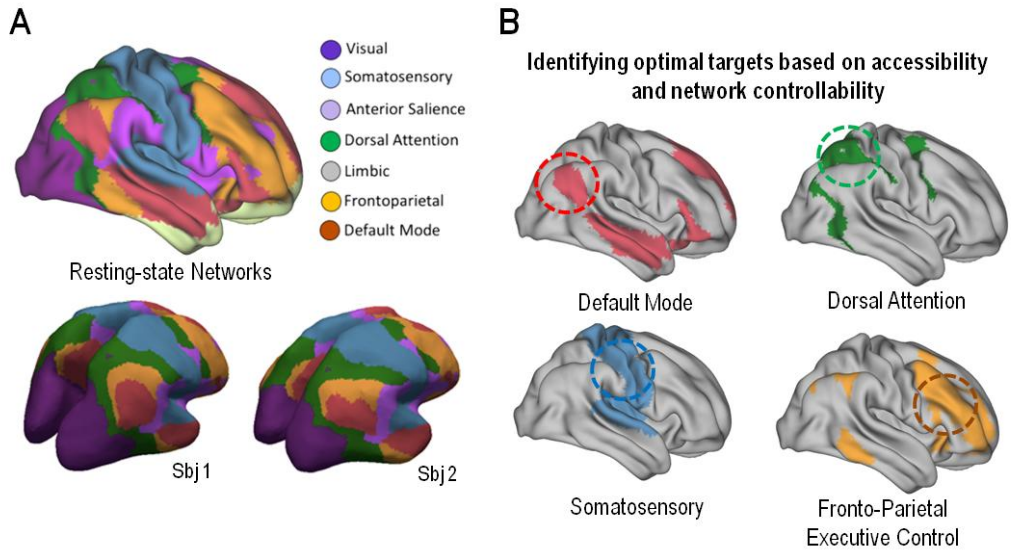


Figure 3. Network Targeting. Panel A. Network mapping can help to identify the topography of known brain networks using structural and functional MRI data. **Panel B.** We can then further identify optimal stimulation site(s) for each network/individual based on criteria including targetability (i.e. location of target area) and propagation ability within the target network.

2.5. Safety and Tolerability of NIBS

TMS is a safe and well-tolerated intervention with generally mild side effects and only rare serious adverse effects. TMS safety guidelines are available under the support of the International Federation of Clinical Neurophysiology (IFCN; Rossi et al., 2009). Parameters that can impact the tolerability of treatment include the intensity of stimulation (relative to patient cortico-spinal activation threshold), pulse frequency, duration of the pulse train, and inter-train interval. The most common TMS adverse effects are local pain under the stimulation, headache, and neck pain (Loo et al., 2008), due to stimulation of superficial nerves or facial muscles, while neck pain is related to prolonged uncomfortable positioning. Headache may relate to local scalp stimulation or changes in cerebral blood flow (Loo et al., 2008). Serious adverse events are typical of

low incidence and the risk is diminished when adequate safety precautions are followed. Overall, the incidence of seizures is low, which can increase with high frequency and more intensive treatment protocols (Loo et al., 2008). The risk of a manic or hypomanic switch appears also low, but it requires particular attention in the case of bipolar patients (Rossi et al., 2009). Absolute counter-indications to TMS applications are metal implants or electronic devices, such as cochlear implants (Rossi et al., 2009).

tES also proved to be a safe and well-tolerated technique. As for tolerability, light adverse effects have been reported, such as tingling and itching sensations, or skin irritation under the electrodes, due to a poor electrode–skin contact and conduction. Phosphenes are elicited by abrupt current onset, and they can be avoided by ramping current intensity for some seconds (Poreisz et al., 2007). As for safety, a review over 33,200 tDCS sessions and 1000 individuals reported no serious adverse effects (Bikson et al., 2016) and no seizure induction has been reported to date (Antal et al., 2017). Mild adverse effects, such as headaches, may be seen in more vulnerable individuals (Bikson et al., 2016). To note, tACS and tRNS induce less sensation than tDCS (Fertonani et al., 2015). A comprehensive guide to tES safety and guidelines has been published by suggesting some precautionary parameters such as duration< 60 min and intensity <4 mA. To avoid the induction of high temperature on the scalp and prevent skin burns, electrode size and placement should also be carefully selected (Antal et al., 2017).

2.6. Advantages Compared to Other Stimulation Techniques

Techniques involving sensory (e.g. visual, auditory) stimulation, have been extensively investigated both in healthy participants and patients. Albeit it may seem like those two techniques are easier to implement in a space program, using tES offers many advantages. Sensory stimuli show a very narrow range of possible choices, allowing, for example, a range of frequencies without manipulation, and precision is given by tES. Thanks to different scripts and investigations, it is, in fact, possible to apply a very specific waveform and combination of frequencies to electrical stimuli that would never be possible with sensory stimuli. tES allows, for example, to modulate complex brain activity patterns such as cross-frequency coupling, administering two different frequencies (e.g. 6Hz and 40Hz) at the same time. Researchers can also create waveforms to select when a burst of stimulation is applied to slower oscillations (e.g. peak, through, continuous).

tES also offers higher spatial resolution compared to sensory stimulation. Recent developments in biophysical modeling allow high-resolution targeting of relatively small regions (~1cm^3). Sensory stimulation, on the other hand, is only able to stimulate visual and auditory networks. Furthermore, innovative tES protocols, involving modeling and investigating electrode positions, can target different areas at the same time with multifocal stimulation (Mencarelli et al., 2020 submitted). Propagation with coupling between frequencies from different areas is a way to transfer information from different cortical areas. A recent paper administered tACS at two coupled frequencies at the same time and in two different brain regions, mimicking and entraining cortical oscillations during a working memory (WM) test in groups of the

elderly and young. Elderly participants were able to perform the task as well as their younger counterparts during stimulation, a sign that tACS increased their WM capacity (Reinhart and Nguyen, 2019).

Even more relevant, tES is hardly noticed by the subject, with studies showing the feasibility of delivering stimulation while subjects were watching movies, or even while they were asleep (Marshall et al., 2004, 2006; Ketz et al., 2018).

Other innovative techniques, such as ultrasound neuromodulation and photobiomodulation have been taken into consideration for potential implementation for example during space explorations. Focused ultrasound (FUS) devices deliver mechanical forces to cells deep within the body in the form of an acoustic pressure wave-inducing mechanic and thermal bioeffects for a comprehensive review see (Blackmore et al., 2019). FUS at low intensity can result in direct neuromodulation of neurons (Khraiche et al., 2008; Tufail et al., 2010). FUS has been reported to modulate human performance in sensory/motor tasks (for a comprehensive review see Fomenko et al., 2018), but more studies are required to show a proven efficacy on higher cognitive abilities.

Photobiomodulation (PBM), on the other hand, relies on red to near-infrared light able to stimulate the part of the mitochondrial respiratory chain and increase adenosine triphosphate (ATP) synthesis (for a comprehensive review see (Salehpour et al., 2018). PBM enhances the metabolic capacity of neurons and stimulates neurogenesis and synaptogenesis (Salehpour et al., 2018). In the last years, various studies suggested its therapeutic efficacy in treating Alzheimer (Berman et al., 2017; Maksimovich, 2015) and Parkinson's disease neurodegeneration (Johnstone et al., 2014), as well as depression (Cassano et al., 2015; Disner et al., 2016; Schiffer et al., 2009). To date, only Gonzalez-Lima and his research team investigated PBM on healthy subjects with the purpose of cognitive enhancement. Although they reported enhancement of higher-order cortical functions such as learning, sustained attention, short-term memory, and executive functions (Barrett and Gonzalez-Lima, 2013; Blanco et al., 2017a, 2017b; Hwang et al., 2016), evidence from other independent groups is needed.

3. REVIEW OF THE LITERATURE

To identify potential domains and subjects that could further benefit from NIBS applications, I studied the existing literature on TMS and tES studies. I wanted to familiarize myself with these techniques, as well as look for potential innovative implementations. While doing so, I found myself drawn to two promising areas in which I think NIBS could further be implemented as a tool for research and as treatment. The first is sleep modulation in healthy and pathological aging. Interventions targeting sleep represent an excellent opportunity not only to maintain life quality in the aging population, but also to enhance cognitive performance and, when pathology arises, to potentially prevent/slow down conversion from MCI to AD. As we age sleep patterns undergo severe modifications in their micro and macrostructure, with an overall lighter and more fragmented nighttime sleep. Sleep abnormalities have been proven to be the earliest recognizable biomarkers of dementia, being partially responsible for a cascade of cortical events that worsen AD pathophysiology, including impaired clearance systems leading to the build-up of extracellular amyloid-β (Aβ) peptide and intracellular hyperphosphorylated tau proteins. Thus, interventions that target sleep problems in elderly people and MCI/AD patients have been suggested as a possible strategy to prevent or decelerate conversion to dementia. Although cognitive-behavioral therapy and pharmacological medications are still first-line treatments, despite being scarcely effective, new interventions have been proposed, such as auditory or light stimulation. In this context NIBS techniques could help investigate the neural substrates of sleep, identify sleep-related pathology biomarkers, and ultimately help patients and healthy elderly individuals to restore sleep quality and cognitive performance. Therefore, I performed and published the first review discussing the role of sleep in normal and pathological aging. However, brain stimulation applications during sleep have so far not been fully investigated in healthy elderly cohorts, nor tested in AD patients or other related dementias. Thus, during a second review of the literature, I focused on available evidence of NIBS applications during both wakefulness and sleep in healthy elderly individuals as well as in MCI/AD patients. From these studies, I created a rationale for potential future brain stimulation studies targeting sleep alterations in the aging brain, including enhancement of cognitive performance and quality of life, as well as increasing protein clearance.

While investigating different areas of research, I realized that sleep alterations seem to create an overall link to different diseases and stressful environments. It is well known, for example, that astronauts involved in space missions show disruptions in circadian rhythms and sleep quality severe enough to require frequent pharmacotherapy. Space explorers also undergo significant brain changes similar to modifications associated with pathological aging. A colleague of our lab previously discussed this in a relevant viewpoint published in JAMA Neurology (Sprugnoli et al., 2021). Reduced gravity is responsible for a cerebrospinal fluid shift that potentially affects protein clearance mechanisms. On the other side, cosmic radiations actively promote the accumulation of amyloid-β in mouse models, induce neuroinflammation, and further alter hippocampal-related cognition. Considering the evidence, long-term space-flight seems to induce an accelerated brain

aging pattern similar to AD progression, in addition to established space-related aging-like effects on cardiovascular and musculoskeletal systems. This complex link between protein clearance, sleep, long-term space-flight, and AD suggests the opportunity to investigate brain adaptation in space exploration as model of pathological aging. This framework could provide a starting point to identify novel diagnostic markers and countermeasures with relevance for both space exploration and MCI/AD patients on Earth.

Following this reasoning, I decided to focus my second research area on NIBS applications in space exploration. Indeed, as NASA prepares for longer space missions aiming for the Moon and Mars, astronauts' health and performance are becoming a central concern due to the threats associated with space stressors, unnatural gravity fields, and life in extreme environments. As aforementioned, in space, the human brain undergoes functional and structural changes related to fluid shift and intracranial pressure. Behavioral abnormalities, such as cognitive deficits, sleep disruption, and visuomotor difficulties, as well as psychological effects, are also a concern. In my third published review, I investigate and discuss the opportunities and challenges of NIBS devices to support space exploration in several ways. Both TMS and tES could be implemented to enhance in-flight performance, supporting astronauts during pre-flight Earth-based training, as well as to identify biomarkers of post-flight brain changes for optimization of rehabilitation/compensatory strategies.

Going further, NIBS could be offered not only as an independent intervention but also as a part of an integrated platform providing a broader tool to track and promote brain health in space during missions. Interestingly, space agencies are exploring behavioral and/or technology-based countermeasures to monitor brain health, reliably target and modulate brain structures, and promote cognitive performance and well-being. More importantly, they are looking for remote solutions. To this endeavor, NIBS could, of course, be implemented to manipulate brain oscillations and activity; the applications would be twofold: first, it would be possible to collect and test new brain biomarkers associated with space-flights; secondly, NIBS could be used as a pure neuromodulatory tool, to support brain health as well as facilitate learning and cognitive performance. Its combination with other tools though could provide a more efficient tool for research and intervention. Physiological measurements, for example, such as EEG, spectroscopy, eye-tracking, galvanic skin response, and heart rate variability assessment could be efficient proxies of the brain's health and adaptation to stress and time spent in space. Going further, virtual reality (VR) could be adopted as an immersive and entertaining platform to deliver any potential cognitive interventions and counteract the downsides of living in the ICE during long space missions. The optimal solution would be to combine all these techniques (i.e., physiological measuring appliances, NIBS, and VR) in a portable platform, to offer a comprehensive and integrated assessment tool to determine adaptation in space and deliver efficient interventions for a wide range of domains. In a perspective paper, I briefly discuss each of the aforementioned techniques and how to combine them to track and promote brain health in space. Below I present modified and re-elaborated work from these four papers.

3.1. First Review: Sleep as Potential Biomarker in Alzheimer's Disease

A similar version of the present article has been published [**Romanella SM,** Paciorek R, Cappon D, Testani E, Roe D, Rossi A, Rossi S, Santarnecchi E. "*The Sleep Side of Aging and Alzheimer's Disease".* Sleep Med. 2020 May 30:S1389-9457(20)30232-X. doi: 10.1016/j.sleep.2020.05.029.]

Growing older is associated with remarkable sleep disruption, characterized by a reduced ability to transition from wakefulness to sleep and to stay asleep without waking up. In an extensive meta-analysis, Ohayon and colleagues (2004) highlighted some of the key aging-related sleep disturbances, such as delayed circadian rhythm, a lighter and more fragmented sleep pattern, lower δ activity, and less time spent in the deeper stage. Moreover, sleep features like sleep spindles and K-complexes (K-c) also dramatically drop in frequency and amplitude (Ohayon et al., 2004). The authors suggest that many factors are involved in causing sleep changes with age. As an example, the aging-associated physiological and metabolic changes, as well as the increased susceptibility to environmental factors increase the risk to suffer from primary sleep disorders, such as Insomnia and Sleep Disordered Breathing (SDB; Ohayon et al., 2004).

Furthermore, disrupted sleep patterns are also a major risk factor for developing MCI, which may convert to AD. Sleep disruptions caused by cortical and environment modifications are often reported years before the clinical onset of the disease in elderly individuals, therefore making them a potential biomarker of the risk in AD. Then, after the onset and during the progression of MCI/AD, the sleep abnormalities undergo an even more accelerated worsening. These indicators suggest a complex bidirectional influence, for which sleep disruption may both causally contribute to AD development, and be a consequence of the onset. The current concept is that sleep quality reduction results from Aβ aggregation that also triggers hippocampal degeneration and, ultimately, memory impairment. The hypothesis is that a reduction of slow-wave activity (SWA) during non-rapid eye movement sleep (NREM) partly arises from amyloid pathology and contributes to cognitive decline in elderly individuals (Ju et al., 2017). Because the worsening of sleep quality is among the earliest observable symptoms of MCI and AD, current theories suggest examining sleep modifications in pursuit of a biomarker to identify the greater risk of developing dementia. Within this framework, a decreased duration of rapid eye movement (REM) and the general slowing down of EEG activity in NREM sleep has been considered as a potential biomarker. It has been argued that the promotion of slow waves during the NREM stage in the elderly population may have a protective effect on AD risk by enhancing Aβ clearance (Xie et al., 2013). On this line, it has been shown that elderly people with narcolepsy have a lower burden of amyloid deposits (Gabelle et al., 2019a).

The up-regulation of SWA may even restore damage to proteins caused by oxidative stress, as demonstrated in animal models (Everson, 2014a). Further, the amplitude and duration of SWA during the NREM stage are important for the long-term consolidation of newly acquired memories. The current hypothesis is that sleep improvement would slow the decline in cognitive abilities in AD patients. Within this framework, restoring slow-wave sleep (SWS) quality and duration would be a fundamental step in

addressing AD symptomatology. Recently, therapeutic attempts aiming at changing sleep oscillatory activity have been proposed. Light exposure in combination with melatonin administration may be a valid way to influence the sleep-wake cycle (Dowling et al., 2008). Auditory stimulation can enhance SWA and improve memory retention (Papalambros et al., 2017).

The present sub-chapter intends to review recent evidence of sleep modifications in healthy elderly individuals and AD patients along with the associated brain changes (for a comprehensive scheme see Figure 4). We aim to foster an understanding of the tight bidirectional relationship between sleep quality, normal aging, and AD pathology.

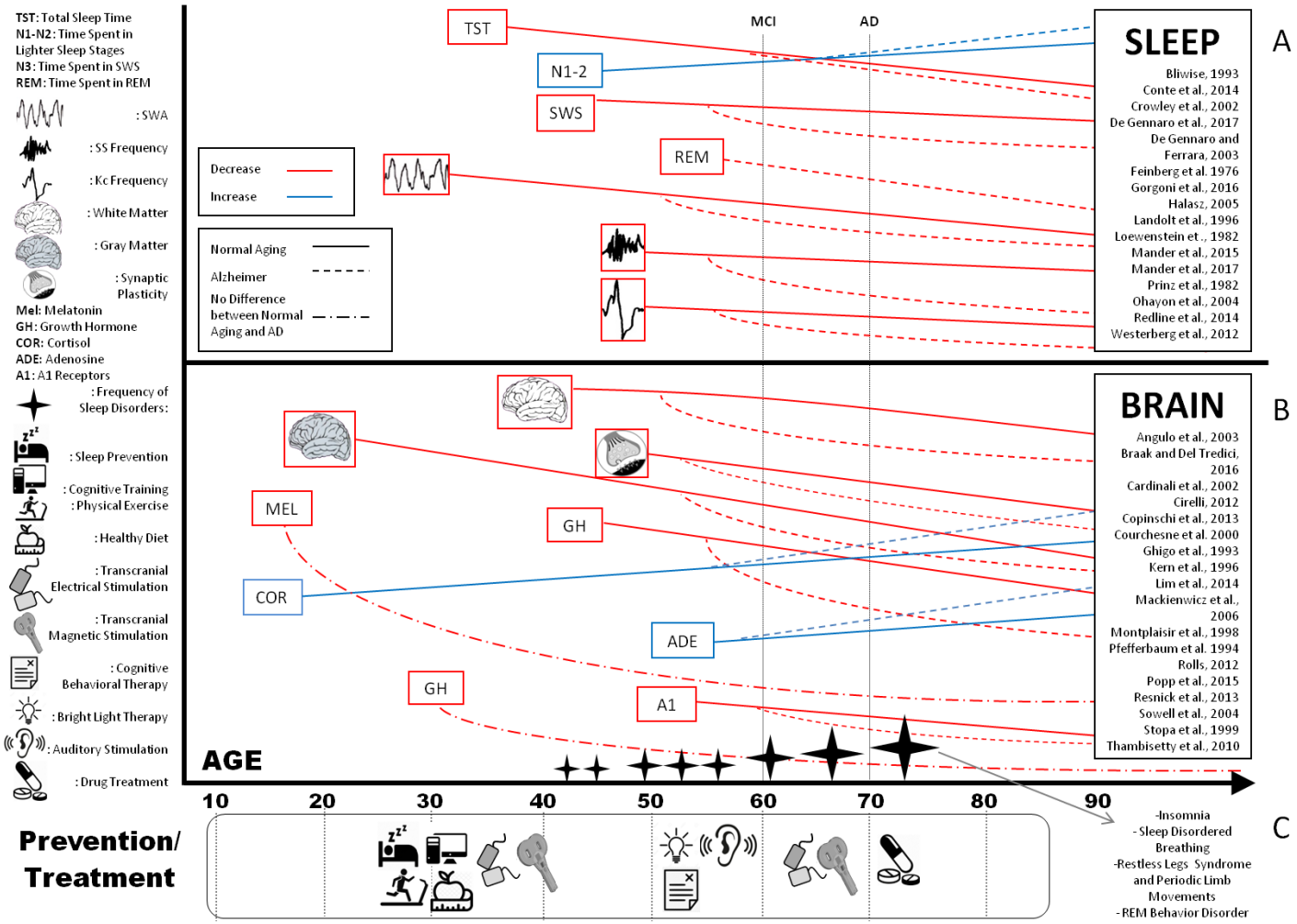


Figure 4. Sleep and Brain changes in elderly and AD patients during the Lifespan. A comprehensive review of sleep modifications (**Panel A**) and brain changes (**Panel B**) in healthy aging individuals and AD patients. The items represent investigated and modified variables (*red* items show a decrease; *blue* items illustrate an increase). The mean age when MCI or AD is diagnosed is illustrated by *vertical black dotted lines*. The *horizontal lines* indicate the trajectories of sleep and brain changes. Sleep disruptions and cortical alterations start earlier than the clinical symptoms' appearance. Horizontal line slopes depict differences in sleep and cortical abnormalities between healthy elderly and MCI/AD. *Black stars* show the prevalence of sleep disorders while growing older. Panel C shows when prevention and potential treatment efficacy would be optimal. NIBS techniques are represented at a different ages for their applications in prevention and treatment.

3.1.1. Sleep Alterations in Healthy Aging

As we get older, substantial modifications of sleep macro and microstructure are part of the normal aging process (Figure 5). Sleep in the elderly population is worsened in both length and internal structure (Ohayon et al., 2004). The whole circadian rhythm decreases in amplitude and shows an early phase-shift (Monk, 2005). Middle and older-aged individuals present higher subjective sleepiness ratings during the late afternoon and early evening compared to younger subjects (Münch et al., 2005).. Total Sleep Time (TST) lowers from around 7.4h in early life to 5.6h in older age (Crowley, 2002). As a consequence, regular diurnal napping increases, growing 25% after the 75th year, therefore worsening the cycle shift (Foley et al., 2007). During nighttime elderly individuals usually spend twice as much overnight time in unwanted wakefulness (Bliwise, 1993), drastically dropping sleep efficiency. Frequent arousals are a result of different concurrent factors. First, elderly individuals are more sensitive to the external environment, showing a lower arousal threshold to auditory stimuli (Zepelin et al., 1984). Furthermore, once sleep is interrupted, the transition from sleep to a fully awake state occurs more rapidly in older subjects without a subsequent increase in sleepiness, thereby delaying the start of sleep again (Dement et al., 1985).

The internal sleep structure is also disrupted. REM-NREM cycles are shorter and fewer, with a mean of 3.46 cycles per night in elderly individuals compared to the usual 4-5 in adults (Conte et al., 2014). Singularly, while time spent in the REM stage overnight seems to slightly decrease (Ohayon et al., 2004; Redline et al., 2004), this drop is not as noticeable as in the N3 (also called slow-wave sleep or SWS) stage. The strongest age biomarker is a steady drop in time spent in N3 stage, as proved by a wide meta-analysis and different studies on great cohorts of participants (Bliwise, 1993; Cauter et al., 2000; Ohayon et al., 2004; Redline et al., 2004). N3 is then replaced by a greater amount in lighter phases, NREM1 (N1) and NREM2 (N2; Bliwise, 1993; Cauter et al., 000; Ohayon et al., 2004; Redline et al., 2004). The increase of time in lighter phases is greater in N1 than N2, but this latter undergoes more changes in its typical EEG features, with a decrement of sleep spindles (transient oscillations occurring at 12-15Hz playing a role in memory consolidation) and both spontaneous and elicited K-complexes (Kc, singular waveforms of about 0.5 seconds involved in preventing sleep fragmentation; Conte et al., 2014; Clawson et al., 2016; Halasz, 2005).

Sleep spindles (SS) drop, in particular, is due to a substantial change in their form and occurrence. With advancing age, spindles undergo a constant decrement in density, amplitude, and duration (Carrier et al., 2011; Crowley, 2011, 2002). Disruptions were particularly marked during the last cycles (De Gennaro and Ferrara, 2003) and in anterior derivations, whereas duration changes were maximal in the posterior prominence (Martin et al., 2013), a sign of a differential propagation through the cortical network in the elderly. These alterations and SS's role in sleep protection may explain difficulties experienced by elderly individuals in maintaining sleep during lighter NREM stages (Dang-Vu et al., 2011). Similarly, N3 modification is not only in its length but also in its EEG microstructure. A drop in total Slow Wave Activity (SWA; spectral power density from 0.5 to 4.5Hz; or delta activity), is a pivotal biomarker of aging and is used to test sleep quality and homeostatic sleep pressure (Bliwise, 1993; Cauter et al., 2000; Feinberg et al.,

1967; Landolt et al., 1996). Similarly to SS, for elderly individuals, SWA fall is maximal over the prefrontal cortex (Carrier et al., 2011; Landolt et al., 1996).

To aggravate brain aging and consequent sleep difficulties, elderly individuals are also at higher risk of suffering from primary sleep disorders, such as insomnia and sleep-disordered breathing (SDB). Insomnia, diagnosed in case of the disrupted sleep-wake cycle or difficulty falling asleep with a consequent impairment in daytime functioning (Diagnostic Classification Steering Committee TMJC; 2014), shows a prevalence that varies significantly between younger and older populations, reaching 40% in over 65 y/o individuals (Foley et al., 1995). The second most common sleep disorder in the older population is SDB, which includes a spectrum of respiratory disorders occurring during sleep with various severity, from benign snoring to obstructive sleep apnea (OSA). The latter is particularly insidious because of airflow cessation due to complete or partial collapse of upper airways. Similarly, to insomnia, SDB has a higher prevalence in the elderly. In a randomly selected cohort of 427 participants, 62% in the range age 65-95 showed an SDB (Ancoli-Israel et al., 1991). When diagnosed with SDB (e.g. OSA), elderly individuals also suffer significantly more than their younger counterparts with the same diagnosis. The influence of OSA on sleep microstructure is, in fact, more disruptive. Less delta activity is observed in EEG recordings of young OSA patients compared with older OSA patients, while the latter shows more theta, sigma, and alpha power (Lee et al., 2016).

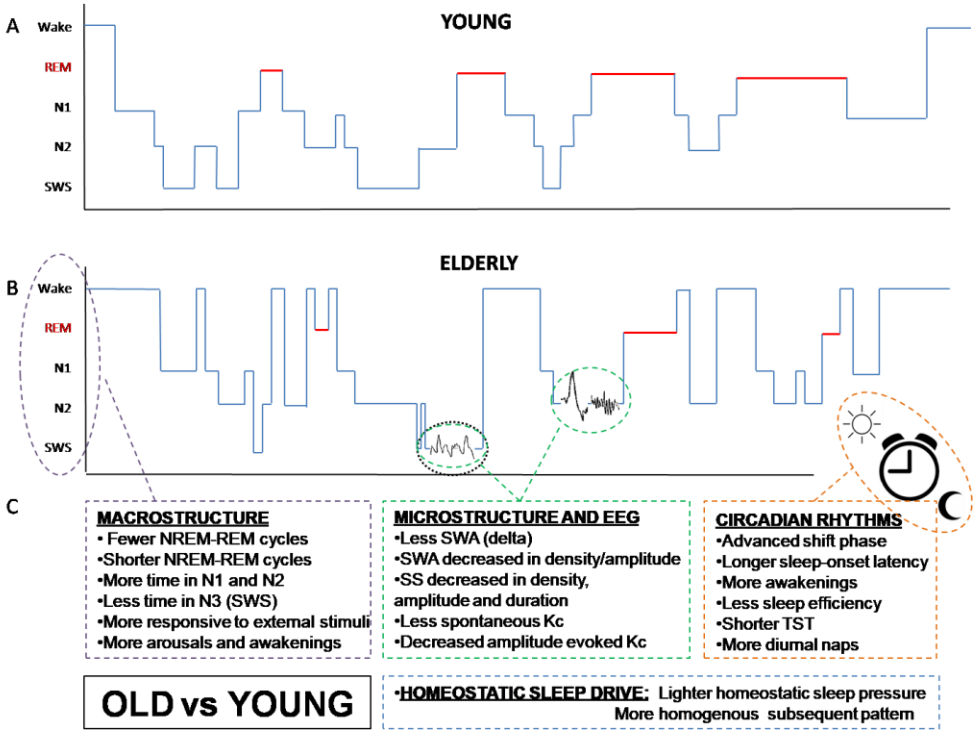


Figure 5. Sleep Differences in Elderly versus Young Individuals. Polysomnographic (PSG) data showing sleep architecture in a young healthy adult (**Panel A**) and an older healthy adult (**Panel B**). The elderly show a more fragmented and less integrated sleep, shifting from deeper to lighter sleep stages multiple times during nighttime. Schematic illustration comprehensive of all sleep differences found in healthy elderly compared to young individuals (Panel C). *Non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), slow-wave sleep (SWS), slow waves (SW), slow-wave activity (SWA), sleep spindles (SS), K-complexes (K-c).*

3.1.2. Aging-related Brain Changes Leading to Sleep Modifications

Age-related sleep, as well as cognition, motor, and living skills, is modified by dramatic alterations at many different levels of the brain, including extracellular changes, cortical atrophy, and neuronal loss. Once the pattern of sleep changes, it creates a cascade of consequences, establishing a positive feedback cycle that often feeds itself. We address the main modifications that happen in the aging brain, linking them to specific sleep disruptions in elderly individuals.

One of the most characteristic biomarkers of the aging brain is neuronal loss resulting in cortical volume fallout. It is marked and replicable (Courchesne et al., 2000; Pfefferbaum et al., 1994; Resnick et al., 2003; Thambisetty et al., 2010), measured through different parameters such as total volume of the brain, cerebrospinal fluid (CSF), gray and white matter, cortical thickness, surface area, cell loss, and neuronal shrinkage (for a comprehensive review see Sowell et al., 2004). The age-related deterioration in white matter is less marked than abnormalities in cell bodies. In older individuals (age 70-80) the former is decreased by 13%, versus 26% for the latter (Courchesne et al., 2000). Whereas white matter decrease is widespread among the whole brain, gray matter deterioration is significantly higher in the frontal and parietal lobes (Resnick et al., 2003; Thambisetty et al., 2010). White matter also starts to shrink considerably later. While gray matter starts to decrease in volume at the end of childhood, white matter does not reach its volume plateau until the 4th decade, and only after it starts declining in volume (Courchesne et al., 2000), as is demonstrated by studies using diffusion tensor imaging (DTI; Westlye et al., 2009).

Because SW requires a large number of neurons to propagate, SWA disruptions may be a result of shrinking in specific regions (Mander et al., 2016), such as lateral and medial prefrontal neuronal loss. Multiple studies showed how a decrement in SW amplitude is predicted by neuronal loss in the medial PFC and the middle frontal gyrus, while impairment in density is correlated with deterioration of the areas surrounding the lateral fissure (insula, superior temporal, parietal, and middle frontal gyrus (Dube et al., 2015; Mander et al., 2013). The prefrontal area is also impaired in its functionality, with a lower resting metabolic rate in older individuals compared to younger ones (Kakimoto et al., 2016). A lack of cognitive activity in the elderly, and a subsequent modification in synaptic plasticity, is also a causal factor in SWA decline. SW requires not only large populations of healthy neurons able to produce oscillations but also efficient synaptic connections among them (Esser et al., 2007). Even a rapid increase or decrease in synaptic strength (in number or efficacy) during awake states will, therefore, reflect a parallel subsequent enhancement or fall in SWA. After wakefulness, slow oscillations renormalize neural activity in N3, promoting synaptic depression thanks to low levels of norepinephrine, serotonin, and acetylcholine (for a review see Hanlon et al., 2011). More synapses are potentiated during wakefulness due to learning and motor tasks, and greater SWA is required during subsequent sleep to balance plasticity. An age-related drop in brain plasticity and a lack of cognitive activity in the elderly will then require less SWA.

3.1.3. Sleep and Cognition in Healthy Aging

As we age substantial changes also occur in various cognitive domains. Several studies tried to determine whether modifications in SWS, REM, and SS in aging directly lead to a general intellective decrease, or if changes in cognition and sleep share a common source, such as reduced brain volume, or cardiovascular, or neurochemical changes (for a review see Scullin and Bliwise, 2015). Many paradigms have studied how sleep deprivation influences subsequent cognitive performance in healthy elderly individuals. Surprisingly, after one or more nights of total sleep deprivation and sleep restriction, elderly people show less impaired cognitive performance during normal waking hours compared to younger adults (Bliese et al., 2007; Bonnet, 1989; Bonnet and Arand, 1989). The older group also presents faster reaction times and fewer lapses in tasks presented during normal sleeping hours (Duffy et al., 1998). Recent studies of experimentally altered circadian phases in subjects of different ages reported maintained reaction times in older versus younger individuals (Donnell et al., 2009; Silva et al., 2010). Therefore, even though sleep disruptions are far more marked in older adults than in younger adults, the former appears to be more resistant to the cognitive effects of sleep deprivation than younger controls. On the other hand, elderly people with self-reported insomnia presented a greater cognitive decline at a 3-year follow-up, underlining how long-term poor quality sleep is strongly associated with a greater risk of cognitive deficits (Cricco et al., 2001).

The main link between cognition and sleep has been provided by memory consolidation, the process that strengthens mnemonic traces. Sleep-dependent memory consolidation has been investigated by a wide range of learning protocols and results have been extensively reviewed (Diekelmann et al., 2009). NREM sleep plays the main role as the promoter of the conversion of episodic representations from a labile hippocampal-dependent state to an increasingly hippocampal-independent one (Diekelmann et al., 2009). In fact, in young adults, SWS and delta power predict the consolidation of episodic memories (Diekelmann et al., 2009). Reduction in NREM features due to aging would result in impoverished hippocampal memory consolidation, and therefore predict a subsequent decline in memory retention, as established in various studies, not only in healthy elderly people (Aly and Moscovitch, 2010; Backhaus et al., 2007; Giambra and Arenberg, 1993; Mary et al., 2013) but also in Mild Cognitive Impairment (MCI) patients (Westerberg et al., 2012). Due to aging, brain areas related to memory, such as the hippocampus and prefrontal cortex, undergo functional, neurochemical, and structural changes (Kalpouzos et al., 2009; Mander et al., 2013; Mueller and Weiner, 2009). Consequently, even with adequate sleep, memories would not be consolidated as efficiently in older adults (Harand et al., 2012; Pace-Schott and Spencer, 2011; Scullin, 2013; Scullin and Bliwise, 2015).

A study by Mander et al. (2015) demonstrated how age-related atrophy of mPFC predicts SW drop, as well as long-term episodic memory impairment (Mander et al., 2013). To complicate the situation, other studies report negative correlations between memory and SWS quantity (Feinberg et al., 1967; Scullin, 2013; Seeck-Hirschner et al., 2012) leaving the question open. Results may be cohesively explained by distinguishing N3 quantity and N3 quality (measured by the density of SWA). The application of various paradigms of transcranial electrical stimulation (tES) has been applied as an innovative and efficient tool to

investigate and manipulate this link between SWA and subsequent memory performance (see dedicated paragraph).

3.1.4. The Relationship between Sleep and Protein Clearance

Several studies showed a strong relationship between sleep quality and Aβ alterations in MCI/AD and healthy elderly subjects (Mander et al., 2015; Spira et al., 2013; Sprecher et al., 2015). It has been demonstrated that sleep disruptions are, indeed, a crucial factor affecting the severity of cortical Aβ burden and the levels of phosphorylated tau in the Cerebrospinal Fluid (CSF; see Figure 6). In this paragraph, we review the causal relationship between sleep abnormalities, like the aforementioned ones explained in the last paragraph, and Aβ plaques, neurofibrillary tangles, and Apolipoprotein Epsilon (ApoE), the three main hallmarks of AD pathology.

Amyloid-β and Glymphatic System. Sleep abnormalities that occur very early in the prodromal phase of dementia accelerate AD pathogenesis through Aβ and tau protein accumulation (Ju et al., 2014; Lucey et al., 2017; Lucey and Bateman, 2014). The potential link between sleep alterations, amyloid-β, and tau accumulation has been already extensively described in healthy elderly (for a review, see Holth et al., 2017). Other studies have stressed the correlation between different subjective and objective sleep measures and various typical AD features, such as cortical Aβ burden, cerebrospinal fluid (CSF) measures of Aβ, and phospohorylated tau (Ancoli-Israel et al., 2005; Liguori et al., 2014; Lim et al., 2013; Mander et al., 2015; Spira et al., 2013; Moraes et al., 2006). Brown and coworkers (2016) investigated Aβ burden by using Positron Emission Tomography (PET) with three different amyloid-binding ligands in 184 healthy elderly, together with measures of subjective sleep factors derived from the Pittsburgh Sleep Quality Index. Longer sleep latency was highly associated with higher neocortical Aβ levels, although sleep duration, sleep efficiency, and daytime sleepiness were not. With a similar paradigm, but in a smaller cohort (51 healthy elderly), Branger and coworkers (2016) supported Brown et al.'s findings linking Aβ levels in prefrontal regions with longer sleep latency, but not with other sleep quality factors. Aβ concentration in the angular gyrus, frontal medial orbital cortex, cingulate gyrus, and precuneus has also been shown to highly correlate with self-reported poor sleep quality and daytime sleepiness in healthy elderly (Sprecher et al., 2017). Studies, where NREM sleep was modulated in healthy, middle-aged participants, have confirmed that SWA suppression increases CSF Aβ levels in the subsequent morning (Ju et al., 2017a). CSF levels of tau and Aβ protein predicted the degree of diminished SWA time in AD patients, together with the decrease in sleep efficiency and REM time (Liguori et al., 2014). Aβ effects on NREM neurophysiology have been described in terms of higher levels of Aβ correlating with deficient SWA and subsequent impairment in sleep-dependent memory (Mander et al., 2015; Varga et al., 2016). Gray matter atrophy in healthy elderly subjects was found to be correlated with age-related decline in SWA between a range of 1 to 4Hz (Mander et al., 2013). Differently, Aβ modifications in AD were mainly linked to changes in <1Hz SWA (Mander et al., 2015).

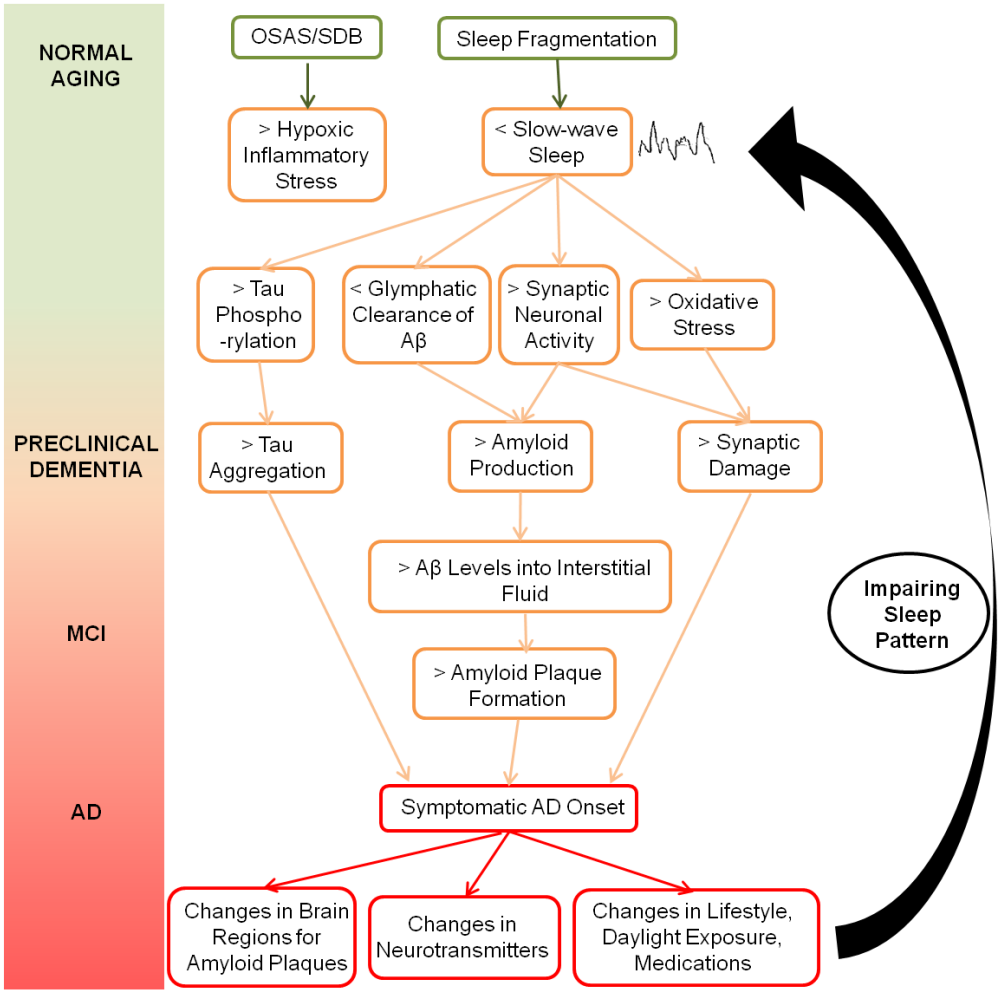


Figure 6. Bidirectional Link between Sleep, Aβ Levels, and MCI/AD Onset. Sleep fragmentation is a key factor that triggers a cascade of pathological processes before clinical onset. Modifications in brain regions, neurotransmitter levels, and lifestyle due to AD diagnosis and prognosis will then worsen sleep patterns establishing a vicious cycle feeding itself.

Animal studies also support the existence of a bidirectional link between sleep and AD, for which rodent AD models display increased sleep fragmentation and shorter NREM stages (Guarnieri et al., 2012). Experimentally increasing cortical Aβ has been reported to cause fragmentation of NREM sleep (Kang et al., 2009). Both the lack of sleep and pattern disruptions contribute to Aβ aggregation, which itself impairs SWS causing a vicious cycle of detrimental events (Ju et al., 2014). A few studies have suggested a major sleep-dependent role of the glymphatic system in dictating Aβ clearance (Xie et al., 2013). During NREM stages, glial cells shrink by almost 60%, enabling CSF flow through the interstitial space. Clearance is therefore enhanced, removing extracellular toxins and metabolic components, including extracellular Aβ. Proteins are vacated twice as fast during SWS compared to wakefulness (Kang et al., 2009; Xie et al., 2013). Because wakefulness requires a higher neurometabolic rate relative to NREM (Buchsbaum et al., 1989), longer time spent without sleep directly impacts Aβ clearance. During awake states, neurons consume greater levels of oxygen and Adenosine Triphosphate (ATP). NREM not only requires less oxygen and glucose consumption, but it is also responsible for ATP replenishment (Dworak et al., 2010). Amplified neurometabolic activity during wakefulness results in increased amyloid precursor protein (APP) production, triggering Aβ

accumulation due to oxidative stress (Misonou et al., 2000). NREM, on the other side, actively regulates oxidative stress and promotes cellular repair (Everson, 2014b; Villafuerte et al., 2015). Moreover, chronic sleep disruptions and OSAS increase blood vessel stiffness by triggering chronic hypertension (Kyrtsos and Baras, 2015). This, combined with cerebral amyloid-β angiopathy (Weller et al., 2009), reduces clearance efficiency, thereby favoring the accumulation of extracellular Aβ. Therefore, when wakeful metabolic distress is not balanced by sufficient sleep, a cascade of neurotoxic and oxidative events promotes AD pathophysiology.

This has been proven in multiple animal trials (Everson, 2014; Villafuerte et al., 2015). Tabuchi (2015) has suggested that changes in neuronal excitability underlie the effects of sleep loss on AD pathogenesis. Aβ accumulation due to sleep deprivation was successfully blocked by actively decreasing intrinsic cortical excitability in a drosophila AD model. Conversely, increasing cortical excitability phenocopied the effects of sleep reduction on Aβ. Through action specific potassium (K+) currents, sleep loss exacerbates Aβ–induced hyperexcitability. Wakefulness neuronal activity also enable AD neurodegeneration due to wake-promoting peptide named orexin A/hypocretin-1 (Kang et al., 2009). Specifically, in transgenic mice that overexpress amyloid precursor protein (APP), Aβ level increases during wakefulness and after orexin-A infusion while it decreases during sleep and after infusion of an orexin-A receptor antagonist (Kang et al., 2009). In APP mice whose orexin gene is also knocked out, Aβ brain load is decreased and sleep time is increased (Roh et al., 2014). Moreover, sleep deprivation by the rescue of orexinergic neurons in APP mice increases the levels of cortical Aβ (Roh et al., 2014).

Similarly, higher CSF orexin-A levels were observed in patients with AD compared with controls (Dauvilliers et al., 2014; Liguori et al., 2014; Wennström et al., 2012). CSF orexin-A levels are also correlated with tau protein levels and sleep-wake alterations in patients with AD (Liguori et al., 2014). Because orexin levels may directly influence amyloid clearance, Gabelle and coworkers (2019) collected PET images, Aβ load, CSF orexin-A level, and cognitive profile of 23 subjects older than 65 years with a diagnosis of narcolepsy type 1 (NT1). NT1 is a chronic disease, characterized by EDS and cataplexy, and caused by destruction of orexin neurons. Because it is usually diagnosed around 16-20 years of age, individuals without orexin influence on Aβ accumulation since young age, may be partially protected by AD risk. The study, in fact, showed lower cortical amyloid burden obtained with all subcortical and cortical reference regions (except cingulum) in NT1 subjects compared to age and sex matched controls. This delayed appearance of amyloid claque in narcoleptic patients proves orexin as one of the influencers in Aβ load.

In the last years, new studies are currently shifting the focus of AD research onto REM sleep. Indeed, MCI/AD patients, in contrast to healthy elderly patients, demonstrate REM abnormalities in overall time spent in this stage, quality, and EEG features (Petit et al., 2004; Prinz et al., 1982; Reynolds et al., 1990). A reduction in REM time is also positively correlated with Aβ levels (Kerbler et al., 2014), presumably mediated by the degeneration of cholinergic projection neurons within the brainstem and basal forebrain (Montplaisir et al., 1998).

Tau-associated Neurofibrillary Tangles (NFTs). Tau-associated neurofibrillary tangles (NFTs) are formed by hyperphosphorylation and intercellular aggregation of tau protein and are the second well-known hallmark of AD (Knopman et al., 2010; Mesulam et al., 2004). Tau pathology has been suggested as the earliest neurodegenerative feature linked to AD with abnormal tau phosphorylation and aggregation in the locus coeruleus, beginning during early adulthood. It then spreads into different cortical areas such as dorsal raphe, tuberomammillary nucleus, parabrachial nucleus, and basal forebrain (for a review see Holth et al., 2017) before Aβ burden could even be detected (Braak et al., 2011; Braak and Tredici, 2011; Knopman et al., 2010; Stratmann et al., 2016). Furthermore, NFTs in the LC are found in AD patients (Dugger et al., 2011), and later on, phosphorylated tau levels in the CSF also predict cognitive decline in preclinical and clinical AD (Mattsson et al., 2009). The mediation of the LC between AD and NFTs is strongly linked to its excitatory role in the cortical ascending arousal system. In healthy individuals, noradrenergic neurons in the LC inhibits sleep (Saper et al., 2005), on the contrary, LC neurons are lost in AD. Interestingly, it has been shown that the number of LC neurons is correlated with cognitive decline in a cohort of healthy elderly (Wilson et al., 2013).

NFTs are particularly disrupting considering the hippocampus's ability to generate ripples linked to the expression of NREM SS and SWA, and how these two features have been shown to support sleep-dependent memory processing (Diekelmann et al., 2009a). Studies on animals showed that hippocampal ripples are diminished and less synchronized due to the accumulation of tau in the medial temporal lobe, therefore changing neural oscillatory patterns (Witton et al., 2016). Tau has been associated with abnormally long hyperpolarized down states during SWA (Menkes-Caspi et al., 2015), explaining part of the correlation between CSF tau levels and SWS drop in patients with AD (Liguori et al., 2014). Furthermore, chronic sleep restriction, already known to be a risk factor for illness progression, impairs hippocampus-dependent memory and increases insoluble tau, helping NFTs formation (Di Meco et al., 2014; Rothman et al., 2013). Ju and colleagues (Ju et al., 2017) reported no increase in tau levels after only one night of disrupted SWS, whereas they found increased CSF tau levels in participants reporting poor sleep during several nights. Conversely, the lymphatic system during sleep promotes tau clearance, explaining why the elderly with good sleep quality showed fewer NFTs at autopsy (Lim et al., 2013).

Apolipoprotein Epsilon (ApoE). ApoE is a class of proteins essential to combine fats to form lipoproteins. Lipoproteins are important to preserve and remodel neuronal membranes. ApoE is polymorphic, with three major alleles: ApoE-ε2, ApoE-ε3, and ApoE-ε4. The latter is well known to be a genetic risk factor for developing AD (Evans et al., 1997; Farrer et al., 1997; Poirier et al., 1993). ApoE-ε4 has been associated with reduced Aβ clearance with consequent pathological accumulation (Castellano et al., 2011). Normal cognitive elderly individuals with the ApoE-ε4 allele have shown a risk of developing MCI or dementia seven times higher (Burke et al., 2016). Sleep disturbances appear to be linked to ApoE-ε4 in MCI/AD patients, especially concerning REM decrease (Hita-Yañez et al., 2013) and delay in circadian rhythms (Hwang et al., 2018). It has also been proposed that increased sleep disturbances in ApoE-ε4 patients could result from alterations in melatonin production (Liu et al., 1999). Besides, ApoE-ε4 has been

associated with an increased risk of SDB and cognitive impairment in patients with OSA (Gottlieb et al., 2004; Hara et al., 2005; Kadotani et al., 2001). While some studies suggested that ε4 allele may be the major cause of sleep disruptions in elderly people at risk for dementia (Gottlieb et al., 2004; Wang and Lung, 2012), others stressed that sleep deficits and ApoE genotype may just amplify each other's negative effects (Kaushal et al., 2012; Spira et al., 2008). The debate on ApoE-ε4 is still open given the fact that some studies showed no influence (Craig et al., 2006) or even a protective role of ApoE genotype on sleep patterns, raising the question of the true nature of this association (Yesavage et al., 2004). Even though more investigation is required, current theories propose that better sleep consolidation could attenuate the increased risk conferred by the ApoE genotype (Lim et al., 2013).

3.1.5. The Bidirectional Link between Sleep and Alzheimer's Disease

As aforementioned, the current concept is that sleep disruptions accelerate AD pathogenesis by enabling Aβ and tau protein accumulation. Because sleep disruption also appears to be among the earliest observable symptoms of a wide range of neurodegenerative diseases, such as AD, Parkinson's Disease, and Multiple Sclerosis (Kay et al., 2018; Mattis and Sehgal, 2016), its function as a biomarker to identify elderly at greater risk has been suggested (Mander et al., 2016). Below we discuss modifications in sleep patterns, macro and microstructure in MCI and AD, and how these disruptions predict clinical symptoms and cognitive performance in patients.

Circadian Rhythms. MCI and AD patients show significantly disrupted sleep (Vitiello and Prinz, 1989) and complain about poor sleep more frequently than healthy elderly (27.6% vs 18.3%; Tractenberg et al., 2005). AD patients tend to spend more time awake during the night, due to increased sleep latency and higher frequency of nocturnal awakenings (Hatfield et al., 2004), thus resulting in more daytime sleepiness and decreased sleep efficiency (Hatfield et al., 2004; Holth et al., 2017). Severe sleep fragmentation generally corresponds with the emergence of a syndrome called sundowning, which is characterized by behavioral symptoms such as hostility, anxiety, agitation, and confusion occurring at the end of the day, and has a great impact on cognitive skills and quality of life (Ferrazzoli et al., 2013). Visual hallucinations during wakefulness are also reported by AD patients. However, hallucinations are reported in one-third of the patients during specific phases of the sleep-wake cycle. Vivid dreams are also reported, together with aggressive sleep-related and dream-related behaviors (Sinforiani et al., 2007).

Even before clinical onset, sleep disturbances have relevance to the development of cognitive dysfunctions. A previous study in community-based populations showed a link between delay and reduction of sleep-wake cycles and the probability of developing dementia (Tranah et al., 2011). Age-related sleep fragmentation is associated with a 1.5-fold increased risk of developing dementia in the following 6-year follow-up period (Lim et al., 2013). Furthermore, a longitudinal cohort study showed that sleepiness is related to twice the risk of developing dementia (Foley et al., 2001), suggesting that daytime sleepiness is also a predisposing factor for developing dementia.

It has been argued whether part of these disruptions is caused by neuronal and synaptic loss occurring in the early clinical stages of dementia. An earlier study in AD showed that alterations in sleep-wake cycles are mainly mediated by degeneration of the suprachiasmatic nucleus (SNC; Stopa et al., 1999). Stopa and colleagues determined that SNC is highly damaged in AD and that the astrocyte/neuron ratio is an accurate marker of SNC pathology (Stopa et al., 1999). Additionally, AD post-mortem studies have established that neurofibrillary tangles located in the hypothalamic preoptic area correlate with the severity of fragmented sleep (Lim et al., 2014). Tau deposition is also present in the LC and the basal forebrain of healthy older adults (Braak and Tredici, 2016). It has been suggested that tau within these regions may trigger sleep disruptions years before symptomatic onset, and this may be used as an early diagnostic biomarker (Holth et al., 2017).

Changes in CSF melatonin levels are also a major cause of sleep pattern disruptions in AD patients. It was proposed that this may be due to modification in suprachiasmatic nucleus functionality (Wu et al., 2005), or due to alteration of melatonin secretion itself (Cardinali et al., 2002). Sleep disruptions may also be linked to changes in CSF cortisol concentrations. MCI and AD patients show a significantly higher level of cortisol, strongly correlated with faster clinical worsening and cognitive decline (Popp et al., 2015). Going further, pathophysiology seems to induce hypothalamic orexin neurodegeneration seen in later AD stages with consequences on sleep-wake rhythms (Mander et al., 2015). In MCI and early AD, orexin levels are higher and predict longer sleep latency, more fragmented sleep, and shorter REM duration (Liguori et al., 2014). With disease progression, orexin levels decrease and are associated with more fragmented daytime wakefulness (Friedman et al., 2007).

Slow Wave Sleep (SWS). MCI patients show a decrease in time spent in NREM related to healthy elderly controls, which already have diminished SWA during normal aging (Westerberg et al., 2012). NREM sleep progressively decreases after the onset and during illness progression (Loewenstein et al., 1982). Tau and Aβ protein levels measured in CSF predict the degree of reduced SWA time in AD patients, together with a drop in sleep efficiency and REM sleep duration (Liguori et al., 2014). SWA reduction strongly correlates with Aβ accumulation in the medial prefrontal cortex (Mander et al., 2015), which is one of the earliest regions damaged by Aβ plaques (Sepulcre et al., 2013). EEG slowing also predicts disrupted hippocampal memory consolidation (Mander et al., 2015). New studies tried to find an answer to this apparent contradiction, explaining that SWA decrease may reflect changes in K-complexes. Following this explanation, <1Hz SWA would not change significantly from healthy age-matched subjects and AD patients, as previously shown.

REM Sleep. While REM sleep seems to be relatively preserved in normal aging, it is significantly reduced in AD patients (Prinz et al., 1982) and characterized by shorter epochs (Petit et al., 2004). AD patients also show a delayed REM sleep onset and a blunted rebound of REM sleep following selective deprivation (Prinz et al., 1982; Reynolds et al., 1990). It has been suggested that the specific degeneration of cholinergic neuron transmission in AD may constitute the basis of REM sleep changes (Montplaisir et al., 1998). The degree of basal forebrain atrophy is correlated with the degree of cortical Aβ burden, not only in MCI and AD patients but also in healthy elderly individuals (Kerbler et al., 2014). Moreover, there is a

general slowing of high-frequency oscillations in AD patients (for a review Cassani et al., 2018; Huang et al., 2000). This phenomenon includes an increase in diffuse SWA and θ activity not only during wakefulness, but also during REM sleep (Hassainia et al., 1997; Peter-Derex et al., 2015; Xie et al., 2013), and this is larger in temporoparietal and frontal regions (Petit et al., 2004).

REM sleep can also predict neuropsychological impairment in older adults and AD patients (Liguori et al., 2014). It has also been shown that REM sleep has a role in emotional regulation and mood states. Thus, the manifestation of hostility, depression anxiety, emotional dysregulation, and memory retention impairment (Kensinger et al., 2004) could be attributed to poor REM sleep quality.

Therefore, a therapeutic intervention aiming at improving REM sleep quality is particularly important, due to the influence of REM sleep on cognition and mood. Cholinesterase inhibitors are aimed at promoting REM sleep quality and duration and their efficacy predicts the degree of memory improvement in AD patients (see below; Wdos et al., 2006).

***Sleep Spindles (SS) and K-complexes (K-c*)**. AD patients show a dramatic reduction, over 40%, in K-c density compared to healthy elderly controls (De Gennaro et al., 2017). Normal aging is associated with a decrease in both spontaneous and evoked K-c, while AD patients present mainly a decrease of spontaneous K-c in the frontal cortex (Montplaisir et al., 1995; Prinz et al., 1982). Lower K-c activity is also correlated with a lower Mini-Mental State Examination (MMSE) score (De Gennaro et al., 2017). AD patients showed faster mean θ frequency in both REM and SWS during post-learning sleep versus elderly controls. This significant difference was associated with the better delayed episodic recall, probably enabling a compensatory mechanism to sustain memory performance (Hot et al., 2011). Similar to the reduction in K-c, various studies found a significant SS reduction in AD patients compared to healthy controls (Bliwise, 1993; Montplaisir et al., 1995; Prinz et al., 1982), mostly involving fast parietal spindle density (Westerberg et al., 2012). Results suggest that pathology-related spindle alterations start in the early stages of the disease, possibly even in preclinical stages. In support of this theory, MCI patients often show a massive decrease in SS (Gorgoni et al., 2016). This reduction comes with cognitive deterioration in patients with dementia, as with many other specific disrupted EEG features. The relationship involves mostly fast central sleep spindles intensity and impaired immediate episodic recall in AD patients (Rauchs et al., 2008). It has been suggested that thalamic damage (Bonjean et al., 2008) and disruptions in pathways of memory consolidation between the hippocampus and neocortical areas may account for spindle density drop.

Sleep Disordered Breathing and AD. Sleep disorders are often co-morbid with neurodegeneration. Over 60% of MCI/AD patients are diagnosed with at least one clinical sleep disorder, mostly SDB or insomnia, during illness progression (Guarnieri et al., 2012). Importantly, successful treatment of sleep disorders can delay MCI onset (Osorio et al., 2015) and improves cognitive function when a patient is already in severe stages of AD (Wdos et al., 2006). There is a complex interaction between SDB and dementia. Although previous investigations showed an increased incidence of Obstructive Sleep Apnea Syndrome (OSAS) with aging, AD patients are particularly affected, with 40-70% having five or more apneas and hypopneas per hour of sleep (Hoch et al., 1986; Kupfer et al., 1985). A diagnosis of SDB is linked with a major risk of

developing dementia (Tworoger et al., 2006). Other studies found that SDB patients had an 85% increased risk to develop AD and MCI (Yaffe et al., 2011). Furthermore, individuals with sleep apnea convert to MCI and AD more frequently and also at a younger age (Osorio et al., 2015). After clinical onset, AD stage and SDB severity positively correlate, worsening together during progression (Ancoli-Israel et al., 1991).

After the clinical onset of SDB, AD patients with a diagnosis of OSAS show sleep with less REM and SWS, and more frequent awakenings compared to AD patients without OSA (Cooke et al., 2006). Frequent apneas and hypopneas during sleep are associated with deficits in memory, attention, and executive tasks. Some authors suggested that cognitive deterioration may be mediated by SDB's effect on daytime sleepiness (Sforza and Roche, 2012). Alternatively, SDB could also directly contribute to neuronal dysfunction through hypoxia, or it may be a consequence of AD-associated neurodegeneration in brainstem respiratory centers. Possible other explanations involve SDB's relation to increased vascular risk, which is itself an independent risk factor for AD (Landry and Liu-Ambrose, 2014).

3.1.6. Network Modifications during Sleep in Healthy and Pathological Aging

As aforementioned, the human brain is organized in a set of functional networks (RSNs) whose synchronized activity spans between spatially distinct interconnected areas. Amongst them, the DMN is particularly relevant due to its pivotal role in the spontaneous activity of the human brain. Anatomical regions belonging to the DMN include inferior parietal lobules, precuneus, posterior cingulate cortex, medial frontal cortices, lateral-medial temporal cortices, and the hippocampi (Kernbach et al., 2018). DMN plays a role in memory consolidation, mental imagery, internal dialogue, and maintenance of long-term memory (Buckner et al., 2008; Uddin et al., 2009). Furthermore, its oscillatory activity is negatively correlated with other resting-state networks and has been promoted as a marker of healthy cognitive functioning and healthy aging (Santarnecchi et al., 2017; R. Nathan Spreng et al., 2016).

As for concerns about the relationship between network alterations and sleep, studies have revealed how FC between DMN regions increases in SWS and decreases in REM stages. This pattern is also similar to hippocampal activity, which is tightly related to long-term memory consolidation and retention (Diekelmann et al., 2011; Diekelmann and Born, 2010; Grosmark et al., 2012). DMN's activity changes during the SWS periods are negatively correlated with those during the REM period (Watanabe et al., 2014). On the other hand, the frontoparietal network (FPN), which consists of regions engaged during attentional cognitive tasks (Dosenbach et al., 2006; Fair et al., 2009), shows the opposite pattern of modulation. Interestingly, local neural activity in frontoparietal areas is reduced during SWS periods (Huber et al., 2006, 2004; Nir et al., 2011).

Networks Modification after Poor Sleep. Sleep disruptions have generally been associated with alterations in the FC of the DMN and attentional networks (De Havas et al., 2012; Scullin, 2017). A nighttime lack of sleep has been associated with a deficit in the FC within the DMN the following morning, as well as within other RSNs (Kaufmann et al., 2016). Interestingly, using resting-state fMRI in healthy controls under controlled sleep deprivation, studies have demonstrated an aberrant functional activity not

only within the DMN but also between the DMN and its negatively correlated regions (De Havas et al., 2012; Verweij et al., 2014). Interestingly, patients with chronic sleep disorders (e.g. insomnia) show greater connectivity modifications during wakefulness. Santarnecchi and colleagues (2018) reported how patients with chronic insomnia present a weaker connection between DMN and the supplemental motor area. Furthermore, the authors found that earlier age of insomnia onset positively correlated with FC within DMN, suggesting the importance of addressing insomnia-related effects on brain connectivity as early as possible to possibly prevent long-lasting DMN connectivity reshaping. Additionally, the further analysis highlighted a reduction of connectivity between the occipital lobe and two bilateral temporal clusters overlapping with the hippocampus (Santarnecchi et al., 2018), in line with the known role of temporal lobe structures in memory consolidation processes (Riemann et al., 2010; Prince and Abel, 2013; Havekes et al., 2016). These studies indicate the potential importance of sleep in the maintenance of DMN activity during wakefulness. This is particularly relevant when taking into consideration the tight relationship between memory deficit, cortical network modifications, and sleep disruptions in aging.

Networks Modifications in Aging. Overall, the most consistent finding across all studies is that older adults have lower FC between regions of the DMN compared to younger adults (Dennis and Thompson, 2014; Ferreira and Busatto, 2013). Age-related differences in functional connectivity have also been observed in other brain networks such as the dorsal attention (DAN), salience, and sensorimotor networks (Allen et al., 2011; Onoda et al., 2012; Tomasi and Volkow, 2012). However, to date, none of these differences have been reported as strong and replicable as those observed in the DMN. New studies are now focusing on age-related differences in between-network FC in addition to just within-network FC. For example, Spreng and colleagues (2016) examined age-related FC differences within and between DMN and DAN. They found lower within-network functional connectivity and higher between-network functional connectivity in older adults compared to the younger controls (R.N. Spreng et al., 2016). Studies also found age-related FC changes in the context of selective attention. The Ventral Attention Network (VAN), specifically, underlies selective attention. Deslauriers and coworkers (2017) reported greater connectivity among posterior regions of the VAN in older adults when compared to a younger cohort, but weaker connectivity among anterior regions (right anterior insula, right medial superior frontal gyrus, and right middle frontal gyrus). Data suggest posterior regions increasing their engagement in older adults as a compensatory consequence of reduced connectivity within anterior regions, suggesting a reorganization of network FC as a potential biomarker of aging-related attention deficits (Deslauriers et al., 2017).

Networks Disruptions in AD. Within the AD pathology, DMN posterior-ventral and anterior-dorsal progressive deterioration have been observed to closely mirror PET-detected amyloidosis and hippocampal atrophy, closely accounting for changes in cognition as well (Buckner et al., 2005; Jones et al., 2016). Furthermore, the carriers of the ApoE ε4 allele, which is the most potent risk factor for AD, also show DMN impairment similar to that of preclinical AD, even in the absence of Aβ deposition in the brain (Sheline et al., 2010). As the pathology progresses, the loss of connectivity within DMN posterior regions is accompanied by an increase in their interaction with ventral areas instead (Jones et al., 2016), reflecting a malignant

hyperconnectivity that outbreaks DMN boundaries and rather start to involve other brain networks. For instance, key areas of the Salience Network (SN), such as the cingulate cortex and ventral striatum, as well as areas belonging to the Executive Control Network, show increased connectivity in AD (Agosta et al., 2012; Zhou et al., 2010). Other studies have pointed out a progressive decrease in Dorsal Attention (DAN) and Sensorimotor network (SMN) connectivity to also accompany AD clinical progression (Brier et al., 2012), with a different profile of disaggregation differentiating different forms of dementia (Zhou et al., 2010).

In general, alterations of network dynamics rather than changes in regional activity seem to constitute better markers of disease, and potentially capture subtle changes characterizing transitions across disease stages. Interventions targeting sleep dynamics might have a beneficial impact on overall cognition and daytime performance in healthy and diseased individuals.

3.1.7. Standard Sleep Treatments in Aging and AD

Along these lines, it has been suggested that treating sleep dysfunctions in young elderly and MCI patients could slow or prevent the progression of dementia (Roberts and Knopman, 2013). Consolidating sleep quality, increasing total sleep time and SWA have been reported to decrease the incidence of AD onset in the elderly community (Lim et al., 2013). Current pharmacological therapies, such as cholinesterase inhibitors, hypnotics, and antidepressants, can have important side effects in older individuals, for example impairing alertness, and cognitive skills, and producing psychomotor effects; therefore, their use must be considered as a last resort (for a review see Bloom, 2009; Gooneratne and Vitiello, 2014). Therefore, the first line of treatment should prioritize a combination of sleep hygiene intervention and cognitive-behavioral therapy (CBT; Gooneratne and Vitiello, 2014). It has been demonstrated that both interventions are highly effective and with no negative consequences (Gooneratne and Vitiello, 2014). Other combination therapies have been proposed, for example, bright light therapy with melatonin has been shown to stabilize the sleep/wake cycle. More recently, the application of Noninvasive Brain Stimulation (NIBS), like transcranial electrical stimulation (tES) to manipulate SWS and sleep quality has been proposed as a promising intervention. In the following section, we will review evidence of innovative sleep therapies, discussing their efficacy in tackling sleep disruptions in healthy elderly and MCI/AD patients.

Pharmacological Medications. Current pharmacological treatments for sleep disruptions are effective for transient insomnia and when sleep disruption is secondary to a pathology (for a comprehensive review see Regestein et al., 1998). Chronic drug therapies can lead to serious adverse effects and tolerance development, frequently affecting daytime alertness and cognitive ability (McCurry et al., 2000). Pharmacological therapy should be considered only in situations where a definite medical condition is diagnosed, or where the use of the behavioral approach (CBT-I) has failed.

Cholinesterase Inhibitors. Memory and vigilance impairments are largely caused by a disruption in cholinergic transmission. The concentration of acetylcholine is high during wakefulness and REM sleep, while it declines during SWS (Coyle et al., 1983). It has been shown that the timing of the administration of

cholinesterase inhibitors plays a crucial role, morning administration causes fewer negative side effects (e.g. nightmares; Ancoli-Israel et al., 2005; Cooke et al., 2006; Rogers, 1998). While positive modifications in sleep patterns due to cholinesterase inhibitors are difficult to replicate, improvement in memory consolidation and clinical global functioning in AD seems to be significant (Ancoli-Israel et al., 2005b; Cooke et al., 2006; Rogers, 1998).

Hypnotics, Antidepressants, and Antipsychotics. Although hypnotics, whether benzodiazepines (Lorazepam) or non-benzodiazepines (Zolpidem) are effective in accelerating sleep onset and prolonging overall time asleep, their side effects can be detrimental. They drastically modify sleep microarchitecture and may cause confusion and ataxia during awake states. Benzodiazepines may even cause paradoxical effects in the elderly (Peter-Derex et al., 2015). Non-benzodiazepines cause fewer negative side effects but in general, they are not generally recommended, except in cases of acute and severe insomnia (Peter-Derex et al., 2015). Sedating antidepressants helps when sleep difficulties are caused by depressive symptoms. Antidepressants result in higher overall time spent asleep and greater sleep efficiency, although side effects, such as diurnal sleepiness and dizziness, must be considered. The first choice antidepressant should be Serotonin Selective Re-uptake inhibitors (SSRIs) for their relative safety (McCurry et al., 2000), although also Trazodone or Mirtazapine proved to be effective to treat insomnia (Jaffer et al., 2017). Antipsychotics are usually administered to treat behavioral and psychiatric manifestations of AD, but they seem to also be effective on insomnia. Atypical antipsychotics, such as risperidone, olanzapine, and quetiapine, should be preferred over typical antipsychotics though, as the latter may cause excessive diurnal sedation and increase the risk of falling (Rocca et al., 2007).

Sleep Hygiene and Cognitive-behavioral Therapy. Sleep hygiene is an intervention that manipulates daily habits to influence sleep quality by preserving a regular sleep/wake schedule (i.e. with the same rise time every day and avoiding diurnal nap) and reducing pre-sleep tension and sleep-onset latency (Gooneratne and Vitiello, 2014). Sleep hygiene might be facilitated by creating a non-disruptive sleep environment. For example, the use of earplugs and "white noise" in a dark and comfortable temperature room decreases nocturnal awakenings and arousal (Gooneratne and Vitiello, 2014). Physical exercise combined with a healthy diet is also an important contributing factor to efficient sleep hygiene. Locomotor activity in the daytime activates neuronal feedback loops in the SCN, and, as a result, the sleep/wake cycle is regulated (Hughes and Piggins, 2012). Cognitive-behavioral therapy for insomnia (CBT-I) consists of six to ten sessions supervised by a trained therapist. CBT-I aims to change maladaptive behaviors and cognitive beliefs that perpetuate insomnia and includes relaxation techniques and tips to reduce arousal before bedtime (e.g. avoiding watching TV, and using smartphones in bed) (Gooneratne and Vitiello, 2014). Various studies in healthy elderly, MCI, and early-stage AD patients proved the high efficacy of CBT-I in improving sleep efficacy, prolonging TST, and shortening sleep-onset. Importantly, CBT-I results, unlike pharmacotherapy, last at least 6 months after the end of the treatment (Cassidy-Eagle et al., 2018; Montgomery and Dennis, 2004; Trauer et al., 2015). However, further studies need to clarify whether CBT-I is also able to modify physiological sleep oscillations (e.g. enhancing SWA) or to regulate Aβ regulation.

Melatonin. Although melatonin has no negative reactions, it is still unclear whether its administration causes significant and direct beneficial effects. Actigraphy, polysomnography, subjective reports, sleep logs, and clinical observations have been used to investigate melatonin's effects in both healthy subjects and subjects diagnosed with AD, with varied results; some studies did not find a significant improvement, while others found a significant effect of melatonin as a hypnotic and circadian controller, mostly when in combination with Bright Light Therapy (Dowling et al., 2008; McCleery et al., 2015; Pandi-Perumal et al., 2005; Rajaratnam et al., 2004; Singer, 2003). Importantly, a significant slowing in cognitive decline has been found in AD patients when treated with prolonged-release melatonin (Wade et al., 2014). Furthermore, melatonin seems to protect against several mechanisms of neuronal death and can prevent Aβ toxicity, an effect probably linked to its cytoprotective and antioxidant effects (for a review see Cardinali et al., 2002).

Bright Light Therapy (BLT). Elderly people tend to spend less time exposed to daylight, aggravating sleep problems. Bright light therapy (BLT) consists of exposing healthy elderly individuals and patients to light with the aid of a full spectrum lightbox for a minimum of 30 minutes per day, preferably during the morning. It has been shown that BLT results in a reduction in overnight awakenings, increased sleep consolidation, and increased TST (Ancoli-Israel et al., 2003). Moreover, BLT also reduces daytime sleepiness and increases daytime alertness (Ancoli-Israel et al., 2003; Satlin et al., 1992). BLT efficacy is even greater when circadian rhythms are severely impaired. The combined administration of BLT and melatonin amplifies efficacy in more severely impaired subjects (Dowling et al., 2008) while showing less improvement in subjects with less severe disturbances (Dowling et al., 2005).

Auditory Stimulation. Auditory stimulation is applied overnight during the N3 stage aiming to enhance <1Hz SWA with the rationale of regulating hippocampus-dependent memory consolidation and sleep stabilization. A promising application is auditory closed-loop stimulation, where short auditory stimuli are presented at the same frequency as endogenous slow oscillations. Ngo and colleagues (Ngo et al., 2013) used an auditory closed-loop feedback system based on an adaptive amplitude threshold method, to detect online SWA to send a brief auditory stimulation (i.e., 50ms bursts of pink noise). The authors demonstrated a significant increase in SWA, an enhancement of phase-locked spindle activity during slow oscillations upstate, and an enhancement of memory performance after closed-loop auditory stimulation. These results were replicated in a subsequent study by the same group (Ngo et al., 2015) and by other groups that used auditory closed-loop systems (Leminen et al., 2017; Ong et al., 2016; Santostasi et al., 2016). All these studies increased SWA in young adults during daytime naps, in contrast, Papalambros and colleagues (2017) tested an automated and adaptive algorithm in 13 older participants (60–84yo) during one night of acoustic stimulation and one night of sham stimulation in random order. Pulses of pink noise were administered during slow-wave upstate. Promisingly, the authors found an increase in SWA and spindle activity for the active stimulation intervals compared to sham intervals. Furthermore, verbal memory was tested before and after sleep and overnight improvement in word recall was significantly greater with acoustic stimulation compared to sham and was correlated with changes in SWA (Papalambros et al., 2017).

SIGNIFICANCE.

Sleep disturbances not only negatively impact the quality of life and cognition in normal aging, but they are a risk factor for MCI/AD development and prognosis. Earlier studies considered sleep abnormalities as a consequence of the neurodegenerative process, while recent investigations confirmed that sleep degradation emerges in the prodromal phase, and play as the collateral cause of AD exacerbation. Going further, the strong link between sleep abnormalities and Aβ and tau protein accumulation suggests that sleep research might be pivotal in addressing AD pathogenesis and promoting healthy aging. Sleep research could guide the creation of rehabilitative and/or cognitive enhancement interventions to improve the quality of life of healthy elderly, detect individuals at risk, and slow down/prevent the progression of MCI/AD. Currently available experimental treatments for MCI/AD include pharmacological medications, diet, Bright Light Therapy, and Auditory Stimulation. Nevertheless, contrasting results have so far been reported. As such, there is a strong need for innovative treatment interventions. In this framework, NIBS techniques might be tested as a research tool able to investigate significant sleep dynamics, as well as a potential treatment to restore sleep quality, preserve or enhance physiologically-declining sleep-associated cognitive functions, and potentially boost nighttime protein clearance.

3.2 Second Review: NIBS as Intervention in Sleep in Healthy and Pathological Aging.

A similar version of the present article has been published [**Romanella SM**, Paciorek R, Cappon D, Roè D, Menardi A, Ruffini G, Rossi S, Rossi A, Santarnecchi E. "*Sleep, Noninvasive Brain Stimulation and the Aging Brain: Challenges and Opportunities"*, **Ageing Res Rev.** 2020 Aug;61:101067. doi: 10.1016/j.arr.2020.101067. Epub 2020 May 4.

The first review outlined the current state of the art of the relationship between sleep modifications in healthy and pathological aging and the neurobiological mechanisms underlying these age-related changes. Furthermore, we provided a critical analysis showing how sleep abnormalities influence the prognosis of AD pathology by intensifying Aβ and tau protein accumulation. In this framework, early interventions targeting sleep disruptions may help avoid, or at least slow, conversion to dementia in vulnerable elderly individuals. Although standard treatments are available, their efficacy is limited. In this context, recent studies have explored the possibility of treating healthy elderly and MCI/AD patients with NIBS techniques to restore sleep quality. It has also been theorized that the promotion of slow waves during the NREM stage in the elderly population may also have a protective effect on the risk of developing AD by enhancing Aβ clearance. Evidence highlights that the amplitude and duration of SWS during the NREM stage are both important for the long-term consolidation of newly acquired memories, suggesting that sleep enhancement would slow the decline in cognitive abilities in healthy elderly individuals. NIBS may help investigate the neural substrates of sleep and identify sleep-related pathology biomarkers. Leveraging sleep research with NIBS could therefore offer a new promising and innovative treatment to find AD biomarkers, address sleep symptomatology, preserve or enhance physiologically-declining cognitive functions and tackle Aβ

deposition. In this second review, I will discuss how NIBS protocols have been previously implemented to improve sleep and cognition in healthy and pathological aging populations.

3.2.1. NIBS Applications in Sleep Research

Historically, the application of an external current to induce sleep-like states started in the early 1900. Robinovitch (1914) was the first one to introduce the concept of electrosleep therapy. Usually, electrosleep applied a pulsating direct current for up to 120 minutes, with electrodes attached to eyes and mastoids (for a comprehensive review see Guleyupoglu et al., 2013). Although most of the studies lack methodological rigor (e.g., no control with the sham condition or no electrophysiological measures) this technique indeed induced sleep improvements (Brown, 1975; Sergeev, 1963; von Richthofen and Mellor, 1979) including inducing sleepiness, damping anxiety, fatigue, and depressive symptoms (Frankel, 1974). During the last decade, several TMS studies have also been conducted to investigate the physiology and pathophysiology of sleep structure in healthy and clinical populations. A growing number of studies exploited a combination of TMS paradigms (sTMS, ppTMS, rTMS, as well as TMS-EEG) to (1) gain insights into the mechanisms of sleep disorders to reveal patterns of abnormal cortical excitability; (2) assess the effects of specific pharmacological interventions; (3) treat patients in attempt to restore physiological excitability levels. We discuss below the successful combination of TMS with EEG to investigate cortical oscillations and their modifications during sleep.

TMS and TMS-EEG to Investigate Sleep Dynamics. Causal relationships between sleep homeostasis, synaptic plasticity, consciousness, and slow waves have been investigated within the theoretical framework of the information integration theory of consciousness (IITC) proposed by Tononi (2004). In this context, consciousness is the ability of the brain to integrate information and effective communication between neuronal assemblies is crucial for conscious experience. The current concept is that the efficient transfer of neuronal information is strictly dependent on effective brain connectivity, which refers to the opportunity for a group of neurons to causally regulate the behavior of other groups of neurons inside a network. In this context, the TMS-EEG approach has been adopted to understand if mechanisms of fading of consciousness (as during sleep) are related to a disruption of effective connectivity. In a series of experiments, TMS-EEG has been applied while participants kept their eyes closed on a reclining chair and proceeded from wakefulness to NREM sleep. Massimini and coworkers (2012, 2005) assessed the cortical reactivity during NREM sleep and compared it to a wakeful state. The authors found that TMS pulses during wakefulness generate a systematically organized propagation along with short- and long-distance cortico-cortical connections. By contrast, stimulation during deep stages of sleep resulted in a local cortical response that did not propagate. Moreover, TMS during wakefulness generated low-amplitude high-frequency waves, while stimulation during sleep evoked high-amplitude low-frequency waves. The authors argued that, while during wakefulness and REM sleep the brain can sustain long-range, complex sequences of activation, during NREM sleep, when consciousness dissolves, this ability is lost. During the NREM stages, the neuronal system disintegrates into independent modules that produce the stereotypical SWA. Tononi and Cirelli

(2003) have also proposed the synaptic homeostasis hypothesis, according to which SWA homeostasis reflects a cascade of functional events. These events may restore the level of energy required for synaptic functioning and may regulate the activity of cellular elements enabling learning. Therefore, if wakefulness is associated with synaptic potentiation increasing synaptic strength, sleep is instead involved in triggering homeostatic regulation of synaptic weights. Consequently, the amplitude of TMS evoked potentials is expected to be higher at the end of a day of wakefulness and lower after a night of sleep (Tononi and Cirelli, 2006).

Because sleep deprivation sensitizes the brain to epileptogenic activity, it is considered a major risk factor for seizure precipitation in epileptic patients (Dinner, 2002). Different studies applied TMS to investigate the link between sleep deprivation and its ability to modify cortical and corticospinal excitability. De Gennaro and coworkers (2007) investigated those mechanisms by sleepiness assessment, EEG spectral power maps, and several TMS measures, such as paired-pulse short intracortical facilitation and inhibition, and different motor thresholds (MTs), such as standard (ST), lower (LT), and upper threshold (UT). The cohort was composed of 33 normal subjects tested before and after 40 hours of sleep deprivation. Results showed that a night of sleep deprivation profoundly affects different measures of cortical activation. EEG slow frequencies increased in most cortical regions with a focus on midline frontal and central areas, accompanied by large increases in delta and theta activity. Standard MTs, LTs, and UTs, all increased as a consequence of sleep deprivation. Short interval intra-cortical facilitation (SICF) after nighttime wakefulness also displays a significant increase, but only in women. Overall neural deactivation was associated with an increase in subjective sleepiness, as well as a decrease in subjective alertness. Importantly, EEG slowing and loss of complexity are strong biomarkers of sleep deprivation, also observed in diseases like Alzheimer's and Parkinson's Disease (Abásolo et al., 2006; Dauwels et al., 2010; Ruffini et al., 2019). The study by De Gennaro et al (2007) partially confirms the synaptic homeostasis hypothesis by Tononi and Cirelli (2003) and it poses the first evidence of applying TMS to study sleep dynamics.

tES to Manipulate Sleep Oscillations. While a unifying theoretical account of cortical SWA is still lacking, some lines of research have provided possible explanations of the underlying mechanisms and functional role of SWA and its link with faster oscillations. SW is caused by brief periods of hyperpolarization in cortical and thalamocortical neurons due to a firing rate reduction of ascending activating neuronal assemblies (down states; Llinás and Steriade, 2006). Experimental evidence has supported a strong link between SWA homeostatic regulation and learning mechanisms. According to the synaptic homeostasis hypothesis (Tononi and Cirelli, 2006), modifications in synaptic bounds during waking (e.g. due to learning) influence SWA formation and propagation. The up-regulation of SWA synchrony is functionally relevant in the consolidation of new memories during sleep. The functional interaction between SWA and spindles (SS) is one of the main factors that support this process. When the firing rate reduction of ascending activating neuronal assemblies generates down-states, SS is suppressed. SWA and SS are phases coupled during NREM and the spatio-temporal coupling between spindles and SWA is believed to trigger the replay and strengthening of mnemonic traces (Diekelmann et al., 2009).

With the foregoing in mind, tES has been applied to enhance SWA during NREM, investigating the relationship between SWA and memory consolidation. Marshall and colleagues (2006, 2004) were the first to investigate the effects of anodal slow oscillation transcranial electrical current (otDCS, combination of tACS and tDCS) during sleep in young adults. Stimulation was applied during SWA in N2 at 0.75Hz on frontolateral areas (F3-F4). Participants performed a declarative episodic memory task before nighttime sleep and in the morning after awakening. The authors reported improved declarative memory linked with increased SWA (Marshall et al., 2004a, 2006a). Ten years after, Marshall's group also demonstrated a positive effect on cognitive function in rodents, similarly triggered by tACS during NREM (Binder et al., 2014). During the following decade, these results were replicated, usually in young individuals. Typical experimental paradigms consisted of sinusoidal waves applied at frequencies of 0.5-1.2Hz over F3-F4 with an open or closed-loop tACS device. Enhanced SWA and delta power, triggering an increase in gamma and sigma waves followed by better performance in declarative memory tasks, has always been reported (Jones et al., 2018; Ketz et al., 2018).

Because subjective sleep quality positively correlates with SWA duration (Akerstedt et al., 2009), tACS or otDCS applied to enhance SWA and SWS time may also be of interest. Ketz and colleagues (2018) not only reported improved memory consolidation following a closed-loop tACS intervention designed to match the phase and frequency of endogenous SWA in NREM sleep (Robinson et al., 2018), but also significant improvements in sleep quality measures. Focusing on different memory domains and EEG features, Lustenberger and colleagues (2016) applied an EEG-controlled approach that restricted the application of 12Hz feedback-tACS (FB-tACS) to bilateral frontal lobes only when sleep spindles were detected, therefore stimulating only when the sigma power (11.5-15.5Hz) was prevalent. The authors reported increased motor memory consolidation after stimulation tested via a motor sequence tapping task. Differently, Lafon and coworkers, (2017) reported an unsuccessful attempt to entrain sleep spindles while applying low-frequency tACS in healthy subjects. The authors measured endogenous spindle power intracranially during NREM sleep using invasive pre-surgical electrocorticography monitoring in 13 patients with epilepsy, finding no stable evidence of entrainment. Even though the main reason for the failure in entraining spindle activity could be attributed to the underlying epileptic activity, it should also be noted that stimulation intensity varied across the two studies, with the latter applying significantly weaker currents (<0.05 V/m).

Finally, even though not immediately translatable to aging-related processes, one study has investigated the possibility of applying tES during REM sleep to modulate dreams. Voss and coworkers (2014) administered frontotemporal tACS following ~2min of uninterrupted arousal-free REM sleep with different frequencies. Participants were then awakened and asked to rate dream consciousness based on a validated scale. According to the authors, lower gamma band (40Hz) stimulation during REM sleep increased self-awareness of participants' dreams (Voss et al., 2014), a potentially indirect marker of a more stable and organized REM cycle.

3.2.2. NIBS Applications in Alzheimer's Disease during Wakefulness

NIBS applications in healthy aging populations during wakefulness can be successfully implemented with various positive outcomes, such as improving performance and quality of life. TMS and tES proved to be excellent tools to treat cognitive functioning in the elderly, promoting plastic effects that could trigger beneficial compensatory activity. As for MCI/AD patients, to date, the Federal Drug Administration (FDA) has approved 5 drugs, mostly focusing on symptom management. Holistic and lifestyle modifications are recommended, including modifications to diet, exercise, and social environment, sometimes combined with computerized cognitive training. Because none of these existing therapies has a direct effect on the underlying neuropathology, NIBS methods may be a potentially crucial tool to slow MCI/AD conversion and progression (for a review see Gonsalvez et al., 2016). Therefore, we will give priority to discussing possible TMS and tES applications in MCI/AD patients, emphasizing outcomes and experimental paradigms. We refer elsewhere for a comprehensive review of NIBS applications in the healthy aging population to preserve or enhance physiologically-declining cognitive functions (Tatti et al., 2016).

TMS in AD during Wakefulness. TMS has been shown to enhance various cognitive skills, such as verbal memory, episodic memory, working memory, and executive functions (Manenti et al., 2012). Several clinical trials tested different rTMS protocols for cognitive improvement in AD patients with encouraging results (Cotelli et al., 2008, 2006, 2012; Devi et al., 2014; Eliasova et al., 2014; Koch et al., 2018). Recent meta-analytic work has highlighted cognitive improvements in patients with psychiatric and/or neurological disease and in healthy controls following high-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC), suggesting this stimulation site is a gold standard (Guse et al., 2010). For example, rTMS over bilateral DLPFCs of 15 AD patients enhanced accuracy in an action naming task but not in object naming (Cotelli et al., 2006a). These findings were replicated with a bigger sample size (24 patients) with varying AD severity (mild AD: >17/30 MMSE score; moderate to severe AD: <17/30 MMSE score). Again, rTMS over bilateral DLPFCs enhanced action but not object naming in the mild AD group. On the other hand, moderate to severe AD patients showed an improved accuracy for both classes of stimuli (Cotelli et al., 2008). In later years, the same research group also investigated rTMS-induced long-term cognitive effects (Cotelli et al., 2012). They divided 10 adults with AD in two groups on a multiple-baseline trial. One group was treated with high-frequency (20Hz) rTMS over left DLPFC, 5 times per week for 20 sessions. The second group received placebo rTMS for 2 weeks and then the same high-frequency rTMS for 2 weeks. After the first 10 sessions, participants who received real rTMS demonstrated significantly better performance than those receiving placebo. Moreover, both groups showed improved performance at 8 weeks follow up (Cotelli et al., 2012). Ahmed and coworkers (2012) applied high frequency rTMS in mild/moderate AD patients with positive effects on their MMSE, Instrumental Daily Living Activity Scale, and Geriatric Depression Scale scores. Results were found to be specific to both stimulation type and stage of illness, for which no effect was found either when low frequency stimulation was applied, nor when severe AD patients were chosen as the active group. Using slightly different stimulation sites, Eliasova and colleagues (2014) applied 10Hz rTMS over vertex and right inferior frontal gyrus (IFG) in patients with

early AD. Significant improvement at Trail Making Test A and B was reported when IFG was the stimulation site. In a short term trial, 12 AD patients received 4 rTMS sessions at 10Hz over the bilateral DLPFC for 2 weeks (Devi et al., 2014). Overall, higher scores were obtained following administration of the Boston Diagnostic Aphasia Examination tests of verbal and non-verbal agility following TMS, accompanied by neuroimaging evidence of enhanced activation during performance of various cognitive tasks 4 weeks post-treatment (Devi et al., 2014). In a long randomized, double-blind, placebo-controlled trial, Zhao and coworkers (2017) stimulated 30 AD patients at different stages of illness. 20Hz rTMS was applied on P3/P4 and T5/T6 for 30 sessions for 6 weeks monitoring for performance levels at verbal memory, short term memory, ability to learn new information, memory on immediate recall and delayed recall, and long delayed recognition. After the rTMS treatment, a significant global cognitive improvement was found, whereby scores on the Assessment Scale-Cognitive Subscale (ADAS-cog), MMSE, Montreal Cognitive Assessment (MoCA), and World Health Organization University of California-Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT) were significantly ameliorated. Furthermore, subgroup analysis showed that rTMS effects on memory and language performance were far superior in mild AD patients than in moderate AD. Koch and coworkers (2018) have also made use of 20Hz rTMS stimulation for 10 sessions over 2 weeks targeting the precuneus, a key area in AD memory impairment. By enhancing the activity of the precuneus and its connectivity with frontal areas, selective improvement in episodic memory was observed in 14 patients with early AD.

Finally, the combined efficacy of rTMS protocols and cognitive training has been addressed by several studies. Bentwich and colleagues (2011) treated 8 AD patients with daily cognitive rehabilitation and rTMS for 6 weeks, followed by 2 sessions per week for 3 months. High-frequency rTMS was delivered over 6 different brain regions, including Broca's area, Wernicke's area, bilateral DLPFC, and the right and left parietal somatosensory association cortices. Researchers found both a significant improvement in the cognitive domain tested using the ADAS-Cog (baseline: 22.5, 6-weeks: 18.3, 18-weeks: 18.5), as well as amelioration of the symptomatology as assessed through the Clinical Global Impression of Change (CGIC; 6-weeks: 1.0, 18-weeks: 1.6 points). The MMSE, the Alzheimer Disease Assessment Scale Activities of Daily Living (ADAS-ADL), and the Hamilton Depression Scale also showed a trend toward improvement, though this did not reach statistical significance. Encouraging results have also been reported following shorter interventions (6 weeks; Brem et al., 2013; Nguyen et al., 2017), with aftereffects that persisted up to 3 months follow-up (Rabey et al., 2013).

tES in AD during Wakefulness. In parallel with findings from groups exploring TMS, various research groups have demonstrated tDCS efficacy in enhancing cognitive function in healthy subjects (for a review see Kuo and Nitsche, 2012). Additionally, several small trials have provided compelling evidence for its efficacy in AD patients. Ferrucci and coworkers (2008) tested performance in a word recognition task and a visual attention task before and after a single tDCS application. They administered 1.5mA for 15 min to bilateral temporoparietal regions in 10 patients with a diagnosis of probable AD. When compared to sham, anodal stimulation improved word recognition accuracy, while cathodal stimulation worsened performance.

No effect was reported for the visual attention task. Boggio and coworkers (2009) tested tDCS effects on recognition memory, working memory, and selective attention in AD patients. They demonstrated that a single session of anodal tDCS over the left DLPFC and temporal cortex was able to transiently improve visual recognition memory in AD patients. As in previous studies, results were task-specific. Long-lasting effects of tDCS in AD were also investigated by the same research group, whereby 2mA tDCS was delivered for 30min per 5 days through two scalp anodal electrodes placed over temporal regions and a reference electrode over the right deltoid muscle. Patients showed improved performance on a visual recognition memory task, which was maintained at the 1-month follow-up. However, visual attention and general cognitive performance did not benefit from stimulation (Boggio et al., 2012). In a similar study comparing the effects of anodal, cathodal, or sham stimulation, 2 mA tDCS administered for 25 min/day per 10 days resulted in a significant increase in the MMSE score for both active conditions (Khedr et al., 2014).

Similar to studies of combined TMS and cognitive therapy, Cotelli and colleagues (2014) investigated the effects of tDCS combined with individualized computerized memory training. Thirty-six AD patients were randomly assigned to 3 groups: one group was treated with individualized computerized memory training and anodal tDCS on left DLPFC at 2mA for 25min over 5 consecutive days for 2 weeks; a second group underwent motor training and anodal tDCS with the same parameters; finally, a third group received placebo tDCS. Only the group receiving combined cognitive and electrical stimulation showed a significant improvement in a Face-Name Associations task (Cotelli et al., 2014).

3.2.3. TES during Sleep in Elderly Individuals

NIBS applications include not only the investigation for pathological biomarker detection but also a potential tool to restore sleep quality and consequently preserve the decline of cognitive functions in the elderly and AD. Since oscillatory activity characterizes human and animal brain activity, tACS may be the best methodology to study and find a possible therapy lay in the link between cognitive/motor/emotional functions and ongoing brain waves. Studies combining sleep and tES stimulation have mostly focused on the modulation of SWA during N3 state, testing the possibility of using these techniques to promote sleep. Below we provide an overview of the most relevant literature studies on tES application during sleep in healthy young and elderly subjects.

The same experimental paradigm implemented by Marshall and coworkers (Marshall et al., 2004a) was tested in the elderly population by Eggert and colleagues. These authors, however, did not observe beneficial effects on memory consolidation in this older cohort, arguing that there might be crucial differences in memory consolidation processes between young and aged individuals (Eggert et al., 2013). Paßmann and colleagues also stimulated older adults using tACS over the frontal cortex during NREM. Authors found increased SWA and spindle activity, similar to previous results on young individuals, but again with no beneficial effects in the consolidation of visuospatial and verbal memories (Paßmann et al., 2016). In a double-blind, crossover design, Westerberg and coworkers (2015) investigated the effect of 0.75Hz slow oscillatory stimulation applied over F7-F8 during a 90-minute daytime nap in 19 elderly. They found

increased SWA associated with an improvement in word-pair performance (Westerberg et al., 2015). A later study with a similar experimental paradigm on afternoon naps in older adults showed how enhancing SWA and fast sleep spindle power led to a benefit in visual memory tasks (Ladenbauer et al., 2016).

To our knowledge, only one clinical trial has been conducted where tES was applied during sleep in MCI/AD patients. Ladenbauer and coworkers (2017) enrolled 16 MCI patients in a crossover design to investigate SWA, sleep spindles, and memory consolidation in neurodegenerative disease. Participants (age range 50-81 with no history of sleep disorders) were tested on verbal memory, visuospatial declarative memory, and procedural memory before and after 90 minutes of sleep. Slow otDCS was applied at frontal locations F3-F4, with the anodal current oscillating sinusoidally at 0.75Hz (between 0 and 262μA), with a maximum current density of 0.5mA/cm^2. Stimulation started after 4 minutes spent in the N2 stage. During each stimulation-free interval, online sleep scoring was performed, allowing the next stimulation block to start only when another N2 stage was detected. The synchronization and locking between SWA and fast spindle power were also measured and used to compute phase values for the estimation of a synchronization index. Results showed increased SWA and spindle power together with stronger synchronization during otDCS compared to sham stimulation. Furthermore, significant performance improvement in visual declarative memory was reported. This study suggests that individualized protocols may be most effective in sleep modulation. Although these results are encouraging, further clinical trials with a larger number of patients are needed. To our knowledge, no clinical trial has tested the effects of tES during sleep on MCI/AD protein clearance.

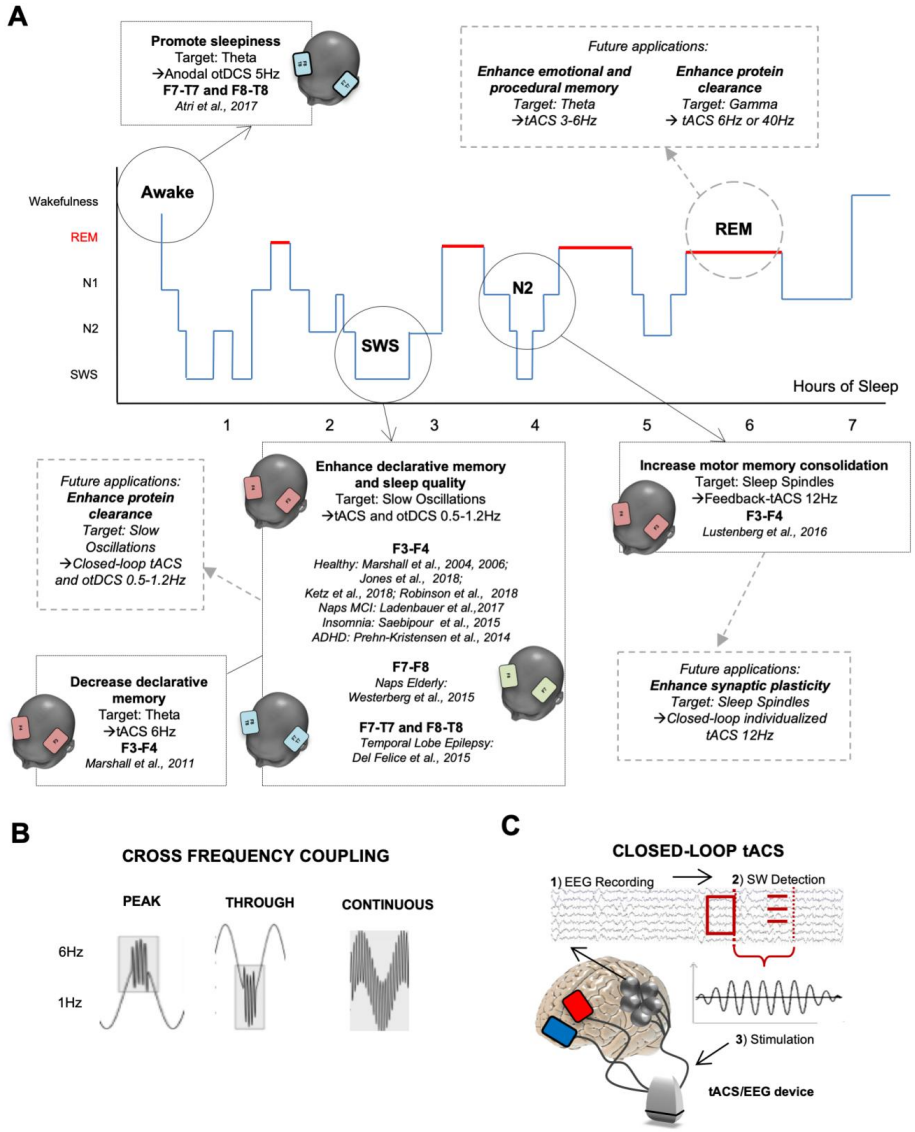


Figure 7. Temporal Framework for tES During Sleep in the Healthy and Pathological Aging Brain. tES can be applied to manipulate various sleep stages, targeting specific cortical oscillations (**Panel A**). Goals include improvement of cognitive and motor performance, as well as modulation of protein clearance and synaptic plasticity. More advanced methods can be applied, including cross-frequency coupling and closed-loop EEG-tES solutions (**Panel B-C**). For instance, CFC allows to combine stimulation of slow frequency carrier activity (e.g. 0.75-1Hz) and faster oscillations in the theta, alpha, beta, and gamma band (e.g. 6Hz or 40Hz), also allowing to couple of the two oscillatory patterns with fine temporal precision (i.e. targeting peak or through of carrier frequency; Panel B). In the case of closed-loop tES (**Panel C**), stimulation is triggered by real-time EEG recording (C1) and detection of slow waves (C2), with semi-instantaneous delivery of tES matching individual SWS frequency (C3).

3.2.4. Future Directions of Sleep Manipulation with NIBS: Challenges and Opportunities

Past and possible future applications of tES during overnight sleep and awake states in healthy and pathological aging populations are presented in Figure 5 and Figure 6, delineating a complex and varied range of opportunities.

Temporal Framework for tES Delivery During Sleep (Figure 7). tACS applications seem to be the preferred choice thanks to their effects on brain oscillations in both the healthy aging population and AD patients (Figure 7A). In different cohorts of individuals, young and old, prior work has already shown

positive results for the use of tES during sleep on consolidation of procedural (Lustenberger et al., 2016) and declarative memory (Jones et al., 2018; Ketz et al., 2018; Marshall et al., 2006, 2004; Marshall and Born, 2011). Sleep interventions might offer the optimal timeframe to elicit SWA and modulate sleep spindles, with possible favorable outcomes in enhancing memory consolidation in healthy aging populations and patients. Although some of these approaches have already been tested, numerous other scenarios remain to be explored. Indeed, sleep is one of the earliest and steadiest biomarkers used to recognize middle/late age individuals at risk of developing dementia. Given the strong relationship between amyloid clearance and some of the EEG features during sleep, manipulating SW sleep may tackle the progression of Alzheimer's pathology in MCI patients and healthy individuals at risk. The rationale for such an intervention derives from the positive outcome of Ladenbauer's study (2017). A clinical trial is now being run applying tACS during sleep to modulate SWS, as well as clinical and cognitive symptoms in MCI patients (NCT03112902). Relative attenuation of gamma activity has also been found to characterize AD patients (Huang et al., 2000). Studies on rodent models of AD have been among the first to suggest new treatment approaches enhancing gamma power. Goutagny and coworkers (2013) underlined how deregulation of hippocampal theta/gamma coupling arises before the overproduction of Aβ, while Iaccarino (2016) found that exogenously-induced flickering lights at 40Hz were able to reduce tau concentrations in pre-symptomatic AD mice. Therefore, the modulation of gamma activity in MCI/AD patients may be a non-invasive and efficient treatment. Clinical trials with this aim are currently being run (Thomson, 2018). Further steps in this direction concern the use of tACS applied at 40Hz (gamma frequency) during sleep in MCI patients. The ultimate aim would be preventing, or at least slowing, neurodegenerative mechanisms by targeting gamma activity and sleep patterns concomitantly, with potentially positive effects in declarative memory consolidation, enhancement of sleep quality, and Aβ clearance.

Going further, new tES approaches allow for more closely mimicking physiological processes that can be implemented during sleep as well. For instance, cross-frequency coupling (CFC) implies stimulation combining multiple frequencies (7B; e.g. 1Hz and 6Hz). CFC provides a mechanism for synchronization between local and global processes across connected areas and cortical networks (Florin and Baillet, 2015). To date, during wakefulness, the most prominent example of CFC is between theta and gamma oscillatory activity during memory encoding/retrieval (Axmacher et al., 2010; Sauseng et al., 2009), but it may also play a role in memory consolidation during REM. Prominent REM theta rhythms coupled with gamma have been seen in rodents (Belluscio et al., 2012; Scheffzük et al., 2011) and monkeys (Takeuchi et al., 2015). Gamma seems to promote synaptic plasticity, supported by theta (Lisman and Buzsáki, 2008; Lisman and Jensen, 2013). This may be specific for phasic REM states, where the synchrony between theta and gamma is enhanced, suggesting that tonic REM phases support offline mnemonic processing while phasic bursts of activity may promote memory consolidation (Boyce et al., 2016; Montgomery and Woodall, 2008). Stimulating theta and gamma in CFC during REM may then help consolidate mnemonic traces as well as SWS stimulation. New studies could investigate this.

NIBS during sleep usually requires the experimenter to start the stimulation after 3-4 minutes of ongoing EEG typical of N2 or N3. A new experimental paradigm recently implemented a closed-loop algorithm able to independently start the stimulation when the subject is in N3 (Jones et al., 2018; Ketz et al., 2018b; Robinson et al., 2018). This algorithm for augmentation of slow-wave sleep first detects the presence of SW oscillations, computing the mean of the power spectra of SW (Figure 7C). The frequency of the sinusoidal wave produced by tACS is then set to an individualized SW frequency mean to match the stimulation frequency and phase with the natural ongoing SW activity.

Targeting Network Alterations and Proteinopathy (Figure 8). One of the biggest challenges in available tES studies in sleep concerns the electrode montage and resulting cortical electric field. While most studies have administered stimulation over frontal and prefrontal derivations (F3-F4, rarely F7-F8), new devices enable multisite stimulation of neural networks, engaging interconnected cortical areas as well as entire networks. As previously mentioned, the DMN possibly represents the cortical network whose FC is mostly altered by sleep deprivation and age-associated brain changes. Therefore, stimulation of DMN may enhance internal connectivity strength and act as an early intervention to counteract the disruption of resting-state brain connectivity patterns. To do so, multifocal stimulation using several relatively small electrodes has been used to achieve more focal stimulation of specific cortical targets (Ruffini et al., 2014). This allows a spatially specific protocol that can simultaneously stimulate different areas belonging to the same (e.g. DMN) or different networks. Studies also found connectivity alterations in aging within anterior VAN regions (Deslauriers et al., 2017), making it a potential target to enhance selective attention in elderly subjects.

To target a specific individual network, the participant may undergo an fMRI able to identify the strongest and weakest areas included in the network allowing a more focal and individualized stimulation. Accurate modeling of the induced electrical currents and fields is now possible through the use of personalized brain models (Miranda et al., 2013). Ongoing trials are testing the feasibility of stimulating target regions with maximum amyloid levels using individualized multifocal montages (NCT03290326). Generally, this allows, in turn, the optimization of electrode montage based on individual neuroimaging data (Ruffini et al., 2014) such as amyloid-β PET (e.g. Florbetapir or PiB), CT and T1-weighted MRI data (Figure 8B).

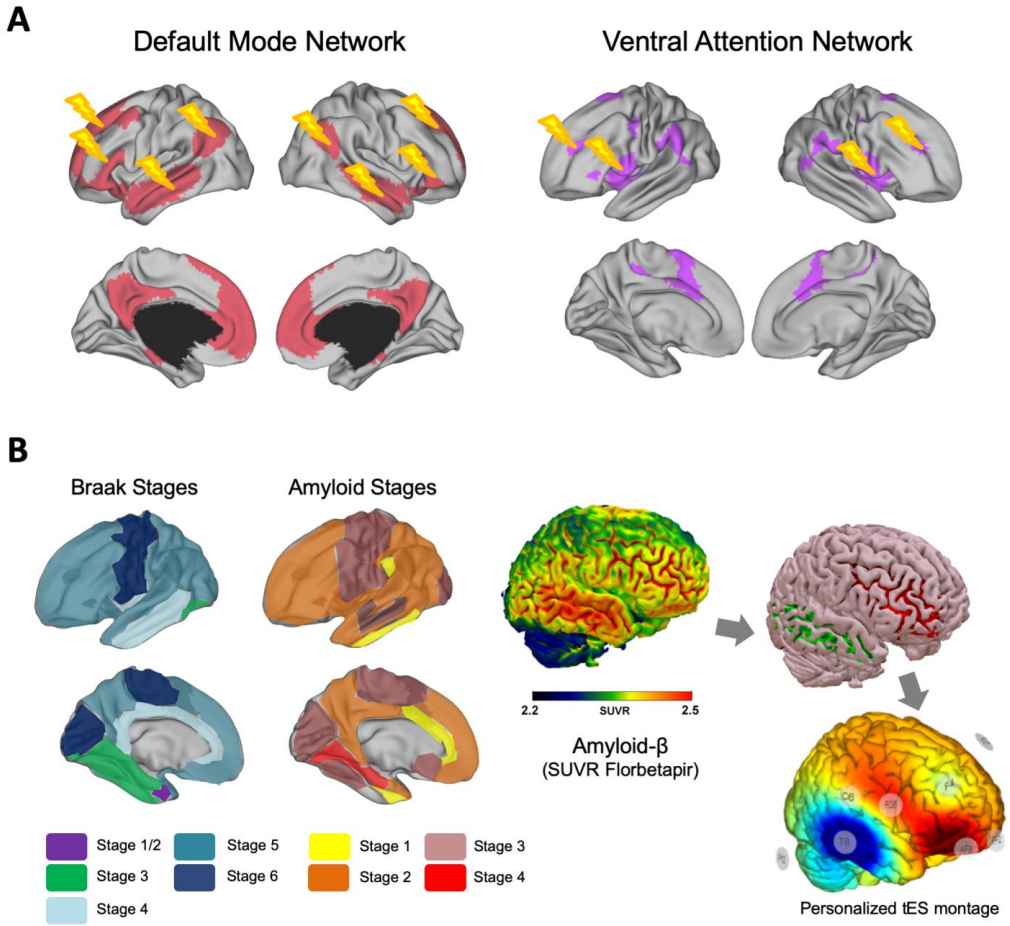


Figure 8. Tackling Network Alterations and Proteinopathy Overnight. tES can be optimized to tackle alterations of spatio-temporal functional networks as those recorded via resting-state fMRI, with particular emphasis on networks previously shown as altered in healthy and pathological aging, e.g. the default mode and ventral attention networks (**Panel A**). Given the relevance of protein clearance processes overnight, and the recent discovery of dominant oscillatory activity (i.e. theta activity) accompanying CSF clearance dynamics during sleep, tES could also be tailored to target individual tau and amyloid accumulation overnight by maximizing stimulation over regions with higher tracer uptake at PET imaging (**Panel B**).

SIGNIFICANCE.

As discussed in this second review, sleep manipulation through NIBS techniques could boost nighttime protein clearance, and slow down/halt the conversion and progression of AD disease. Although early results from NIBS application during sleep in healthy elderly individuals and patients with dementia are promising, further research is needed to improve our understanding of mechanisms and investigate potential target definition and model-driven optimization of NIBS protocols allowing the efficient modulation of cortical activity.

3.3 Third review: Neurodegeneration In Space Missions And NIBS Applications.

A similar version of the present article has been published [Romanella SM, Sprugnoli G, Rossi S, Ruffini G, Seyedmadani K, Santarnecchi E. *"Noninvasive Brain Stimulation and Space Exploration: Opportunities and Challenges".* Neurosci Biobehav Rev. 2020 Sep 13:S0149-7634(20)30561-3. doi: 10.1016/j.neubiorev.2020.09.005.]

As aforementioned, NIBS techniques might represent a valid set of potential countermeasures to target a wide range of space-flight risks (Figure 9). Space travel presents significant challenges to human physiology. The average length of space-flights has increased from a few days up to several months, with the forthcoming first Mars landing (scheduled by NASA for the year ~2034) expected to require approximately 2 years of travel. Even shorter missions, such as the ~30/60 days Moon landing in ~2024 will present challenges, ultimately leading to the complexity of building long-lasting space installations on Lunar and Martian surfaces. Space exploration involves multiple classes of stressors, ranging from microgravity and cosmic radiations affecting human physiology to those related to living in a confined and isolated environment impacting mood and cognition. Currently proposed solutions are mainly directed at the spacecraft design level to mitigate some stressors: thick shields incorporated into the walls of the spacecraft habitat to minimize radiation exposure, and rotating habitats designed to produce an artificial gravitational field to mitigate the effects of microgravity. Although these ideas can be effective, additional solutions directly targeting and interacting with human physiology could ensure more protection of astronauts' health. Albeit TMS application may be unpractical during actual space-flights due to its weight and size, its use before and after missions could help to collect data on cortical excitability, plasticity, and connectivity levels in the brain (Bestmann, 2008; Ferreri and Rossini, 2013). TMS can thus constitute a valuable tool to uncover the (patho)-physiological brain response to space missions and reveal specific biomarkers of astronaut brain adaptation to space-flight. On the other side, due to tES safety profile and portability, its application in out-of-the-lab environments is particularly appealing (Antal et al., 2017). Studies have shown an improvement in cognitive and motor performances with results translating outside the laboratory walls, also in terms of performance enhancement on professional athletes, soldiers, surgeons, and air force pilots (Ciechanski et al., 2017, 2018; McKinley et al., 2013a; Okano et al., 2015). Considering the promising results obtained on "ground-based" populations, tES could be a useful tool to enhance the visuomotor and cognitive skills of astronauts and cosmonauts, accelerating training efficacy and possibly preventing detrimental effects of space-flight.

This third review offers an overview of the opportunities and challenges in NIBS applications for space exploration. I start by summarizing the main space-related stress factors such as gravity changes, cosmic radiation, and ICE-related consequences. Considering the reported detrimental effects of space missions on the central nervous system (CNS), I then discuss in detail how some NIBS protocols could be easily implemented as a potential tool to enhance crew performance and well-being in a wide range of cognitive, motor, and psychological domains. Such an approach could be particularly helpful for a long-duration stay in space installations on Lunar and Martian surfaces, as well as on the International Space Station (ISS). Applications also include the facilitation of pre-flight Earth-based training, to consolidate and potentially

accelerate procedural learning. We also suggest NIBS implementation for the measurement of perturbation biomarkers pre and post-flight.

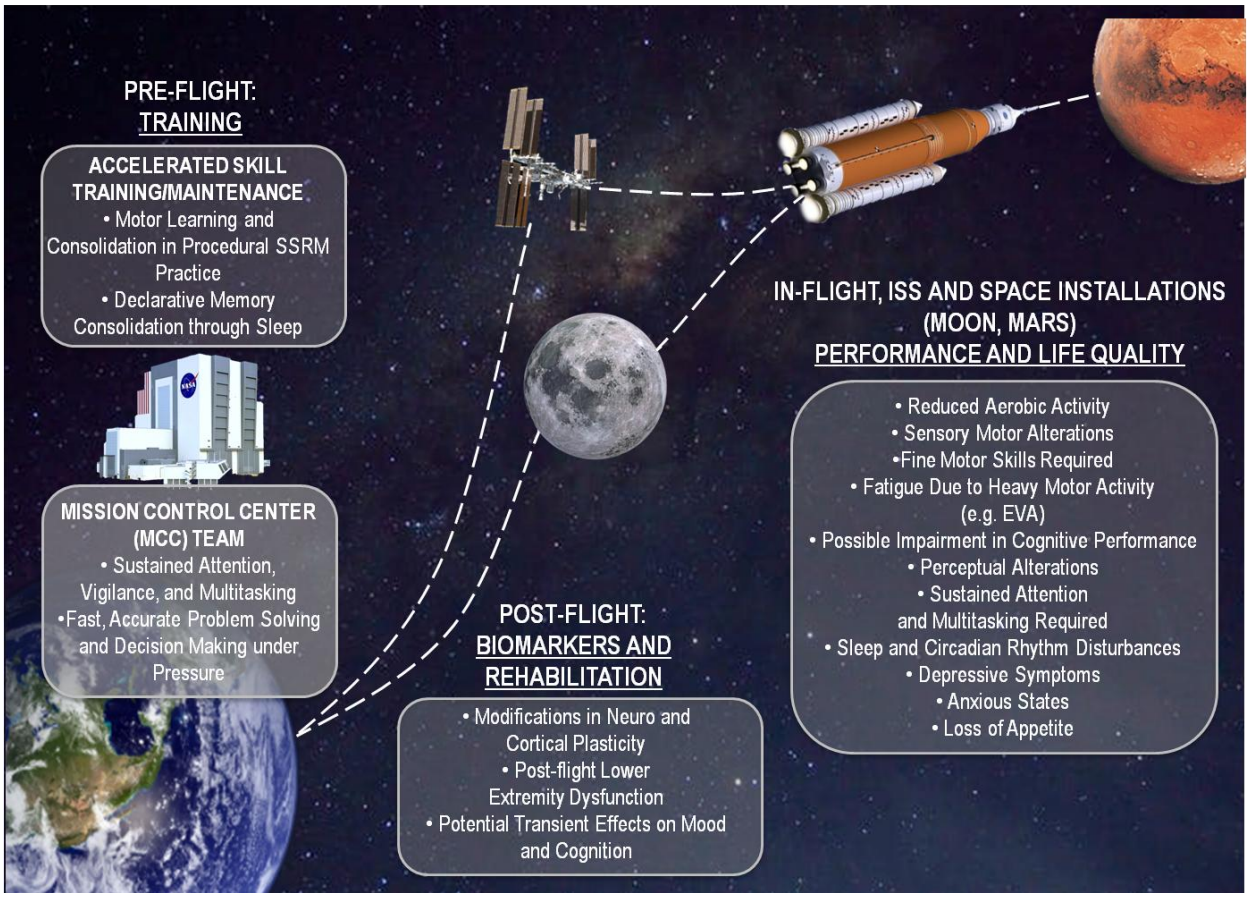


Figure 9. Areas pivotal for space exploration that could potentially benefit from NIBS applications. NIBS could be adapted to (i) improve astronaut physical and psychomotor training, cognitive performance, and adaptation to space-related stressors on Earth, as well as enhance and support the performance of the team at the Mission Control Centre during operations. NIBS could also (ii) mitigate the impact of ICE, microgravity, and cosmic radiation during space-flight or long-duration missions on the ISS, and (iii) further tackle these issues in a habitat on Moon and Mars. Finally, NIBS-based measures of cortical excitability, plasticity, and excitation-inhibition balance could be used to investigate brain changes and support the post-flight return to baseline/recovery.

3.3.1. Space-flight-related Stressors

Many factors can play a role in threatening or maintaining astronaut well-being. These can be divided into *environmental* stressors, including gravity variance, cosmic radiation, pressure, extreme temperature, and changes in light/dark cycles; *spacecraft* stressors, such as vibration, noise, internal temperature, light, life support systems, and habitable design; *psychological* stressors, like isolation, danger, monotony, workload, and teamwork (Kanas and Manzey, 2008). Several gaps identified by NASA HRP open potential implementations compatible with the capabilities of NIBS. Below we introduce three classes of stressors and their consequences on human physiology, such as weightlessness (Microgravity), Galactic Cosmic Radiation (GCR), and life in Isolated, Confined, and Extreme environment (ICE).

Weightlessness (Microgravity). Future space missions will consist not only of longer time spent in spacecraft but also longer periods of exposure to weightlessness with several transitions between different

gravity levels, from 1g on Earth to 0.16g on the Moon, to 0.38g on Mars. Gravity changes introduce physiological deconditioning, involving for example hydrostatic shift and neuro vestibular adaption, and, ultimately, potential modifications in brain anatomy and neurophysiology (Demertzi et al., 2016). For instance, investigations conducted on actual space-flight reported an increase in α frequency (8-12 Hz) in parieto-occipital and sensorimotor areas, possibly related to decreased gravitational input (Cheron et al., 2006). Because of the inverse relationship between α power amplitude and BOLD signal (Feige et al., 2005), the increase in α oscillations during permanence on the ISS has been associated with a general decrease in cerebral blood oxygenation (Schneider et al., 2008), further underlined stronger α power desynchronization (event-related desynchronization: ERD) from occipital-parietal (α ERD) to central areas (μ ERD). Interestingly, authors also found a significant contribution to this α rhythm of the cerebellum and vestibular network in microgravity (Cebolla et al., 2016), possibly due to increased processing effort and demand necessary for postural stabilization to integrate incongruent vestibular information.

To date, only two studies reported functional MRI (fMRI) results related to space-flight. The fMRI protocol was applied twice on a 44yo male cosmonaut during his first long-duration mission (169 days) on the ISS, i.e., 30 days before launch and 9 days after earth re-entry. The authors reported a decrease in resting-state functional connectivity of the right insula as well as between the left cerebellum and right motor cortex. The functional modification detected in the insula can be explained by its role in the integration of neurosensory input (i.e., vestibular, visual and proprioceptive) and its functions in the processing of self-motion, spatial orientation (Brandt et al., 2005), perception of vertical (Lopez et al., 2007), and visual processing related to gravitational cues (Lopez et al., 2009). The motor cortex appeared less connected during the resting-state and it was activated more during a motor imagery task (e.g. playing tennis or walking) probably due to compensatory and adaptive response to a microgravity environment. Regions showing adaptation to microgravity, such as the precentral/postcentral gyri and cerebellum, are associated with voluntary motor initiation, proprioception, and motor coordination (Demertzi et al., 2016). Functional alterations in these brain areas due to weightlessness, are followed by decreased speed and accuracy of fine goal-oriented movements, somatosensory difficulties, and movement-timing impairment (De la Torre, 2014a). A second study explored task-based functional connectivity alterations of 11 astronauts after long-term missions concerning healthy controls not involved in space missions (Pechenkova et al., 2019). A plantar stimulation was applied with an on-off paradigm to elicit the mechanoreceptors responsible for the postural and locomotor control that are strongly impaired during space-flight as well as upon return to Earth. The investigators found a post-flight increase in connectivity in the right posterior supramarginal gyrus (involved in vestibular input processing and perception of upright position) as well as a decrease between the vestibular nuclei, right inferior parietal cortex, cerebellum, and motor, visual, vestibular, and proprioception areas. Furthermore, the post-flight to the pre-flight difference in connectivity between the right supramarginal gyrus and the left anterior insula was found to be positively correlated with the severity of space motion sickness symptoms (Pechenkova et al., 2019). Authors referred the functional connectivity alterations to the long-term microgravity exposure that cause an important sensory deprivation, while on the

other hand, the absence of differences in pure brain activation due to plantar stimulation might be attributed to the fast recovery upon returning to Earth (Pechenkova et al., 2019). In any case, microgravity seems to induce changes in the multisensory and locomotor brain domains, that however require long-term investigations and larger samples to appropriately disentangle its (patho)physiological consequences (Pechenkova et al., 2019).

It is pivotal also to discuss a recognized ophthalmological health risk that often evolved during long-duration space-flight, the Space-flight Associated Neuro-ocular Syndrome (SANS), previously called Vision Impairment and Intracranial Pressure (VIIP). This syndrome affects two-thirds of US crew members who flew on ISS (NASA, Human Exploration Research Opportunities: HERO, 2015), consisting of visual performance decrements and ocular structural changes (Kramer et al., 2012; Mader et al., 2011). Following their return to Earth, some astronauts showed partially reversed modifications to previous conditions, while changes persisted in others (Mader et al., 2011). SANS seems to be triggered by a cephalic fluid shift due to microgravity, disrupting the balance between hydrostatic and local tissue pressures. An impaired CSF absorption would then increase intracranial pressure, directly swelling the choroid, and affecting the eyes (Hargens and Richardson, 2009; Herault et al., 2000).

Space neuroscience includes different ground-based analogs aimed at reproducing the impact of microgravity on the human body on Earth, such as dry immersion, head-down bed rest (HDBR), and parabolic flights. Since 1986 HDBR has been one of the most implemented space analogs, enabling insight on bodily and mental changes induced by immobilization, isolation, and monotony of activities. During HDBR, the subjects lie in an inclined bed with the head down (-6 or -12 degree in most cases) for a period ranging from a few hours to several weeks. HDBR causes a cephalic fluid shift thought to be responsible for SASN, alterations in cerebral oxygenation, and changes in cerebral perfusion (Pavy-Le Traon et al., 2007). However, this solution does not provide any gravitational and vestibular modifications (Pavy-Le Traon et al., 2007). Instead, during dry immersion subjects are immersed in thermoneutral water while covered in an elastic waterproof fabric to keep them dry, avoiding direct contact with water. Immersion is an adequate alternative since it mimics several spaceflight features, such as lack of a supporting structure against the body, centralization of bodily fluids, confinement, immobilization, and hypokinesia (Navasiolava et al., 2011). Finally, during parabolic flights, a specific flight trajectory is carried out by an airplane, so that normo-, hyper-, and micro-gravity phases are experienced by subjects on board. The plane can modify the parabolas trajectory to simulate Martian gravity (0.38 g) and lunar gravity (0.16 g). Albeit a typical duration of microgravity onboard of parabolic flights is 25-30s, aircraft are usually able to perform around 30 parabolas during one mission (Karmali and Shelhamer, 2008).

Analog-based studies only partially corroborated findings of actual spaceflight research, underlining the limitations of such space analogs. A recent dry immersion study reported decreases (instead of a general increase and desynchronization) in α power and a widespread increase in θ (4-7 Hz) power (Kuznetsova et al., 2015). Parabolic flight studies showed a decrease in β (15-30 Hz) power, possibly related to different factors such as emotional reaction to weightlessness (Schneider et al., 2008), baroreceptor stimulation

(Lipnicki, 2009), or lower arousal levels (Wiedemann et al., 2011). The first study using low-resolution brain electromagnetic tomography (LORETA) in low gravity demonstrated that microgravity phases of parabolic flights result in a considerable increase in the spectral power of β activity (18-35 Hz) specifically in the right superior frontal gyrus (Schneider et al., 2008), possibly explaining part of the modifications in performance in cognitive tasks and emotional processing (Faw, 2003; Miller and Cohen, 2001). HDBR studies corroborated the increase in α power as seen during actual spaceflight, but have also reported contrasting findings, probably due to the constant gravitational input still present in these settings (Han et al., 2001).

As for MRI, a study on parabolic flight showed a decreased intrinsic connectivity strength in the right angular gyrus, known to be involved in multisensory integration, as well as in cognitive and spatial tasks (Van Ombergen et al., 2016). Many different MRI-based studies have been run on subjects in HDBR for short or longer experimental time (Van Ombergen et al., 2017), reporting alterations in fine motor skills (Liao et al., 2015), executive function (Liao et al., 2012), and spatial working memory (Cassady et al., 2016). No MRI-based studies of dry immersion have been performed so far.

Cosmic Radiations. Cosmic radiation (CR) is composed of high-energy particles of GCRs and solar particle events, including protons, helium nuclei, and HZE ions. Humans on Earth and in low Earth orbit (LEO) are protected from space radiation by Earth's magnetosphere, which deflects these high-energy particles. However, humans beyond LEO and outside the bounds of Van Allen Belt have no such protection, suffering from direct and indirect damage due to radiation exposure. ISS is still also partially protected by the magnetosphere, while the journey to Moon and Mars will involve a heavier and longer exposition to radiations. Data collected by the Curiosity Rover roaming on Mars surface till February 2019, found unusually high levels of space radiations on the Martian surface. Apart from the well-known lifetime increase in cancer risk, space radiations are linked to acute and late brain effects. Acute CNS risks include altered cognitive function, reduced motor function, and behavioral changes, all of which may affect performance and health. Cognitive deficits include short-term memory, learning, spatial orientation, motor function, emotion recognition, risk decision making, vigilance, reaction time, processing speed, circadian regulation, and fatigue (NASA SP-2009-3405, Strangman et al., 2014). Late CNS risks may include brain atrophy and accumulation of amyloid-β, possibly leading to neurological disorders such as Alzheimer's disease (AD) and premature aging (NASA SP-2009-3405). A lack of human epidemiology data on CNS risk complicates research for countermeasures. Possible observation of CNS effects in astronauts participating in past NASA missions is highly unlikely because lengths of past missions were relatively short and small sample sizes, as well as because astronauts were partially protected by Earth's magnetic field and LEO, which together reduce the GCR dose-rate. To characterize radiation effects on the CNS, radiotherapy patients (Greene-Schloesser et al., 2012) and ground-based studies in animals have been conducted for more than two decades using charged particle accelerators delivering doses of charged particles similar to those expected during a mission to Mars. These models confirmed not only direct and indirect damage to DNA and proteins (for a review see but also an impact of HZE nuclei on neurogenesis and (possibly consequent) cognitive impairment. HZE nuclei are capable of producing a column of heavily damaged cells along their

path through tissues, described as “microlesions” (Todd, 1989), responsible of detrimental consequences on CNS function. Investigation on irradiated animal models showed different mechanisms behind consequences of GCR on CNS that have been reviewed elsewhere (NASA SP-2009-3405).

Incorporating animal research into actual space missions, other than reproducing similar conditions on Earth, is vitally important to understanding the biological impacts of deep space. A relevant new metabolic control technology seems to give great advantages in deep space transition. Synthetic torpor consists of artificially inducing regulated, reversible depressed metabolic states of experimental animals (Cerri et al., 2016). Compared to active metabolic states, the advantages include reduced mass, volume, and power life support within the spacecraft and mitigated negative health effects induced by radiation and microgravity (Cerri et al., 2013; Gemignani et al., 2015; Tupone et al., 2013), (for a comprehensive review see Cerri et al., 2016). Synthetic torpor-inducing systems may also start as preliminary tests for hibernating systems to maintain human crewmembers in similar metabolic states on long-duration missions. Below we review the main symptomatology associated with exposure to GCR. Recent neuronal morphometry investigations using Golgi silver stain in mice and rats demonstrated that γ-rays, protons, and ^{56}Fe radiation cause reductions in hippocampal neuron arborization (>50% at 30 days) as well as the loss of dendritic spines, each of which can limit the complexity of signal processing (Chakraborti et al., 2012; Parihar and Limoli, 2013; Quasem et al. 2007). Notably, spine density positively correlates with cognitive performance using novel object-in-place paradigms (Parihar et al., 2015). Denisova and coworkers (2002) exposed rats to moderate doses of ^{56}Fe particles and tested their spatial memory in an eight-arm radial maze. Cognitive behavior deficits were observed, specifically exposed rats committed more errors than control rats. The former was, in fact, unable to adopt a spatial strategy to solve the maze (Denisova et al., 2002). Britten and colleagues considered that neurocognitive tasks regulated by the prefrontal cortex could be impaired after exposure to low doses of HZE particles, which would prevent astronauts from performing complex executive functions. The authors used rats receiving either sham or real irradiation treatment and tested their ability to perform attentional set-shifting 3 months later. Rats that received low doses of ^{56}Fe particles showed significant impairments in their ability to complete the test, with only 17% of irradiated rats completing all stages as opposed to 78% of control rats. These observations suggest that exposure to mission-relevant doses of ^{56}Fe particles results in the loss of functionality in the prefrontal cortex (Lonart et al., 2012). More recently, a new experimental protocol on mice simulating exposures from GCR during a prolonged mission in space (mixed field of neutrons and photons for 6 months with a dose rate of 192 mGy/day), showed a decrease in hippocampal neuronal excitability and disrupted cortical LTP (Acharya et al., 2019). Moreover, mice developed social avoidance, anxiety, impaired fear extinction memory, and difficulties in recognize location and object novelty, all features that can threaten the crew and that the authors estimated will be developed by at least one astronaut during the trip to Mars (Acharya et al., 2019).

Anxiety can be measured in rodents by an aversion to enter and/or remain in open, often brightly lit areas (Walf and Frye, 2007). Anxiety-like phenotypes have been reported in rodents chronically after GCR exposure and up to one-year post after helium exposure alone, suggesting a link between anxiety-like states

and GCR exposure (Acharya et al., 2019; Walf and Frye, 2007). Conditioned Taste Aversion. The conditioned taste aversion (CTA) test assesses avoidance behavior when the ingestion of a normally acceptable food item is associated with illness (Riley and Tuck, 1985). Deficits in CTA seem to be partially induced by very low doses of heavy ions (Hunt et al., 1989; Rabin et al., 2000, 1994, 1991, 1989). Terrestrial Human Data. Data on radiotherapy patients confirmed the deleterious effects of ionizing radiation on CNS (Greene-Schloesser et al., 2012). Behavioral changes, such as chronic fatigue and depression, occur in many patients undergoing irradiation for cancer therapy. Neurocognitive effects are observed at lower doses, especially in children. Radiotherapy treatment in oncology for several tumors found impairments in cognitive functioning, language acquisition, visual-spatial ability, memory, and executive functioning, as well as changes in social behaviors. Similar effects did not appear in patients treated with chemotherapy (Goldberg et al., 1982; Keime-Guibert et al., 1998). Atomic bombing and Chernobyl accident victims, receiving low to moderate doses of radiation, showed evidence of memory and cognitive impairments (Bromet et al., 2011; Loganovsky and Yuryev, 2001; Loganovsky and Loganovskaja, 2000; Yamada et al., 2009).

Isolated, Confined, and Extreme (ICE) Environments. Manned space missions entail unusual conditions that astronauts must adapt to. They include not only life-threatening conditions such as microgravity and cosmic radiations but a wide range of stressing factors such as isolation from family and friends, confinement in cramped spaces, and coping with extreme working conditions. Spacecrafts are artificial areas with a preset of environmental conditions including Environmental Control and Life Support System (ECLSS), limited habitable volume, and living conditions. Spacecraft's normal life is stressed also because of monotony, restricted consumables, and non-24h light-dark cycles. Longer distances from Earth and delays in communication increase the sense of isolation, requiring the crew to work more independently without assistance from NASA’s Mission Control. Some of these factors induce more risk to the health of crew members such as increasing levels of CO^2 in the cabin at all times or light conditions causing a change in the circadian rhythm of the crew (Law et al., 2014; NASA/TP–2010– 216126). To better understand potential consequences, studies on Earth-based analog ICE environments have been performed. At these facilities, crewmembers spend months in isolation and harsh weather conditions, performing a variety of tasks and procedures like those carried out in space missions. Some examples include *Antarctica* which is perhaps the best-known and most commonly studied analog environment (Lugg, 2005); *Aquarius*, a submarine installation with atmospheric control capability; remote locations in the desert (NASA’s Desert Research and Technology Studies or DRATS); and mission control based (NASA JSC Human Exploration Research Analog, HERA). ICE environmental characteristics contribute to creating a state of anxiety, lack of motivation, irritability, and apathy. Going further, isolation and high prolonged alertness are some of the stressing factors that could trigger anxiety and high levels of cortisol (also given by shift in sleep-wake cycles) impacting upon appetite-regulating hormones, immune system, and hypothalamic-pituitary-gonadal axis, which plays a critical part in reproductive and immune system regulation. Impaired physical and social interactions may impact teamwork, especially in long-duration missions where the crew has to work together

and without another human contact for a long time. These issues may result in several potentially hazardous conditions, such as lower performance, mood disorders, and other psychological conditions (Van Baarsen et al., 2009). Because behavioral, mood, and cognitive impairment may put the crew members and the missions at risk, new potential solutions need to be explored. NIBS includes safe and portable techniques that have been widely applied therapeutically in cognitive and sensory domains.

3.3.2. Framework and Targets for NIBS applications

NIBS protocols are frequently administered in "online" sessions, meaning stimulation is applied while participants are involved in tasks or other activities. Especially in the case of tES, brain stimulation can represent a versatile tool applicable at multiple stages in the astronaut's lifetime, ranging from cognitive and motor training on Earth in preparation for space missions to actual space-flight (Figure 10). Online stimulation is not always possible during space-flights (e.g. EVA or cognitive training in some ICE environments). In those situations, stimulation can be performed before the task, triggering different forms of cortical plasticity that would potentially boost performance/learning. For instance, tDCS specifically induces online and offline effects (Labruna et al., 2016; Ridding and Ziemann, 2010), as reported in multiple TMS studies on M1 cortical excitability (e.g. Jamil et al., 2017). Additionally, both of these effects have been proven to outlast the stimulation period and be even more robust offline than during stimulation. Cathodal tDCS on M1 leads to an offline long-lasting inhibition in cortical excitability, as measured by a drop in MEP amplitude up to 90 minutes after stimulation (Nitsche and Paulus, 2001, 2000). Similar after-stimulation effects of tDCS have been shown also in different areas, such as somatosensory cortices , DLPFC (Keeser et al., 2011), and cerebellum (Grimaldi et al., 2016). In various contexts, it is also possible to perform stimulation after a training session to enable knowledge/learning consolidation, or in-between cognitive and motor tasks to prime/consolidate memory traces (Rumpf et al., 2017). Moreover, tES can also be used during sleep, modulating deep sleep stages involved in the consolidation of declarative memory (Jones et al., 2011; Ketz et al., 2018; Marshall et al., 2006, 2004).

TMS and tES are also powerful tools to investigate biomarkers of adaptation to space-flight. By controlling the input sent to cortical areas by TMS or tES, it is possible to quantify local responses, speed of signal propagation across networks, and network resilience to perturbation. In astronauts, TMS and tES assessments combined with EEG and neuroimaging before and after a mission could help identify potential biomarkers of local plasticity, cortical excitability, connectivity, and changes in brain oscillations (Bestmann, 2008; Ferreri and Rossini, 2013) previously associated with, e.g., depression and neurodegeneration. More details on specific NIBS applications are available in the dedicated sections below.

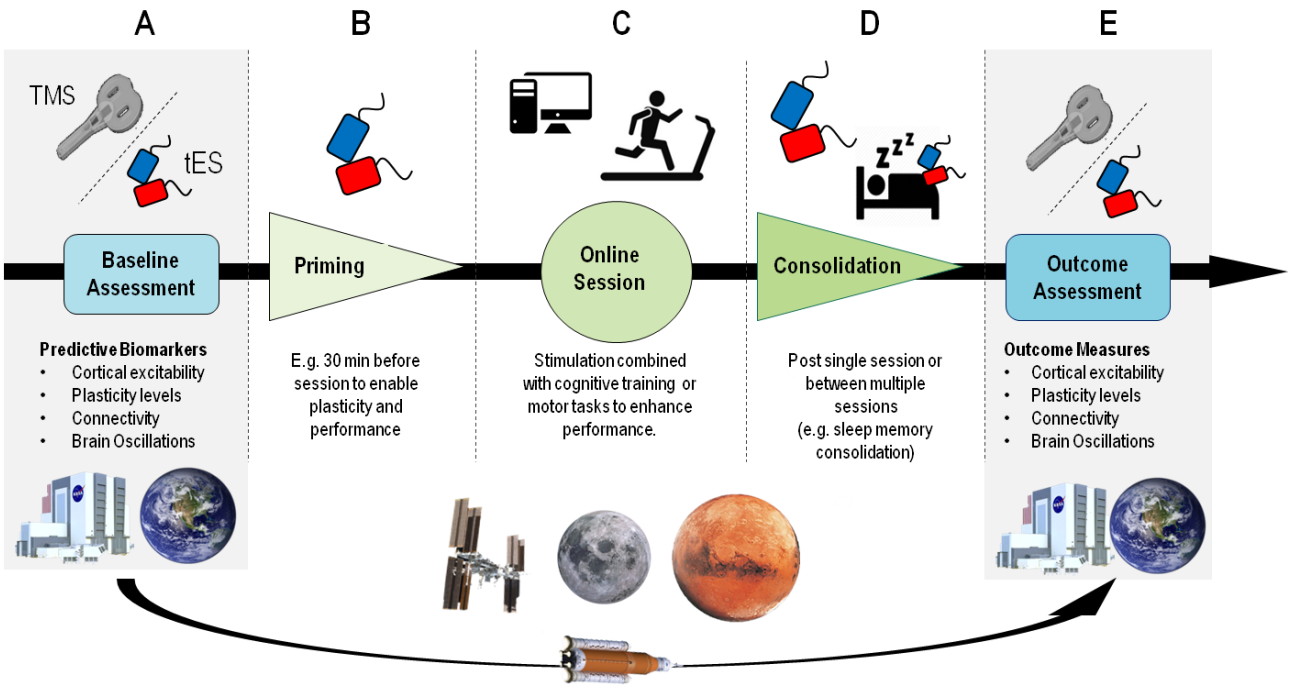


Figure 10. Framework for NIBS application. NIBS can be applied with different outcomes depending on the specific goal and chosen time of administration. Both TMS and tES could be implemented for Earth-based assessment to investigate biomarkers and modifications in cortical parameters, such as excitability and brain oscillations, testing astronauts before and after space-flights (**Panel A and E**). On the ISS, in space installations, as well as on Earth, tES could be applied to enhance performance in different domains. In the case of activities that do not allow concurrent tES application (e.g., EVA), stimulation could be performed before a specific task to enable plasticity (**Panel B**). The most common paradigm involves "online" stimulation, i.e. tES/TMS performed concurrently with a subject performing a motor or cognitive task (**Panel C**). Stimulation can also be administered after a task/training, to consolidate learned abilities and memory traces, also during sleep (**Panel D**). Finally, the same biomarkers collected at baseline could be used to assess the impact of long-term space-flight on brain structure and function **(Panel E**).

3.3.3. Pre-flight NIBS Applications: Training

Before facing the challenging environment of deep space, future astronauts are carefully trained on Earth. This includes medical tests, physical and EVA training, and procedure knowledge test, as well as preparation for experiments that the crew will accomplish during their mission. Pre-flight training usually lasts 2-4 years, and it is geared to special conditions and environments astronauts will be confronted with during launch, in space, and during landing. For instance, motor learning and consolidation are particularly relevant to operate the Space Station Remote Manipulator System (SSRMS) on ISS. The appropriate manipulation of this robotic arm is essential to perform advanced reparation at modules and on ISS itself, thus requiring 4 years of training in preplanned motor patterns and sequences on different simulators. Astronauts need to maintain a high level of visuomotor coordination, continuously checked and corrected by leveraging multitasking ability and sustained attention. In this context, tDCS protocols have been administered to enhance the consolidation of motor processes and procedural learning (Buch et al., 2017). During years-long training, astronauts are also required to learn a great number of procedures and high-detailed knowledge of a wide range of domains, from space physiology to geology and spacecraft engineering. tES has been applied during sleep to improve declarative memory learning, consolidation, and recall (Marshall et al., 2004, 2006). Below we provide an overview of domains where NIBS could be implemented in pre-flight operations.

TMS to Induce Neuroplasticity and Motor Learning. Changes in synaptic strength (i.e. neuroplasticity) are governed by various mechanisms, such as LTP and LTD (Malenka and Bear, 2004). LTP can be naturally induced following learning (Rioult-Pedotti et al., 2000), but can also be experimentally triggered by external stimulation delivered at certain patterns to mimic natural brain rhythms. Theta Burst Stimulation (TBS) is a TMS protocol widely known for its plasticity-inducing ability (from Larson et al., 1986; for a comprehensive review see Larson and Munkácsy, 2015). As aforementioned, early reports suggested that an intermittent pattern of stimulation (iTBS) resulted in increased cortical excitability (similar to LTP) (Huang et al., 2005). These findings have been widely replicated (for reviews see Huang et al., 2017; Suppa et al., 2016). iTBS could, therefore, be used to induce neuroplasticity and enable performance in learning tasks, with a focus on motor and visuomotor abilities.

Intermittent TBS provides a potential tool to enhance performance specifically in the early phase of motor learning (Honda et al., 1998; Iezzi et al., 2010). As an example, excitatory iTBS over M1 administered 10 minutes before a motor task enhanced the learning of ballistic movements (Agostino et al., 2008; Teo et al., 2011). Koch and coworkers (2020) administered cerebellar iTBS to accelerate the adaptation in a visuomotor adaptation task (VAT) (Krakauer, 2009), a specific form of motor learning task which evaluates errors in response to a novel perturbation. iTBS accelerated the error reduction slope in response to new perturbation (Koch et al., 2020). This may be a relevant application in speeding the adaptation of Earth-based learning motor tasks.

Interestingly, TBS protocol may also help in the training of non-dominant hands while engaging in tasks such as operating the SSRMS, Moon and Mars landing, and EVA operations. The performance of the non-dominant hand after intense motor training can outperform the dominant one (Platz et al., 2012b, 2012a; Ridding and Flavel, 2006). Platz and colleagues (2018) stimulated healthy right-handed subjects performing arm ability training (AAT) for one week, administering iTBS over either S1 or M1 contralateral to the trained left arm. The authors reported that the excitatory priming of S1 or M1 directly before a daily training session enhanced sensorimotor learning (Platz et al., 2018). Participants not only showed better performance at the AAT task when stimulated with iTBS, but they also saw an improvement in the generalization task for the trained left hand. iTBS could be used to enhance motor learning across different sensorimotor abilities (Platz et al., 2018).

tES, Motor Learning, and Motor Memory Consolidation. In the context of motor learning, tDCS has also been shown to modulate both overall motor performance as well as specific processes involved in learning and consolidation (Kang and Paik, 2011; Krause et al., 2016; Orban de Xivry and Shadmehr, 2014). As aforementioned, M1 is the most involved in early learning phases, while motor learning is mediated by different areas such as premotor and parietal association areas (Honda et al., 1998). Different studies applied excitatory-anodal tDCS over M1 during or immediately after a motor sequence learning task, showing facilitation in early consolidation of procedural learning (Antal et al., 2004; Nitsche et al., 2003; Tecchio et al., 2010), although this has not been reproduced in all available studies (Ambrus et al., 2015; Ehsani et al., 2016). Stagg and coworkers have shown polarity-specific effects of tDCS during explicit motor learning,

with performance improvement observed only with anodal stimulation and when stimulation was performed concurrently with the task (Stagg et al., 2011). Along the same line, implicit motor learning was enhanced with tDCS applied concurrently with training by positioning the anode over M1, while stimulation of frontal and prefrontal areas did not affect performance (Antal et al., 2004; Nitsche et al., 2003). In the context of motor adaptation (i.e., modifying movements in response to different sensory inputs or motor outputs, leading to a reduction in errors introduced by the altered conditions), Hunter and coworkers (2009) tested the motor performance of reaching a target with the arm experiencing different physical environments such as robot-induced velocity-dependent force fields. The authors administered active or sham tDCS over the M1 during the adaptation phase of the movement when the velocity-dependent force field was applied. Although the global error in arm reaching was similar in both conditions, real 1mA anodal tDCS induced a significantly better global reaching performance. These results suggested that tDCS enhances the development of an internal representation of a novel adapted movement. Importantly, tDCS effects could persist for months when applied in multiday protocols, due to its ability to modify brain plasticity. Reis and coworkers showed that tDCS delivered over 5 consecutive days combined with a motor learning protocol improved performance, not only during the experimental paradigm but for at least 3 months after training. Similarly to tDCS, tRNS applied over the M1 for 10 minutes improved implicit motor sequence learning and caused excitatory aftereffects lasting up to 1.5 hr (Terney et al., 2008). In the context of motor adaptation (i.e., modify movements in response to different sensory inputs or motor outputs, leading to a reduction in errors introduced by the altered conditions; Tanaka et al., 2011, two studies have shown cerebellar tDCS being more effective for M1 stimulation (Galea et al., 2011; Herzfeld et al., 2014).

While tES applied during tasks (i.e. online) seems to be the best protocol to enhance motor memory learning, sleep modulation may promote memory consolidation of previously learned motor sequences. The authors applied the EEG-feedback-controlled approach that restricts the application of tACS at 12Hz to an NREM sleep spindle detection. This targeted modulation increased motor memory consolidation tested by a motor sequence tapping task. Differently, Lafon and coworkers, (2017) reported an unsuccessful attempt to entrain sleep spindles while applying low-frequency tACS in healthy subjects. The authors measured endogenous spindle power intracranially during NREM sleep using invasive pre-surgical electrocorticography monitoring in 13 patients with epilepsy, finding no stable evidence of entrainment. Even though the main reason for the failure could be attributed to the underlying epileptic activity, it should also be noted that stimulation intensity varied across the two studies, with the latter applying significantly weaker currents (<0.05 V/m).

3.3.4. Mission Control, Spacecraft, Space Installations, and In-flight/ In-transit NIBS Applications: Performance and Life Quality.

Any space mission occurs in an extreme environment that has unique stressors. Even with careful selection methods and after detailed training for potential behavioral problems among space-flight crews, the mission success remains threatened. NASA Human Research Program (HRP) underlined three behavioral and

cognitive main risks happening during flights and on space installations: (1) risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload; (2) risk of performance and behavioral health decrements due to psychological stress, inadequate cooperation, coordination, communication, and psychosocial adaptation within a team; and (3) risk of adverse cognitive or behavioral conditions and psychiatric disorders (NASA SP-2009-3405). We discuss performance impairment in different domains typically seen in astronauts, such as cognition, motor, and sensorimotor coordination, sleep loss and shift, and altered psychological states (for a comprehensive scheme of NIBS applications in space see Figure 11). Because NIBS, specifically tES, have been extensively applied to overcome similar impairments in healthy participants and patients, their applications to tackle detrimental space effects on CNS should be taken into consideration.

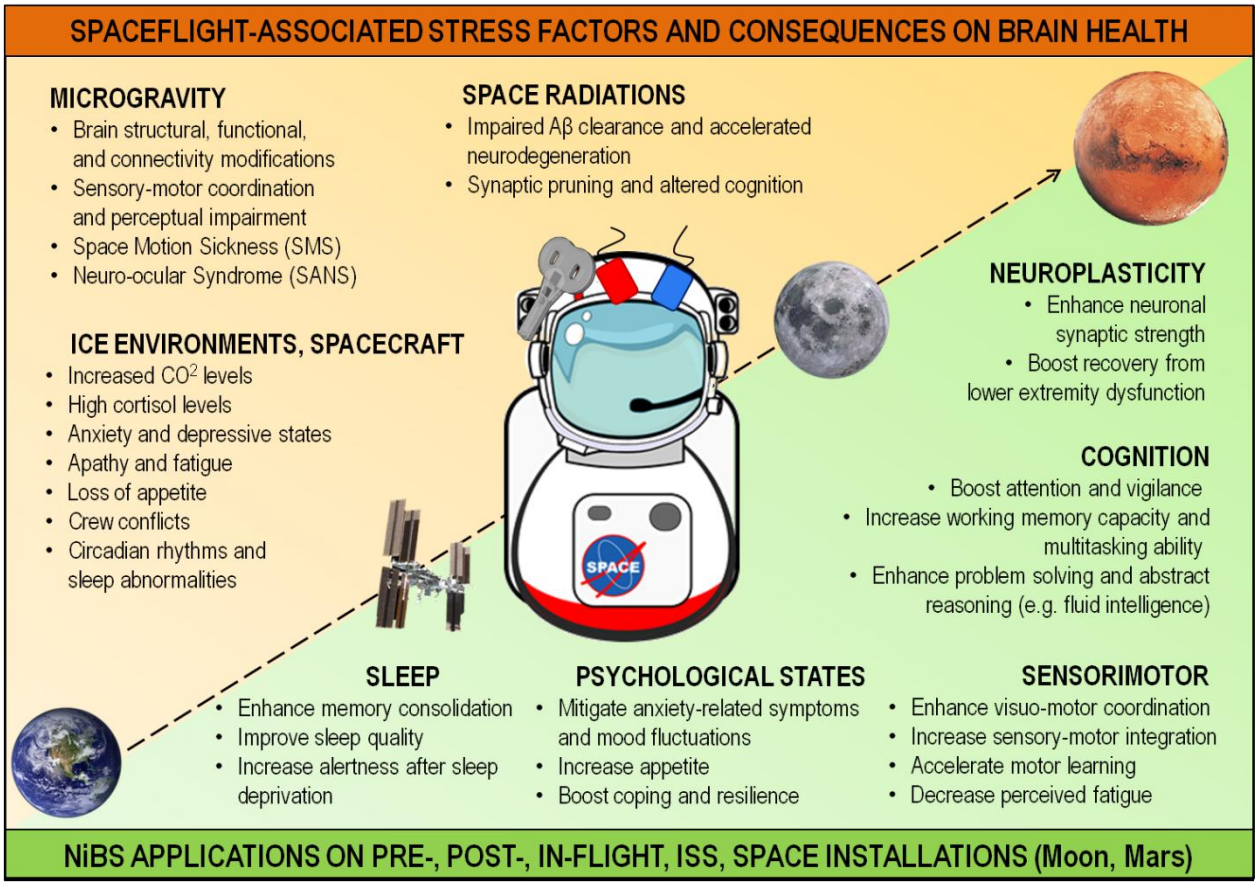


Figure 11. Major Stressors and Possible In-Flight NIBS countermeasures. In green, we show domains that can be targeted by NIBS during space missions. The orange panel represents major stress factors due to the space environment that can trigger adverse reactions and threaten crew health.

Visual System. The brain, as a control function of the visual system, is a critical pathway even for ocular health. Two tES protocols may help mitigate SANS-related cortical modifications. Particularly, a stimulation on α frequency (10Hz) may be chosen due to its dominant role in visual system oscillatory behavior and its relevance for attentional processes and visual processing. Even though the following hypothesis should be

considered purely speculative, external perturbation of visual regions via tACS in the α band may help contrasting modifications in cortical activity due to SANS. Similarly, anodal tDCS over the same area could also be beneficial in treating visual impairments.

Motor System. Even though the plasticity of the human central nervous system allows individuals to adapt to altered stimulus conditions encountered in a microgravity environment, the integration of signals from all sensory and motor systems is drastically modified in an environment lacking gravity force. The magnitude of sensory, sensory-motor, and perceptual disturbances, as the time needed to recover from them, tend to vary as a function of mission duration and space travelers prior experience with stimulus rearrangement of space-flight. These alterations trigger motion control disturbances, altered eye-hand coordination, unstable vision, and illusory motion of self and visual scene. Furthermore, approximately 70% of astronauts experience Space Motion Sickness (SMS) during the first week of the mission. Astronauts become easily disoriented when sensory input received from his or her eyes, muscles and joints, or vestibular organs conflicts with one another, and this can produce this syndrome causing nausea and vertigo. Going further, the transition from different gravity fields back and forth (earth: 1g, ISS: partial gravity; Mars: 0,38g) affects also manual manipulation of objects and tools. Accordingly, MRI-based HDBR studies have reported alterations related to motor-related tasks, such as fine motor control (Liao et al., 2015).

Another pivotal activity, requiring specific experience, is represented by the EVA, a term applied for a spacewalk outside the ISS, on lunar surface exploration, and hopefully Mars exploration. EVA is not only a delicate and dangerous action but also an extremely fatiguing activity. The suit is pressurized as a countermeasure for microgravity and dangerous space conditions outside earth-crafted vehicles. Therefore, due to the stiffness of the whole spacesuit, the force applied to make simple movements requires a lot of energy as well as extreme accuracy to maintain high performance, while also causing high fatigue.

Sensory Motor Integration and Visuo-Motor Coordination. tACS has been used to investigate motor enhancement and sensory-motor integration. investigated the effect of 10 and 20 Hz tACS for 10 min over left M1 while assessing movement speed and accuracy of the right hand. While 10 Hz tACS particularly increased movement variability, especially in tasks requiring internal pacing, 20 Hz tACS resulted in movement slowing. A few years later, the γ band entrainment of M1 proved to enhance movement acceleration and velocity in visually triggered movements (Moisa et al., 2016). During the same year, administered different protocols of TMS were during tACS at motor and nonmotor resonance frequency over M1 and showed promotion of sensorimotor integration by β band stimulation (i.e. 20Hz tACS). Replication studies suggest that the direction of the effect of a NIBS protocol may not always be easily predictable. For example, different cortical interneuronal populations are differentially modulated by the phase and frequency of tACS-imposed oscillations (Guerra et al., 2016). NIBS protocol may produce a mixture of inhibitory and facilitatory effects, and the measured effect would be the added-effect of both (Huang et al., 2011). Finally, Santarnecchi et al. (2017) applied tACS at a different frequency (5Hz, 20 Hz, 60 Hz, and 80 Hz) over dominant M1 during a visuomotor coordination task reporting that, while 20Hz administration slowed participants, high γ tACS (80 Hz) increased performance, promoting visuomotor coordination. Therefore,

tES could enhance sensory-motor integration and visuomotor coordination, helping astronauts to tackle difficulties due to motion control disturbances and altered eye-hand coordination during space-flights.

Motor Performance and Fatigue. Different comprehensive reviews underlined how tES can affect non-motor aspects relevant during long and intensive fine motor procedures, as well as enhance physical performance in professional athletes and amateurs (Angius et al., 2018; Colzato et al., 2017). Stimulation over M1, specifically, seems able to improve the isolated groups of muscles and endurance. showed that anodal tDCS stimulation on left M1 improves right-hand finger sequence performance, whereas cathodal stimulation of the same area improved performance of the left hand (. Moreover, the same group reported that concurrent left M1 cathodal tDCS for 20 min at 1mA and right M1 anodal stimulation improved motor performance of the left hand compared to anodal stimulation of the right M1 alone (Vines et al., 2008). During the last few years, other positive reports of tDCS effects have been shown with the anode over M1 on isolated muscle groups, such as the elbow flexor (Abdelmoula et al., 2016; Cogiamanian et al., 2007). Flood and coworkers (2017) changed the target area also investigating different parameters of motor performance. They noted that tDCS over the sensorimotor cortex reduced the perception of pain during fatiguing lower limb exercise in 12 subjects (Flood et al., 2017). Even though they found no significant effect on muscle endurance or maximal production of force, other studies reported an enhancement of muscle endurance due to tES (Williams et al., 2013). The authors examined sustained submaximal contractions of the elbow flexion in 18 healthy participants during fatigue task performance. In the meantime, either anodal or sham stimulation was administered to M1 for up to 20 min. These results indicate that anodal stimulation increased time to task failure and the amount of muscle fatigue, suggesting that tDCS administration can enhance the capability to exercise under challenging conditions (Williams et al., 2013). It is relevant to point out that the effect induced in the M1 by NIBS may be vulnerable to voluntary muscle activity (Huang, 2016), particularly when this activity happens simultaneously with stimulation. As an example, tonic contraction immediately after tDCS tended to eliminate the aftereffects of both anodal and cathodal stimulation in one study (Thirugnanasambandam et al., 2011). Because of the relevance of brain state during and after stimulation, more systematic studies are needed to explore this dynamic interaction to maximize NIBS' ability to enable behavioral learning and performance.

More interestingly, noninvasive brain stimulation might be able to enhance physical performance, as reported in studies on professional athletes. Okano and coworkers studied the effects of 20 min tDCS with the anode over the left temporal cortex on trained cyclists during an incremental cycling test. They found significantly improved peak power, as well as reduced heart rate and perception of effort at submaximal workloads (Okano et al., 2015). Angius and colleagues (2017), likewise, reported reduced perception of effort and increased endurance in 9 cyclists following anodal stimulation over M1 when the cathode was placed on the contralateral shoulder but not when placed over the prefrontal region (Angius et al., 2017). Similarly, Vitor-Costa and colleagues (2015) investigated the enhancing effect of tDCS over M1 on muscle fatigue and exercise tolerance in 11 cyclists. Anodal tDCS enhanced the time to exhaustion at 80% of peak power output. Interestingly, no significant effect was found on perceived exertion and heart rate. Therefore,

anodal tDCS selectively enhanced performance without affecting physiological and perceptual variables (Vitor-Costa et al., 2015). The beneficial effects of tDCS on motor performance during physical exercise in athletes and healthy individuals may be explained by tES interaction on perceived fatigue. Various authors suggested that the improvement in workload was achieved by a significant reduction in the perception of effort (Lattari et al., 2018, 2016). This may be due to a reduction in excitatory inputs from the supplementary motor area (SMA) and other brain regions (Morree et al., 2012; Zénon et al., 2015). Other authors linked improvement in endurance performance following anodal tDCS over M1 to increased neural drive and reduction in central fatigue (Oki et al., 2016; Vitor-Costa et al., 2015). Accordingly, fatigue reported in different pathologies seems to benefit from rTMS and tDCS applications, such as Multiple Sclerosis, Parkinson's Disease, and Fibromyalgia (for a review see Lefaucheur et al., 2017).

In conclusion, tDCS seems to be a promising tool to enhance muscular strength, muscle endurance, and fatigue which are all crucial not only for professional athletes but potentially also for astronauts and cosmonauts. Although, before its implementation on the in-flight crew, research needs to clarify whether tDCS might be useful in highly trained individuals. One study, indeed, failed to further improve maximum performance in fine motor control in elite pianists (Furuya et al., 2013).

Cognition. An even bigger threat to the success of space missions is inadequate and ineffective crew cognitive performance (Clément and Reschke, 2008). Results from Earth-based research highlighted the importance of studying the effects of stress on cognitive performance. Right now, cognitive measurements are routinely performed by astronauts aboard ISS before or after their periodic health status test. Some outdated cognitive tests and batteries are sometime still administered, such as MINICOG (Shephard and Kosslyn, 2005), AGARD (Draycott et al., 1996), and Space-flight Cognitive Assessment Tool for Windows (WinSCAT; Kane et al., 2005). *Cognition* (Basner et al., 2015) is a time-constrained test that covers main cognitive domains, such as executive, episodic memory, complex cognition, social cognition, and sensorimotor speed, now the current standard for check-ups in space operations.

Evidence of the effects of space-flight on cognitive functioning is controversial. Strangman (2014) examined attention, memory, learning, executive or higher-order functioning, emotion processing, and social processing in his extensive review of cognition in space-flight and other ICE environments. While empirical results reviewed failed to find significant objective decrements in cognitive functioning during space-flight, the study highlighted a high prevalence of anecdotal reports of difficulties attending to tasks, complaints of cognitive slowing, and memory problems while in orbit. As aforementioned, various animal studies proved cognitive deficits due to a synaptic pruning for cosmic radiation exposure (Britten et al., 2016, 2012; Chakraborti et al., 2012; Denisova et al., 2002; Lonart et al., 2012; Parihar et al., 2018). This makes it difficult to conclude that there is no significant cognitive decrement occurring. A possible explanation involves the concept of “reserve capacity”. Higher functioning individuals are postulated to possess a reserve factor that moderates the expression of impairments in cognitive functioning in the face of brain pathology (Jones et al., 2011). Reserve capacity is further conceptualized in terms of two models: brain and cognitive reserve. Brain reserve refers to structural aspects of the brain (e.g., size, number of neurons, synapses),

whereas cognitive reserve involves aspects of complex cognitive processes (efficiency, capacity, or flexibility; Barulli and Stern, 2013). More intelligent or better-educated individuals are thought to possess a greater level of cognitive reserve and during the brain, pathology will manifest lower amounts of cognitive impairment than those with lower amounts of cognitive reserve (lower educated or IQ individuals). Before starting the challenging Earth-based training, future astronauts are carefully chosen from a big pool of candidates, usually holding a high-level degree (M.D. or Ph.D. in astrophysics/engineering) or involved in a job requiring high and fine skills (Air-Force pilots, test pilots, military). Subjects of this profile are probably candidates with a high cognitive reserve that would help them to countermeasure detrimental cognitive performance in space.

An interesting window of observation is also offered by studies involving highly specialized professional figures, where a "ceiling effect" in terms of behavioral improvement after any intervention is expected. These individuals have reached their capacity via standardized training, making it hard to enhance their abilities in general. However, targeted, personalized CNS changes induced by NIBS can offer an advantage over other enhancement interventions (e.g. drugs, exercise, diet, supplements), allowing for accelerated learning or boosting performance in individuals otherwise performing at their physiological peak.

Even though cognitive impairment may not always be tested and visible among crew members, an astronaut's performance should be constantly monitored and possibly enhanced to allow better outcomes for space missions. During space missions, astronauts are daily required to keep sustained attention and be able to perform in a hostile environment, and under stressful, and time-pressing situations. Other than attentional ability and working memory, human multitasking capability is a crucial key interest. Space-flights, and even normal standard situations on ISS, require a human operator to monitor and respond to multiple events simultaneously over a long period, risking a decline in performance as a result of information overload (Cheshire, 2015). Perceptual problems are also related to microgravity environment characteristics that make astronauts see objects in non-customary orientations. The proper perception of objects might be therefore negatively affected. One well-known example is the impairment in the perception of faces during space-flights (Kanas and Manzey, 2008). Among the thousands of potentially threatening situations that astronauts and cosmonauts face, some of them require more than just applying standard protocols but also finding new and creative solutions, such as the example of the famous fix during the mission of Apollo 13 (King, 1997). Different protocols of tES proved to be able to entrain and modulate cognition in various domains (for a comprehensive review see Kuo and Nitsche, 2012). We review NIBS applications in cognitive domains, selecting pivotal studies from the multitude conducted during the last years.

Attention and Vigilance. Bolognini and coworkers (2010) coupled a 30 min multisensory visual field exploration training with anodal-excitatory tDCS over the posterior parietal cortex (PPC) with right and left hemispheres stimulated in different experiments. They tested the performance in visual exploration speed, visual scanning, and visuospatial orienting. tDCS applied to the right PPC increased training-induced behavioral improvement of visual exploration. Results also proved that tDCS applied on the right parietal lobe can enhance visual search even when not associated with training (Bolognini et al., 2010).

Using α and γ tACS during two spatial cueing tasks, Hopfinger and Parsons (2016) investigated the modulation of endogenous and exogenous attention. Because γ tACS (40Hz) significantly facilitated endogenous attention with no difference in exogenous one, authors suggested that γ waves play a dominant role in attentional disengagement and reorientation, further proving a way to enhance it.

In a study supported by the U.S. Air Force, tDCS improved vigilance (sustained attention) and target detection of pilots. Twenty-seven Air Force pilots received 90 minutes of preparatory training for a "synthetic aperture radar target learning task" during a tDCS session (2 mA for 30 minutes, the anode in area F10- forehead side) or sham. The task consists of a radar simulator with circular patterns in which participants had to identify target stimuli (for example, vehicles or missiles), which could appear in different points of space. Anodal tDCS during training produced an improvement in the accuracy of visual search during the task by about 25% compared to the sham group (McKinley et al., 2013b). This application might specifically be valuable for Earth-based mission control operations.

Multitasking and Working Memory. tDCS application on working memory (WM) has been proved in different studies, with a focus mostly on the dorsolateral prefrontal cortex (DLPFC) stimulation. Fregni and colleagues (2005) administered anodal, sham, or cathodal tDCS during a sequential-letter working memory task (3-back letter task). Results indicated that anodal stimulation over left DLPFC was able to increase accuracy by enhancing working memory capacity. Zaehle and coworkers (2011) described similar positive effects of anodal tDCS on response accuracy in a 2-back WM task, also increasing α and θ power, while cathodal tDCS impaired performance triggering a drop of these frequencies. A similar paradigm has been applied to study the time-dependent effect of stimulation. Ohn and coworkers (2008) administered 20 min of 1mA anodal tDCS during the 3-back verbal task. The beneficial effects of anodal tDCS on performance accuracy were not only evident during online stimulation but also maintained up to 30 minutes after the end of the session (Ohn et al., 2008b). Similarly, Hoy and colleagues (2013) found that anodal tDCS applied to left DLFPC generated significant improvements in accuracy during a 2-back test. In fact, in most studies on tDCS and WM, the anode was placed over the left DLPFC rather than the right (for a meta-analysis, see Brunoni and Vanderhasselt, 2014). The same research group that showed tDCS ability to improve spatial recognition accuracy in Air Force pilots, applied anodal tDCS over DLPFC in 20 Wright-Patterson Air Force participants to enhance multitasking capability (Nelson et al., 2016). The stimulation significantly improved information processing capability resulting in improved performance compared to the placebo protocol.

Although tDCS ability in modulating behavioral performance seems to be widely replicated, a 2015 review of tDCS studies found no statistical evidence to support strong changes in cognitive performance after a single session tDCS in healthy subjects (Horvath et al., 2015a). A second study also found a small statistically reliable impact of tDCS on various neurophysiological outcomes (Horvath et al., 2015b). Ambiguous outcomes in the case of tDCS sessions on cognitive enhancement may be explained by individual differences, considering how the effect induced by external stimulating such as low current stimulation is highly influenced by the state of the brain (Hsu et al., 2016). Moreover, the reviews explore cognitive measures collected during or following one single tDCS session. Many studies investigated multi-

day stimulation paradigms (Antonenko et al., 2019; Talsma et al., 2016) reporting successful effects on cognition. In this context, future studies should consider, overnight consolidation as a crucial component supporting NIBS effects (Marshall et al., 2006b).

On the other hand, tACS has been proven effective in inducing a frequency-specific effect on short-term memory capacity (Feurra et al., 2016). Oscillatory stimulation in θ (5Hz), α (10Hz), β (20Hz), and γ (40Hz) range were delivered during a digit span task over the left posterior parietal cortex, a cortical region thought to sustain maintenance processes in short-term memory through oscillatory waves in β range. As expected, Feurra and coworkers found the β-tACS robustly increased the forward memory span (Feurra et al., 2016).

Problem Solving, Insight, Fluid Intelligence, and Creativity. Dockery and coworkers (2009) described a phase-specific effect of tDCS over left DLPFC on performance in the Tower of London task, which involves strategic planning. Cathodal tDCS improved performance during the early acquisition phase of task performance, probably due to its reducing effect on distractive cortical noise, whereas anodal stimulation improved performance in later stages of task performance, presumably via its activity-enhancing effect on task-related neuronal activity (Dockery et al., 2009b).

Santarnecchi and colleagues (2019) administered tACS to modulate insight ability, a particular form of problem-solving consisting of a sudden realization of a solution for the problem presented (Santarnecchi et al., 2019). 10Hz tACS and 40Hz tACS were administered during two insight tasks on the parietal (P4) or temporal (T8) area respectively, along with sham stimulation, according to neurophysiological pieces of evidence of α and γ band activity raised during an insight moment (Jung-Beeman et al., 2004). As expected, γ-tACS applied on the right temporal lobe increased accuracy, correlating also with an increase in γ spectral power over bilateral temporal poles.

Fluid intelligence (*Gf*) represents the capacity to reason and solve novel problems independently from previously acquired knowledge (e.g. logical problems). This higher cognitive domain has also been modulated in a single session tACS intervention. Santarnecchi and colleagues (2013) administered tACS over the left middle frontal gyrus on 20 tACS-naive, right-handed, healthy volunteers while performing an extended version of Raven's matrices, a classic task to assess *Gf* (Matzen et al., 2010). The experimental paradigm compared the accuracy and timely responses in performance during four tACS conditions: 5 Hz (θ), 10 Hz (α), 20 Hz (β), and 40 Hz (γ), and placebo stimulation. Gamma-band stimulation resulted in a shorter time required to find the right solution during the task. The performance was enhanced only during this particular frequency stimulation and in complex trials involving conditional/logical reasoning (Santarnecchi et al., 2013).

While γ tACS can enhance abstract reasoning, α stimulation over the frontal cortex (10Hz tACS) has been shown to correlate with another high-order cognitive function: creativity, as the ability to produce innovative ideas. In a randomized, balanced cross-over design on 20 healthy participants, Lustenberger and coworkers (2015) reported a frequency-specific significant improvement of 7.4% in the Creativity Index during stimulation at 10Hz.

Sleep. Sleep loss, fatigue, and poor sleep quality, with various consequences, have been reported and replicated on numerous space missions (Barger et al., 2014a; Stampi, 1994). The causing factors are related to modifications of classical Earth environmental cues, such as altered light-dark cycles, light exposure and low light intensity, sleep-disrupting noise levels in the spacecraft during rest which produces disturbances on the circadian rhythm and consequent psycho-physiological effects (Dijk et al., 2001a). Particularly, noise levels 4–24dB higher than normal limits have been registered on ISS, which sometimes calls for extra measures in the form of anti-noise earplugs and hearing protection devices. Although in some studies sleep patterns seem to differ minimally from Earth-based sleep (Dijk et al., 2001a; Pavy-Le Traon and Taillard, 2010), a reduction of total sleep to 5-6h sleep per night has been registered along with a clear alteration of circadian sleep (Dijk et al., 2001a; Frost et al., 1976). Monk and colleagues (1998) analyzed the sleep of four astronauts finding no alterations of REM sleep, but a general decrease in slow-wave activity indicating how sleep was shallower in space compared to Earth. Other studies found a considerable increase in REM sleep total time and a reduction of REM latency during the first week after return to Earth (Dijk et al., 2001a; Frost et al., 1976). On long-duration missions, major sleep disruption problems related to this may appear and compromise performance levels, leading to more mistakes, depression, anxiety, and higher cortisol levels (Buckey, 2006). A reduction in melatonin has also been reported in microgravity (Holley et al., 1991). Although the use of drugs is usually not indicated due to their side and sedative effects, some sleep medications have been used in long-duration missions upon the approval of the medical team. I refer to Chapter 2.2 on NIBS applications to modulate sleep.

Sleep Deprivation and Alertness. tDCS effects on vigilance have been observed in sleep-deprived research participants. Using the same tDCS paradigm McKinley and colleagues used to enhance vigilance and multitasking capability, McIntire and coworkers (2014) demonstrated that tDCS mitigated vigilance decrement due to sleep deprivation for at least 6 hours, 3 times longer than the effect of caffeine. Additionally, both tDCS and caffeine led to improvements in reaction time and fewer lapses on a simple reaction time task, both of which are highly sensitive to fatigue. Subjective reports revealed that participants receiving tDCS experienced also less fatigue and/or drowsiness and more energy following stimulation as compared to subjects who received sham tDCS. The same research group examined the effects when tDCS was applied 10 hours earlier in the sleep deprivation period (McIntire et al., 2017). The study confirmed that tDCS prevents declines in vigilance performance for approximately 6 hours post-stimulation. Moreover, the effects on arousal and mood were found to persist much longer, at least 24 hours post-tDCS. These findings suggest that it may be possible to administer tDCS before the start of the shift on ISS or on Earth-based mission control to provide performance benefits that last until the end of the workday.

Psychological States. Stressing situations (such as hypoxia and cosmic radiation) causing dysfunction of the prefrontal area can not only lead to mistakes in cognitive performance and sleep disruptions but also dramatic modifications in emotional processing. ICE environments, as aforementioned, are usually triggers of stressing reactions. Astronauts are required to adapt effectively to ICE situations they encounter. It is well

known that people differ in how quickly they adapt to space-flight and other extreme conditions, such as analogous situations on Earth (Kanas et al., 2010; Sandal et al., 1995).

Clinical conditions such as a following severe depressive state, even in only one crew member, can interfere with performance and, unfortunately, terminate a space mission, as happened with Salyut 7 in 1985. Anxiety is also a common problem in a dangerous and stressful environment, and it has been detected in crewmembers of Antarctic missions. It is, however, not common in space missions, even though it may appear, as indicated by some MIR missions (Kanas and Manzey, 2008; Linenger et al., 2000). In summary, although reports of depressive and anxious states are often vague or subjective, they are encountered in astronauts (Barger et al., 2014a).

As aforementioned, high levels of cortisol due to dangerous situations reduce appetite-regulating hormones. Loss of appetite is common in astronauts, and it has been documented from Project Mercury in 1961-1963 (Carpentier et al., 2018). Cosmic radiations are also responsible for anorexic behavior, as seen in animal models (Fajardo et al., 2001; Hunt et al., 1989; Rabin et al., 2000, 1994, 1991, 1989).

Depressive States and Anxiety. Various protocols of tES have been suggested and applied to mitigate clinical symptoms of patients affected by different neuropsychiatric disorders, such as depression, schizophrenia, anxiety, autism, and craving, with good results (for a review see (Kuo et al., 2017, 2014; Philip et al., 2017). Depression represents the more treated and investigated psychiatric condition in efficacy studies with tES. The classical tDCS protocol typically involves an anode placed over the left DLPFC. Although initial tDCS studies generated mixed results regarding potential efficacy (Boggio et al., 2012; Fregni et al., 2005; Loo et al., 2010), the latest and more extensive trials showed positive effects. To date, the largest randomized study (n=120) with tDCS administered twelve 30-minute sessions of 2 mA tDCS: 10 consecutive workday sessions followed by a single session delivered every other week comparing the outcome with sertraline in a 2x2 factorial design. Albeit a greater drop in depressive scores was seen in tDCS and sertraline combined therapy group, active tDCS monotherapy was superior not only to sham tDCS but also to sertraline monotherapy (Brunoni et al., 2013). In 2016, a European meta-analysis attributed level B evidence (probable efficacy) of tDCS for depression (Lefaucheur et al., 2017a).

What could be used for a clinical population may also be generalized for healthy subjects, as seen in different studies. In various experimental paradigms focused on investigating other domains, mood improvements have also been found as a collateral outcome. Marshall and coworkers (2004), found also that anodal tDCS on bilateral DLPFC triggered an improvement in mood measured with Eigenschaftswörterliste (EWL), an adjective checklist describing the subject's mood, while the main aim was to enhance memory consolidation overnight. Similarly, as aforementioned before, McIntire and colleagues (2017) tested healthy participants with a 15-items Likert Scale Mood Questionnaire and the Profile of Mood States (POMS), a 65-item questionnaire that measures mood using 6 categories: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment while studying the ability of tDCS on DLPFC to countermeasure fatigue due to sleep deprivation similarly to the caffeine effect. Researchers reported a drop in depressive scores. Participants receiving early intervention tDCS also reported feeling

more able to do the task and less bored (McIntire et al., 2017). tDCS efficacy to alter mood state in healthy subjects could be explained by its ability to mitigate the negative effects of stressing factors such as fatigue.

Loss of Appetite. Although tDCS research mostly focused on food cravings (Boggiano et al., 2017; Goldman et al., 2011; Montenegro et al., 2012), this stimulation protocol seems to be a valuable countermeasure also for loss of appetite. Pieces of evidence have been provided that food craving is reduced when excitatory (anodal) tDCS is applied over the right DLPFC as the opposite effect on anorexia nervosa (AN) where excitatory stimulation is applied over the left DLPFC. For example, Fregni and coworkers (2008) compared both tDCS protocols, anode right/cathode left and anode left/cathode right, to sham stimulation, and found that food craving was reduced, remained stable, and increased in these conditions, respectively. tES has been also proven to reduce AN-related behaviors and thoughts (Lee et al., 2018; McClelland et al., 2013). Finally, tDCS applied bilaterally on DLPFC in a cohort of AN patients was able to significantly increase appetite, resulting in a higher Body Mass Index persisting also 1 month later, compared to the standard Family-Based Intervention (Costanzo et al., 2018).

3.3.5. Post-flight NIBS Applications: Biomarkers and Support

Even after the space mission, astronauts are not yet spared from potential effects on their health, cognitive, and psychological states. If on one hand, a long-duration mission can cause a direct modification of the brain anatomy-physiology, on the other it can also trigger long-term adaptation mechanisms that, upon return to Earth, are no longer beneficial but may be harmful since the abolition of the space-related stressors. NIBS applications can be a powerful tool to investigate space-induced modifications in neurophysiology, particularly regarding the neuroplasticity and cortical excitability field via TMS and tACS assessment before and after the flight. Astronauts also shift from working for months on spacecraft to readjusting to Earth-based normal life. Cognitive deficit and depressive states are two of the possible consequences of this stressful transition. NIBS, as seen in in-flight applications, may support the cognitive and psychological rehabilitation of crewmembers after the end of the mission.

TMS to Assess Neuroplasticity and Cortical Excitability. Neuroplasticity is pivotal for functional recovery after injury and has been suggested as a potential resource to counteract the effect of microgravity (Ombergen et al., 2017). TMS has been frequently used to investigate cortical plasticity in healthy participants and patients (for a review on TMS in neuroplasticity studies see Bestmann, 2008; Ferreri and Rossini, 2013) as well as investigate corticospinal excitability to hyper- and micro-gravity. In a preliminary investigation, Davey and coworkers (2004) administered TMS over M1 on 3 healthy subjects during 10 parabolas to produce MEP and recording in the deltoid and left and right erector spinae (ES) muscles. Data showed a similar pattern in all participants, revealing the facilitation of MEP responses in left and right ES muscles in periods of 0g. MEPs increase suggested that microgravity produced activation of ES muscles through an increase in corticospinal excitability (Davey et al., 2004).

Concerning ground-based analog, Roberts and colleagues (2010) combined TMS and fMRI to investigate whether simulated gravity through 90 days of HDBR induced changes in corticospinal tract excitability.

They found reduced cortical activity in motor areas (specifically the leg cortical representation) and a decrease in corticospinal excitability after HDBR. According to the authors, these reductions in cortical motor function could underlie motor-related difficulties in astronauts (Roberts et al., 2010). Additionally, in the post-HDBR period, they reported an increase in corticospinal excitability that inversely correlated with functional mobility impairment, leading them to assume that TMS could be used as a possible countermeasure against lower extremity dysfunction. The authors suggest TMS become part of a countermeasure regime for astronauts on long-duration space missions to counteract lower extremity dysfunction, for example before operations on a planetary surface (Roberts et al., 2010).

Cognitive and Mood Enhancement. A recent study investigated the consequences of prolonged space exposure on two identical twins, one who spent a year on ISS and one on Earth. Cognitive speed decreased for all tests of Cognition except for the digit symbol substitution task, and accuracy decreased for all domains except for spatial orientation post-flight. The decline was significantly greater in siblings who went on space post-flight and persisted up to 6 months after the end of the mission in both speed and accuracy domains (Garrett-Bakelman et al., 2019). Some explanations for this persistent cognitive deficit seem to involve a depressive state due to being back on Earth after a space-flight. Therefore, every in-flight application presented here may be also implemented as a support for a cognitive and affective readjustment of crew members on their return to Earth. Specifically, tES application to mitigate depressive states has been suggested, considering its good outcomes on depressive states, whether alone or in combination with antidepressant drugs (Brunoni et al., 2013b). More important, during a space mission, tES could be the only NIBS technique able to be implemented in-flight, while astronauts on Earth-based post-flight rehabilitation can be successfully treated with TMS. Prefrontal rTMS therapy repeated daily over 4–6 weeks (20–30 sessions) is FDA approved for the treatment of Major Depressive Disorder (MDD) in adults who have not responded to prior antidepressant medications (for a review see Perera et al., 2016). Depression involves a distributed network of cortical and limbic regions including the left DLPFC, hippocampus, and subgenual cingulate among others (Pascual-Leone et al., 1996) and TMS studies have focused on the left DLPFC as one accessible node of this depression network. The efficacy and safety of TMS using a specific, defined treatment protocol of high-frequency, left prefrontal TMS was confirmed in two large, multisite, randomized controlled trials (George et al., 2010; O'Reardon et al., 2007a) and one large, multicentre trial that used a form of more focalized TMS (Deep TMS; Levkovitz et al., 2015). In conclusion, rTMS may be implemented as well with astronauts on an Earth-based treatment in case of post-flight depressive episodes.

SIGNIFICANCE.

In this third review, I discussed how NIBS could become a useful tool to support space exploration to (i) facilitate learning in motor tasks during pre-flight Earth-based training, (ii) mitigate the impact on the brain health of ICE, microgravity, and cosmic radiation during space-flight or long-duration missions and planetary surface installations, by promoting psychological well-being and maintaining cognitive

performance when combined with various forms of training or therapy, as well as directly intervening on disruptions in brain activity. Going further, noninvasive brain stimulation might then help in (iii) investigating brain adaptation to changes produced by space missions and defining specific biomarkers of brain adaptation to space-flight, by collecting data on cortical excitability, neuroplasticity, and brain connectivity levels.

3.4 Perspective on Future Directions: Integrated NIBS Solutions to Track and Promote Brain Health in Space

A similar version of the present article will be submitted to Nature Microgravity [**Romanella SM**, Turrini S, Seyedmadani K, Burkhart C, Wuyts FL, Santarnecchi E. "*Tracking and Promoting Brain Health in Space]*.

As extensively discussed in the previous review, while agencies prepare for space missions aiming for Mars, the crew's brain health is becoming a central concern due to the threats associated with galactic cosmic radiations, microgravity, and life in confined environments. Space stressors could start a cascade of harmful brain modifications that would potentially lead to disruptions in cognitive and operational performance, and negatively affect the psychological well-being of the crew. We discussed how NIBS may prove exceptionally fruitful as a standalone research tool and intervention at different stages of space exploration. In this perspective, I introduce the idea of implementing its combination with the recording of physiological measures (e.g. EEG, eye-tracking, heart rate variability) to remotely assess emotional and cognitive responses to daily activities in space missions. Addressing the issue of a confined and isolated environment, I also discuss evidence that any intervention should be offered in an immersive virtual reality (VR) setting to facilitate training in real-life scenarios and provide a more entertaining experience. Therefore, an integrated and wireless platform combining these three techniques, i.e., NIBS, physiological recordings, and VR, could both assess and address flight-associated modifications of the overall brain and mental health, as well as cognitive and brain performance (see Figure 12). Within this approach, we discuss the integration of VR, NIBS, and physiological measurements and their potential space-flight-related applications.

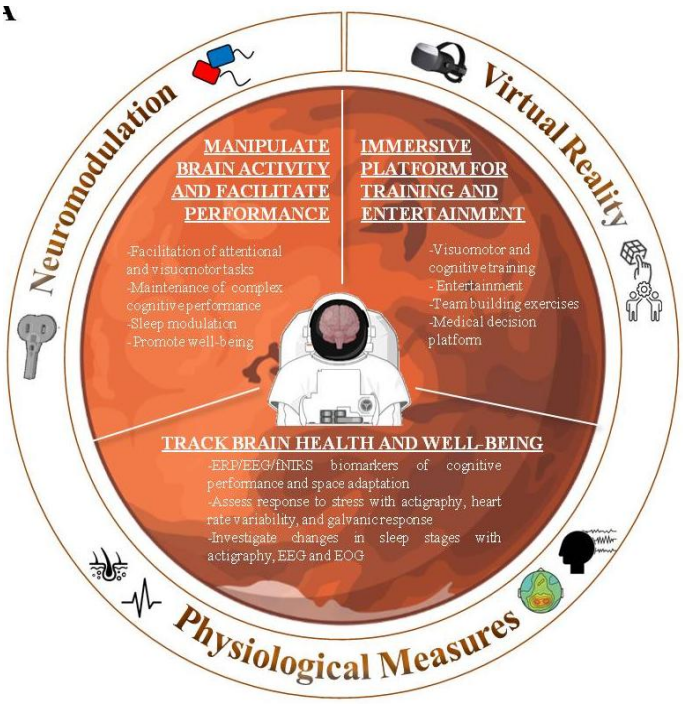


Figure 12. A combined VR-EEG-NIBS device. We propose a multimodal system for reliable brain monitoring thanks to EEG, simultaneous brain stimulation, VR-based cognitive training, and assessment. The platform could also integrate additional physiological measurements including heart rate variability, galvanic skin response, actigraphy, and eye-tracking integrated into the VR headset. A combination of VR, biometric measurements, and NIBS could be adapted to (i) improve astronaut physical and psychomotor training, cognitive performance, and adaptation to space-related stressors on Earth; (ii) mitigate the impact of ICE, microgravity, and cosmic radiation during space-flight or long-duration missions on the ISS; (iii) further tackle these issues in a habitat on Moon and Mars. Finally, (iv) NIBS-based measures of cortical excitability, plasticity, and excitation-inhibition balance could be used to investigate brain changes and support the post-flight return to baseline/recovery.

3.4.1. Physiological measurements

Although acute physiological adaptations to space have been previously investigated and reviewed (Clement and Ngo-Anh, 2012), detailed consequences of long-term space missions on brain health and cognitive performance still need to be evaluated. Here, we review a few tools to record bio-signals that could be implemented to assess brain activity and oscillations, emotional response to stress, cognitive workload, performance during daily activities, and sleep-wake cycle.

Previous studies employed *EEG* to investigate disruptions in oscillatory brainwaves associated with space missions (Cheron et al., 2009, 2006). Due to its portability, EEG has been incorporated during actual space-flights to study biomarkers associated with changes in microgravity and cosmic radiations. For instance, investigations reported an increase in α frequency (8-12 Hz) in parieto-occipital and sensorimotor areas during time spent in space, possibly related to the decreased gravitational input (Cheron et al., 2006). EEG also offers a window on space-flight-related alterations in the electrocortical markers of emotional stress and the cognitive status during space missions. A variety of markers have been identified to track vigilance (Kamzanova et al., 2014), drowsiness (Sahayadhas et al., 2012), workload (Roy et al., 2016), and emotional responses (Suhaimi et al., 2020), to measure the brain correlates of different interventions, such as physical exercise, and cognitive performance during confinement (Schneider et al., 2013). In the context of space missions, the most promising application or biometric recording could be the integration of EEG-

neurofeedback-based training in the astronauts' daily routines, as a means of maintaining optimal function. EEG-neurofeedback enhances the effectiveness of training by providing the user a visual or auditory representation of relevant features of their brain's ongoing activity in real-time, allowing users to progressively learn how to modulate it (see Enriquez-Geppert et al., 2017 for a review and tutorial). A meta-analysis showed that gaining active control over one's ongoing brain oscillatory activity facilitates performance in multiple cognitive domains, such as sustained attention, orienting and executive attention, memory, spatial rotation, reaction time, complex psychomotor skills, implicit procedural memory, recognition memory, perceptual binding, along with general mood and well-being (Gruzelier, 2014). EEG could therefore represent an exceptional tool not only to assess brain health but also to actively promote it. However, although it has been transported aboard the ISS (Columbus module launched in 2008), to this date EEG equipment does not appear to have been used to its fullest potential (De la Torre, 2014b), possibly because of some usability issues (i.e., setup, non-wirelessness). Shifting to more recent devices, using fewer easily applied electrodes (i.e., dry electrodes) and battery packs could facilitate EEG application on multiple missions and daily use.

While EEG can record electrocortical activity, changes in cerebral hemodynamic responses could be detected by *functional near-infrared spectroscopy (fNIRS*; for a recent review on its applications see Chen et al., 2020). fNIRS is a technique that indirectly measures neuronal activity in the cortex via neurovascular coupling, making it highly sensitive to blood oxygenation and volume. fNIRS is less sensitive to motion artifacts than EEG, extending its use outside the lab in different environments (Pinti et al., 2015). Like EEG, fNIRS could noninvasively detect biomarkers of brain adaptation to space. Previous work on a parabolic flight using fNIRS showed a local decrease of oxyhemoglobin in frontal areas in the hypergravity phase and increases in weightlessness (Brümmer et al., 2011). fNIRS is also widely used to assess task-related cortical function and has been applied to investigate regional cerebral blood flow signals in experiments of particular relevance to astronauts, such as cooperation/competition (Cui et al., 2012) and confinement-triggered stress (Sasahara et al., 2020) studies. fNIRS can also provide information on functional connectivity, computed as correlations between the hemodynamic responses of spatially distinct regions of interest, making it a candidate method to collect online data on potential disruptions in resting-state network activity during space missions. Going further, new studies could incorporate fNIRS to assess brain hemodynamic changes and functional connectivity during cognitive tasks performed by astronauts in spacecraft.

Additionally, *eye trackers and pupillometry tools* could be integrated to collect further non-invasive and rich indices of brain function and cognition. Recent eye-tracking technologies allow for the online assessment of dynamic vision and attention allocation through the recording of fixation and saccades (Liston & Stone, 2014). Gaze analysis, for example, reveals attentional focus and cognition strategies (Eckstein et al., 2017), while pupil dilation reflects mental effort (Granholm et al., 1996). Eye-tracking devices have already been used in parabolic flights, to study visual function in microgravity (Clarke and Haslwanter, 2007), but their applications for space missions haven't been fully exploited yet.

Other bio-signals could be incorporated during space missions to assess stress levels and attention. As an example, *heart rate variability (HRV)* is notoriously associated with bodily response to stressors (Kim et al., 2018). HRV is the fluctuation of the length of heartbeat intervals and represents the ability of the heart to respond to a variety of physiological and environmental stimuli (Rajendra Acharya et al., 2006). As a noninvasive electrocardiographic method, HRV has been implemented in a variety of psychological stress studies, showing that stressful tasks will trigger the default stress response, resulting in a physiological activation in healthy individuals (Held et al., 2021) (for a detailed review see Kim et al., 2018; Thayer et al., 2012). HRV has been previously implemented in space-flights to investigate changes in cardiovascular dynamics, altered due to the microgravity influence on blood volume distribution and blood pressure (Baevsky et al., 2007; Verheyden et al., 2010), but has never been collected for long periods during space missions to investigate the online response to stressful cognitive tasks and the ability of astronauts to copy with increasing anxiety levels. The combination with another bio-signal frequently used to measure strong emotional responses, such as *galvanic skin response (GSR)*, may also be instrumental. GSR is an "electrodermal" signature of the sympathetic innervation of the skin and can be measured on the skin surface (Boucsein, 2012). An increase in sweat gland activity, which can be triggered by an aroused emotional state, will enhance porosity, resulting in an increased electrical conductance, which translates to an increased GSR. GSR is a reliable online indicator of cognitive load and general emotional activation (Nourbakhsh et al., 2012), although it doesn't discriminate between positive and negative emotional triggers, as the increase in sweat gland activity can be triggered independently by both.

Recording bio-signals at nighttime could provide useful insight into the astronaut's sleep pattern. The NASA Human Research Program (HRP) stressed sleep loss and circadian desynchronization as the main factors leading to the risk of performance decrements and adverse health outcomes during space missions (NASA SP-2009-3405). In the last two decades, *actigraph devices*, devices worn on the wrist able to record movements to estimate sleep parameters and circadian rhythms, have been frequently used during space missions to investigate sleep-wake cycles over weeks or months. Evidence shows a decreased sleep duration reaching only 6-6.5 h/day during space missions (Barger et al., 2014b; Dijk et al., 2001b; Monk et al., 1998b) and a disrupted sleep-wake circadian rhythm maintenance during Mars500 simulations (Basner et al., 2013). Future missions will benefit from an extensive investigation of circadian rhythm to control long-term adaptation and the potential loss of sleep in astronauts living on planetary installations.

These physiological measurements previously offered useful information on brain adaptation, cognitive performance, and emotional response to space missions. New space-flights should incorporate them into the daily routine to continuously track the online brain health of the astronauts.

3.4.2. Virtual reality environment

Any behavioral or cognitive interventions during space missions could be offered in an ad-hoc VR environment, to exploit its immersive potential. Because the subject interacts with items or other people while moving in the VR environment, manipulating objects, and performing a series of actions, this platform

offers an immersive environment that is frequently applied for video games and entertainment. Recently, VR has been explored as a potential tool in the treatment of motor deficits and psychiatric diseases, such as cerebral palsy (Reid, 2004, 2002), Parkinson's disease (Esculier et al., 2012; Mirelman et al., 2011), stroke (Laver et al., 2015; Thomson et al., 2014), schizophrenia (Park et al., 2011), autism (Karami et al., 2021), and anxiety disorders (Côté and Bouchard, 2005; Klinger et al., 2004). In the contest of mental health, it has been implemented as a tool to deliver cognitive-based therapies (Kandalaft et al., 2013; Kim et al., 2011). Outside of its therapeutic potential, VR has been successfully applied in healthy subjects to enhance the efficacy of various forms of training, by creating simulations of particularly difficult-to-replicate scenarios and/or activities. For instance, VR has been successfully implemented for military training and developing coping and stress management mechanisms in veterans and active soldiers (Linde and Kunkler, 2016; Pallavicini et al., 2016; Siu et al., 2016).

For astronauts, VR could be particularly relevant both pre-flight, to enhance cognitive training, and during long space, missions to ensure performance maintenance. On Earth, NASA already incorporates VR during the pre-flight training for astronauts. The Virtual Reality Laboratory (VRL) at the Johnson Space Center is a training facility providing real-time immersive brain-computer interface and interaction. In this lab, VR is integrated with a tendon-driven robotic device able to simulate the kinesthetic sensation of, for example, moving a large object. Astronauts are trained to handle robotics operations and rescue scenarios. Offering the opportunity to acquire skills in the context where they will then be applied, VR makes the training more meaningful and effective as compared to learning out-of-context (Nieuwenhuijsen et al., 2006). Its uses could be expanded: for example, VR training could include specific training in visuomotor coordination and motor learning tasks through hyper-realistic space-flight-related scenarios, including landing and extravehicular activity (EVA). The combination of VR and recently developed robotic and haptic interfaces(Jung et al., 2012; Yeh et al., 2014) offers further opportunities. For example, VR has been implemented as a training tool for surgeons to learn fine motor skills associated with precision surgery (Fang et al., 2014; Wang, 2012; Zahiri et al., 2018). A VR framework would also provide a highly motivational way for educational purposes. This could also be offered as in-flight activity during the mission to reach Mars, to encourage the crew to maintain a high-level performance for a longer time.

VR could also provide various applications on spacecraft and planetary surface installations. During years-long training, astronauts are required to learn a great number of procedures and high-detailed knowledge in a wide range of domains, from space physiology to geology and spacecraft engineering. An interactive platform combined with VR that may facilitate crew knowledge acquisition. Going beyond its educational potential, VR could be used to implement on-board decision-support comprehensive of an integrative knowledge system (Fiore et al., 2014) would help crew members in decision-making, particularly in case of medical emergencies, as already applied in the military (Linde and Kunkler, 2016; Siu et al., 2016). This may be particularly pivotal during the long journey to Mars and on planet surface installations, where the delay of communications will hamper the ability of the Mission Control Center (MCC) to intervene.

VR training may also be beneficial to team building when incorporating competition and/or cooperation during tasks. A group environment would promote social interaction and teamwork within the crew. This is not trivial in long-term flights and missions where social interaction is limited to crew members. Finally, VR could be used to hamper the monotony and boredom of ICE environments, whose absence of external stimuli is one of the major factors in leading astronauts to interpersonal conflicts, depressive symptoms, sleep abnormalities, and cognitive difficulties (Acharya et al., 2019; Cheron et al., 2006; Demertzi et al., 2016). VR may provide a parallel individual and/or social immersive game platform, with a wide range of purposes, from pure entertainment to motivating daily physical exercise required for astronauts.

3.4.3. An integrated device to track and promote brain health in space

These techniques, i.e. the recording of bio-signals, neuromodulation, and VR, could individually be implemented to investigate long-term consequences of brain adaptation in space and promote cognitive performance and well-being in space missions. Due to their different and complementary advantages, though, their combination could offer a comprehensive and integrated assessment tool to track and promote brain health in space (see Figure 13). For example, a new portable device could integrate TMS/tES with EEG and/or fNIRS in a cap with VR-eye-tracking glasses, and simultaneously record GSR, HRV, and/or actigraphy. We briefly introduce up-to-date literature on the intersection of these techniques and their practical operation that we think could be more beneficial in space exploration.

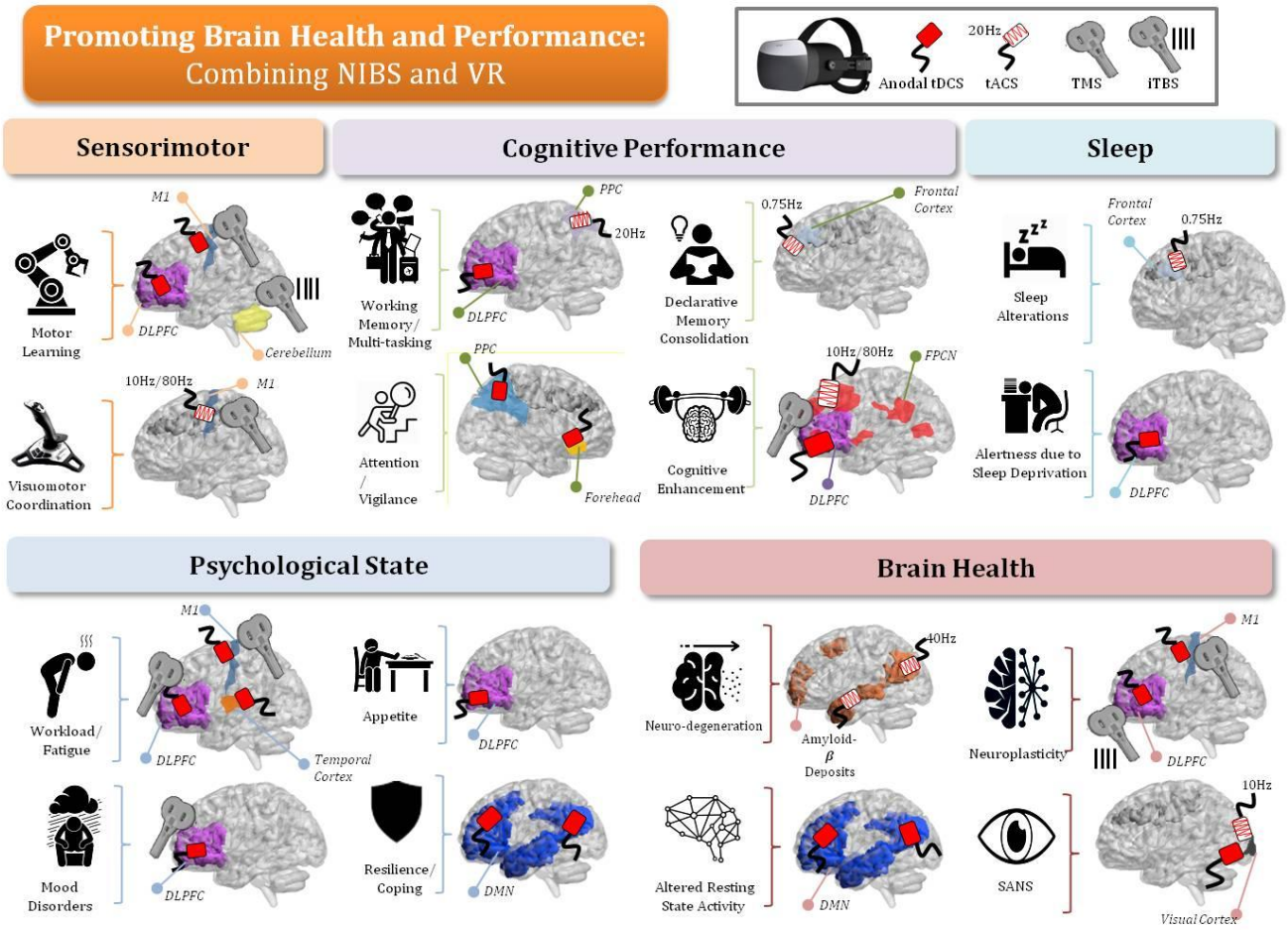


Figure 13. Potential Applications in Modulating Brain Health and Improving Performance. We offer a comprehensive graphical review of potential applications of NIBS methods (with a focus on excitatory TMS, iTBS, anodal tDCS, and tACS) in domains relevant to space-flight and Moon or Mars installations. For every specific implementation, we show up to 3 potential targets and corresponding montages. tDCS: transcranial direct current stimulation. tACS: transcranial alternating current stimulation. otDCS: oscillatory transcranial direct current stimulation. TMS: transcranial magnetic stimulation. iTBS: intermittent theta-burst stimulation. M1: primary motor cortex. DLPFC: the dorsolateral prefrontal cortex. FPCN: frontoparietal control network. DMN: default mode network. PPC: posterior parietal cortex.

Identify perturbation-based biomarkers associated with brain health in space. First of all, a combination of physiological measurements recorded simultaneously with neuromodulation could provide extensive and comprehensive information about perturbation-based biomarkers associated with space-flight. One of the most promising protocols combines TMS with EEG (for a comprehensive review of its use and applications see (Tremblay et al., 2019). Specifically, by controlling the input to the cortical areas (the perturbation, i.e., the TMS pulse) and recording brain responses through EEG (TMS-EEG), we can quantify the transmission of generated activity as well as local response, propagation speed, and the dynamic spatial spreading of the current. TMS-EEG investigates causal communication between brain areas with a high temporal resolution, providing insights into mechanisms of effective connectivity. It could identify long-term space-associated biomarkers of changes in local plasticity, cortical excitability, and changes in induced brain oscillations. Moreover, TMS-EEG could test the effect of the reported space-flight-related increase in intracranial pressure (ICP; Van Ombergen et al., 2017) on the topology and organization of brain networks,

such as changes in modularity or resilience (Massimini et al., 2012b; Ozdemir et al., 2020). A TMS-EEG application could track brain health at different stages of space missions. A test-retest pre- and post-flight can be easily implemented as part of routine health screenings and follow-up visits, to assess any potential effects of space missions and time spent on planetary installations.

Although TMS showed high safety and feasibility in healthy and clinical populations (Antal et al., 2017; Rossi et al., 2009b), its applications during space-flights require some considerations. In-flight NIBS, and especially TMS, applications should carefully be tested. ISS, spacecraft, Moon, and Mars call for more innovative solutions than earth-based non-laboratory settings. They differ from Earth in many features, such as temperature and pressure (NASA IG-18-021) that could potentially damage TMS devices. Recently, interest in the use of TMS outside the experimental environment, and the absence of trained operators, has grown. Although potentially impractical due to its weight and interference in the magnetic field, it is worth noting that TMS application for future space missions has been already explored (Badran et al., 2020b, 2020a). As an example, a recent study of an individually-tailored TMS helmet applied over M1 suggested it as a feasible and reliable alternative to traditional laboratory settings (Badran et al., 2020b). The same group also validate this helmet in zero-gravity (Badran et al., 2020a). The authors successfully recorded the resting motor thresholds (rMTs), stimulating M1 with single-pulse TMS on 10 participants before, during, and after a parabolic flight, opening the opportunity for TMS used in non-laboratory settings with variable gravity. Nonetheless, further research is needed to create TMS hardware that will not be damaged during longer space-flight while facing extreme temperature swings and radiation. tES, on the other hand, owing to its portability and size, could provide a more practical neuromodulation technique to be incorporated into an integrated device with physiological measurements and VR during actual space-flights. For this reason, we prioritize discussion on tES applications that could be easily implemented on space missions and planetary installations.

Furthermore, combined tACS-EEG can be used to evaluate specific changes in brain oscillations in a specific area or the entire brain. It could also aide in detecting early signs of pathologies, such as depression and neurodegeneration, that have been associated with signature brain oscillations abnormalities (Bestmann, 2008b; Ferreri and Rossini, 2013b). More specifically, in the case of deep space flights, astronauts change ICP and fluid shifts that might affect brain function and induce SANS. Increased ICP can also trigger changes in the topology and organization of brain networks, such as changes in modularity or resilience, which can be investigated by TMS-EEG (Massimini et al., 2012; Ozdemir et al., 2020). Similarly, it is relevant to test changes in brain efficiency as measured by the propagation of electrical activity injected by TMS. TACS-EEG, on the other hand, may help in studying long-distance synchronization and modifications in oscillatory activity, while offering the crucial element of portability.

Improve sleep pattern and response to stress. tES efficiency can be maximized by implementing a closed-loop system interacting with the EEG. As aforementioned in the second review, a closed-loop algorithm allows the personalization of stimulation so that it is prompted by individual EEG signals, such as the detection of specific cortical wave frequencies. By aligning the stimulation with the ongoing spontaneous

activity, a closed-loop tACS-EEG paradigm provides a timely-precise stimulation and allows for personalization to match the individual frequency of the participant. This kind of device could be used both to record sleep data and to test the applicability of the closed-loop stimulation technique to promote healthy sleep patterns in space expeditions. As mentioned, a reduction of total sleep to 5-6h sleep per night has been registered alongside a clear alteration of circadian sleep (Dijk et al., 2001a; Frost et al., 1976). Monk and colleagues analyzed the sleep of four astronauts finding no alterations in REM sleep, but a general decrease in slow-wave activity indicating how sleep was shallower in space compared to Earth (Monk et al., 1998b). On long-duration missions, major slow-wave sleep disruptions may be even more severe and compromise performance, mood, and stress levels (Buckey, 2006). Previous studies already successfully applied this paradigm to modulate slow waves during sleep in healthy participants, resulting in a significant rise in sleep quality (Jones et al., 2018b; Ketz et al., 2018b; Robinson et al., 2018). A similar closed-loop protocol was also successfully tested on subjects with severe sleep disorders, resulting in a sleep-deepening effect in participants affected by primary insomnia (Saebipour et al., 2015). These findings suggest that a closed-loop tACS-EEG could intervene in facilitating a healthy sleep-wake pattern and a deeper and more relaxing sleep overnight (Sara M. Romanella et al., 2020). This issue could be tackled with a closed-loop tACS-EEG system combined with VR. This platform could track daytime emotional responses to stress and anxiety. Previous EEG studies showed how a user's mental activity can be translated into a measure of mental states, such as relaxation or agitation, by measuring amplitude changes in the alpha band (8-12 Hz) waves (Marshall et al., 2013; Santarnecchi et al., 2021). Studies examining EEG changes in response to relaxing nature slides have demonstrated increases in cortical alpha amplitude associated with a relaxation response (Ulrich, 1981). Increases in alpha power are associated with lower levels of anxiety, increased calmness, and a range of other autonomic changes associated with decreased sympathetic arousal (Cahn and Polich, 2006). On the other hand, growing evidence proved that mindfulness-based practices can result in reduced stress, anxiety, and an increase in alpha waves (for a detailed meta-analysis see (Goyal et al., 2007)). Incorporating mindfulness exercises into a VR experience during space missions could counteract anxious states in response to stressful situations; incorporating EEG-biofeedback to actively modify online alpha waves would probably increase the effectiveness, providing a low-cost, portable, and easy-to-implement tool to promote psychological well-being during long space-flights.

3.4.4. Practical Suggestions for Neuromodulation in Space: Technical Challenges and Caveats

Although NIBS techniques showed high safety and feasibility in healthy and clinical populations (Antal et al., 2017; Rossi et al., 2009), their applications in space missions require some considerations. In the last years, there has been a growing interest in offering TMS treatment outside the experimental environment, and in the absence of trained operators. A recent study of an individually-tailored TMS helmet applied over M1 suggested it as a feasible and reliable alternative to traditional laboratory settings (Badran et al., 2020b). This opens the opportunity to administer TMS in non-laboratory settings with variable gravity and minimal training.

Furthermore, space environments, such as ISS, spacecraft, Moon, and Mars call for more innovative solutions than earth-based non-laboratory settings. They differ from Earth in many features, such as temperature and pressure (NASA IG-18-021). These could potentially harm stimulation devices. In-flight NIBS applications, specifically, should carefully be tested. Below we address the feasibility of NIBS techniques as well as characteristics of new environments that will need to be evaluated to meet the technological requirements of TMS/tES devices. We also discuss how stimulating the brain through electrical currents in astronauts may open a new challenge, due to cerebrospinal fluid shift in microgravity conditions.

Feasibility of NIBS. Even though TMS application may seem impractical on ISS or space-flights due to weight and interference in the magnetic field, it may still be a useful tool to investigate differences in cortical excitability before and after missions (i.e. perturbation-based biomarkers), or during experimental paradigms in space analog environments. As aforementioned, a protocol of test-retest paradigm on astronauts upon returning from a mission or after a simulation could be easily implemented as part of routine health screenings and follow-up visits performed to investigate possible response changes to external perturbation due to microgravity/cosmic radiation. tES, on the other hand, is a more practical technique during actual space-flights. A tES session is usually not longer than 30 minutes and since the stimulation is noninvasive and it does not trigger any sensations, the subject can move, talk, and perform tasks.

Environmental Challenges. The environment can be categorized into three timeframes:

On Planetary Surface. On Earth, NIBS technology is designed for applications in clinical settings via a trained specialist with a medical background and unlimited access to technical support. On other planets, like Mars or the Moon, the environment is not as controlled. Assuming the hardware would not be damaged during the space-flight, the equipment will face extreme temperature swings and possible radiation. Furthermore, the device has to be used by crew members with limited training. The interaction with ground control would be very limited and in the case of Mars with at least 20 min delay. Therefore, testing both the hardware and software of the existing technologies for this environment is crucial (Seyedmadani, 2019).

During launch or recovery. Due to the limitation of volume and cost associated with the mass, small profile, and lightweight devices are highly desired. Payloads usually launch on cargo systems that experience a variety of profiles of gravity, temperature changes, and extreme vibration. Therefore, the chosen technology for each mission must tolerate such impacts (Duncan, 2007).

On-Board of Spacecraft. On-board of space-flight, the environment is under control, meaning the temperature, humidity, and oxygen level are carefully defined. Temperature and humidity conditions required to administer tES need to match with those experienced-on board. For example, atmospheric pressure is maintained on ISS thanks to a module called ECLSS (Environmental Control and Life Support System) at 101.3 kPa (NASA/TP-2015–218570), right above the limit of the influence of the device (700-1.000hPa). The effect of weightlessness also impacts hardware performance, including lack of heat rejection. Besides, radiation consequences should be further investigated.

Technological requirements. Beyond environmental factors and launch limitations, any existent technology resource on board the craft should be addressed and carefully selected for the mission. NASA Standard SSP 30423 and MIL-STD 810-G are the guidelines followed by NASA Research Operation and Integration Group for use on the board of ISS of off-the-shelf hardware. Factors to be addressed include material compatibility in a closed system, thermal exchange, limited or no resupply possibility, no lithium battery allowed to reduce the chance of combustion, the necessity to control electromagnetic noise generated (EMI), radiation impact, toxicology, and training time.

Albeit the tES device is feasible and simple to use, some of the above standards need to be addressed. A theoretically simple concern could also be the supply of gel electrodes and EMI limitation during the sessions. On the other side, the risk of increasing or decreasing current during the protocol due to solar particle events represents the main concern for the tES application. Going further, tES software needs to be checked with load capacity and technology on board the craft. EEG data also requires space and time to be downloaded. Finally, crew training is pivotal to managing protocols and modifying protocols and parameters through the interface. Interaction between software and hardware over WiFi or Bluetooth goes back to craft capabilities. Unfortunately, radiation and particle events could directly affect the electrical board of the system and cause a false positive or negative. Considering NIBS applications and the possible outcomes of such an event, a full radiation test has to be performed on the device.

SIGNIFICANCE.

Due to longer space missions aiming to reach and colonize Moon and Mars, new tools need to be provided to investigate the long-term consequences of brain adaptation to microgravity and radiation, as well as promote cognitive performance and well-being during the missions. Physiological measurements, neuromodulation, and virtual reality could individually be implemented for a range of different purposes for space exploration, but the integration of these techniques in an integrated wearable and wireless systems device could represent a potential all-in-one tool with outstanding potential in a wide range of space-related domains. The combination of this technology could provide potentially endless personalized applications to track and promote brain health in space.

4. OPTIMIZE AND PERSONALIZE NIBS WITH BIOPHYSICAL MODELING

Although the potential applications of NIBS protocols to modulate cognitive and motor abilities are well-known and replicated, particular attention should be given to factors that may affect the results of stimulation (for a comprehensive review see Krause and Cohen Kadosh, 2014). Individual differences can highly impact NIBS efficacy and need to be carefully considered before any practical applications (Peterchev et al., 2012). Changes in the tissue anatomy and the intrinsic electromagnetic properties have been shown to alter the NIBS-induced stimulating currents thanks to modeling studies (Miranda et al., 2003). The main reason for this is that the altered distribution of cerebral spinal fluid (CSF) to brain tissue modifies the conductive tissue properties of the brain. The conductivity of CSF is considerably greater than the conductivity of any other brain tissue (by a factor of 15–30 at 4 kHz (Gabriel et al., 1996). Both TMS and tES-induced current preferentially follow the path of least resistance, meaning that electric fields propagate more through CSF. Morphological changes, such as loss in gray matter and increase in CSF volume or redistribution, will, therefore, modify the path of lower resistance where the stimulating currents would flow and consequentially affect the location of the peak-induced electric field. A famous modeling study showed that the current densities induced on the cortex are, in fact, dependent upon the degree of cortical atrophy (Wagner et al., 2008). The authors also reported that the electric field decreases in magnitude as the distance from the scalp to the cortex increases (Wagner et al., 2008). Alterations derived from cortical atrophy can drastically modify the electric field induced by TMS and tES, and therefore the beneficial efficacy of these interventions. TES, specifically, applies low transcranial electrical currents that generate weak electric fields to target specific brain areas, allowing for the sub-threshold modulation of firing properties of cortical neurons and ongoing rhythmic brain activity. In case of cortical atrophy, the induced electric field could not reach a strength enough to modulate brain activity. Previous literature showed how electric fields need to be above 0.3 V/m to modulate neurons (Alekseichuk et al., 2022). Biophysical modeling offers an opportunity to investigate the propagation of the NIBS-induced electric field, as well as ensure that the e-field in each participant reached at least this minimum effective dose.

These issues can be tackled by predicting the distribution of an electric field following a TMS pulse or tES montage using individual neuroimaging data, such as structural magnetic resonance imaging (MRI). Software models running biophysical modeling algorithms have been developed to create realistic computational models of the head and run simulations of the TMS pulse. Individual anatomical MRI images are segmented into major tissue classes of the head, and a 3D head volume conductor model of the head is created by surface reconstruction with specific intrinsic tissue conductivities. After setting the parameters and specifications of the stimulation (e.g., coil type or electrodes, protocols, position, and orientation, the intensity of stimulation), the biophysical modeling software will compute the propagation of the induced electric field in the head. The output is the heat map of the NormE induced by the TMS pulse or tES montage in the individual 3D head. The key factor of these models is a precise description of the geometry of the head as a volume conductor, assuming the tissues' electric properties with a finite element method (FEM)

model (Guilherme B. Saturnino et al., 2019; Axel Thielscher et al., 2015). This allows us to create models of the induced-electric field individualized on each participant enrolled in a study to compute the exact strength of the e-field reaching certain regions, or studying the propagation of one montage compared to another.

Going further, biophysical modeling can provide an essential tool to offer a personalized and optimized NIBS intervention. To provide efficient and focal stimulation, it is important to take into consideration different variables that significantly influence the resulting electric field. For TMS, the position, orientation, and tangentiality of the coil need to be controlled to induce the maximal E-field in the targeted cortical region of interest (ROI). On the other side, a successful tES montage needs to achieve the target field strength in one or more target regions while maintaining a good focality and minimizing it elsewhere. At the same time, it also needs to comply with safety constraints and can be limited by the number of active electrodes. Furthermore, because tES-induced neural effects depend on the field direction, for superficial regions the field should be oriented perpendicular to the cortical surface in the target areas, to achieve maximum efficacy. For subcortical targets, however, a preferential direction might not be easily defined. tES-induced current propagation also dramatically changes with electrodes different for shape (square vs. circle), and size, if used with sponges or gel. Innovative algorithms have been now been perfectioned to provide the best TMS coil placement and orientation or the most efficient tES montage upon choosing definite targets that the experimenter wants to stimulate. We referred to published literature on the subjects for more details (Gomez et al., 2021; Saturnino et al., 2021).

Even more relevant, such optimization of the e-field can be done on individualized head models, to overcome morphological modifications that could hinder the efficacy of the stimulation. These issues are pivotal when planning NIBS protocols in both AD cohorts and space exploration. As extensively discussed in the first review, AD patients show a plethora of significant changes in brain morphology, such as cortical atrophy and deterioration of white matter. If not taken into consideration, this could dramatically hinder the efficacy of stimulation in this cohort. On the other side, this is also particularly relevant due to the functional and structural cortical modifications that astronauts undergo during space missions. Indeed, as extensively discussed in the third review, space stressors seem to induce changes in brain anatomy, particularly in CSF volume and distribution, gray matter shape change, and local skull-to-brain distance, due to the upward shifting of the brain (Roy-O'Reilly et al., 2021). For this reason, in this chapter, I will be presenting different studies where I used biophysical modeling in AD patients and astronauts. Specifically, the first three sub-studies involve AD patients in different experimental paradigms. In each one of them, biophysical modeling was performed with a different goal. In the fourth study, I use biophysical modeling to investigate brain changes in astronauts after a space-flight and to provide personalized and optimized NIBS solutions for space exploration.

4.1 Biophysical Modeling for AD patients in Neuromodulation Studies

In the present chapter, I will discuss three sub-studies where I performed biophysical modeling on AD patients with different aims. I think this sets examples of the versatility and advantages of including biophysical modeling at any stage of experimental studies. Because the main focus of the chapter is on the practical applications of the biophysical modeling, I refer to the cited/submitted papers for details on the statistical analysis and results.

In the first project, the goal was to identify the propagation of the induced electric field resulting from different tACS montages. Thanks to neuroimaging data from one of the AD patients enrolled in this tACS-EEG study, I created an AD head mesh and ran computational simulations of the four montages used during the data collection. The second study allowed me to investigate how the same TMS pulse in a cohort of different AD patients would result in significant differences in current strength reaching the interesting areas. The experiment was a TMS-EEG data collection on 15 AD patients, to identify the correlation between neurodegeneration, cognition, and perturbation-based features. I created head models individualized on each participant's neuroimaging collected data and ran simulations to compute the average strength of the TMS-induced e-field. Because of the difference in the severity of the cortical atrophy for each participant, the same TMS pulse induced dissimilar e-field strength and efficacy. The third study aimed to investigate whether the optimized gamma-tACS intervention could improve cognition and enhance gamma oscillatory activity in MCI and AD patients. The cortical target areas included temporal and parietal regions, encompassing areas mostly affected by beta-amyloid and tau deposition. To find the optimal tACS montage that could specifically target only these regions I ran an optimization algorithm that result in a specific tACS montage. This was then included in the experimental protocol. Although the data collection is still ongoing, I present here the preliminary cognitive data on 10 patients.

4.1.1 First Sub-study: Analyze electric field propagation in a tACS-EEG study on AD patients

A similar version of the present article will be submitted for publishing [Palmisano A, Pezanko L, Cappon D, Tatti E, Macone J, Koch G, **Romanella SM**, Smeralda CL, Rivolta D, Press D, Pascual-Leone A, El-Fakhri G, Santarnecchi E. "*Preliminary Evidence for Perturbation-based tACS-EEG Biomarkers of Gamma Activity in Alzheimer's Disease*"]

The rationale of the study. From a neurodegenerative point of view, AD is characterized by impaired inhibitory circuitry and GABAergic dysfunction, leading to reduced fast brain oscillations in the gamma band (γ, 30–90 Hz). Assessment of this rapid oscillatory activity could lead to the identification of novel biomarkers of diagnostic and prognostic value. The current study aimed to test a multimodal "perturbation-based" tACS-EEG protocol to detect how responses to external stimulation in AD correlate with clinical characteristics and symptomatology.

We included 15 participants with mild to moderate AD that underwent a multimodal assessment including cognitive status, neuroinflammatory markers, and brain cortical plasticity measured via theta-burst

TMS and resting-state EEG. The tACS-EEG recordings included brief (6 minutes) tACS blocks administered in the gamma band (40Hz) with 4 different electrode montages [F3-P4; F4-P3; T7-O2; T8-O1]. Given the theta and gamma alterations, co-occurrence in AD, and its link with memory impairment, a theta (6Hz) stimulation protocol was also included. A pre/post 32-Channels EEG for each block was recorded. Delta values of Pre-Post spectral power were adopted as a metric of induction and correlated with cognitive scores and blood/plasticity markers.

Biophysical modeling of one AD patient enrolled in the study as a sample. We chose one AD participant who underwent a T1-weighted (T1w) anatomical MRI scan. MRI data were acquired on a 3T scanner (GE Healthcare, Ltd.) using a three-dimensional spoiled gradient echo sequence: 166 axial-oriented slices for whole-brain coverage; 240-mm isotropic field-of-view (FOV); 0.937-mm × 0.937-mm × 1-mm native resolution; flip angle = 15°; echo time (TE)/repetition time (TR) ≥ 2.9/6.9 ms; duration ≥ 432 s. We preprocessed the T1w scan to graphically represent the E-field induced by the different tACS montages. Specifically, MRI data quality assurance (sample homogeneity), and preprocessing were performed with the CAT12 Toolbox (version 1727) (Gaser and Dahnke, 2016) (http://www.neuro.uni-jena.de/cat) within the SPM12 framework (Wellcome Department of Cognitive Neurology, London, UK), using Matlab R2019a (Mathworks, Natick, MA, USA). London, UK), using Matlab R2019a (Mathworks, Natick, MA, USA). The induced E-field of the tACS montages was computed in SimNIBS v3.2, an open-source simulation package that integrates segmentation of MRI scans, mesh generation, and finite element method (FEM) model E-field computations (Guilherme B. Saturnino et al., 2019; Axel Thielscher et al., 2015). The software provides a realistic volume conductor head model, created as default in the FEM model generated using the individual T1-weighted image. The head model for the participant was reconstructed by applying the *headreco+CAT* pipeline to the subject's T1-weighted scans (see left panels in Figure 14). In our simulation, we kept the isotropic conductivities given by default (Axel Thielscher et al., 2015) here provided for the main tissue volumes, in S/m: gray matter: 0.275; white matter: 0.126; CSF: 1.654; bone/skull: 0.01; scalp/skin: 0.465. The final mesh, comprehensive of gray (GM) and white matter (WM), scalp tissue, bone, and cerebrospinal fluid, comprises approximately 200,000 nodes and 3.6 million tetrahedral elements (see Windhoff et al., 2013 for further modeling details).

To investigate the E-field resulting from the tACS montages, we started by modeling the electrodes as the ones used during the data collection. Specifically, the electrodes were small cylinders (1 cm diameter, 4mm thickness) with homogeneous conductivity and added 0.5mm in height corresponding approximately to electrode gel. We ran simulations to compute the E-field resulting from each tACS montage: left frontal-right parietal (F3-P4), right frontal-left parietal (F4-P3), left temporal-right occipital (T7-O2), and right temporal-left occipital (T8-O1). The stimulation reached 2mA of intensity on each electrode.

Results. The resulting E-field for each tACS montage is presented in the right panels in Figure 14. Cognitive scores, neuroinflammatory markers, and plasticity measures were all significantly correlated with perturbation-based oscillatory activity recorded with tACS-EEG. The general findings showed that fronto-central 40Hz-tACS- and 6Hz-tACS-induced gamma activity positively correlated with cognitive and

memory scores. 40Hz stimulation-induced occipital parietal gamma and parieto-occipital beta (15–30 Hz) activity negatively correlated with pro-inflammatory cytokines. 40Hz-tACS also generated spread activity correlated positively with TMS cortical plasticity measures. The same analysis performed with rsEEG data collected separately from tACS sessions resulted in no significant correlations, supporting the value of perturbation-based metrics over resting-state ones. This study provided preliminary support for the use of perturbation-based tACS-EEG markers in AD, with potential implications for the development of novel physiological biomarkers and therapeutic targets.

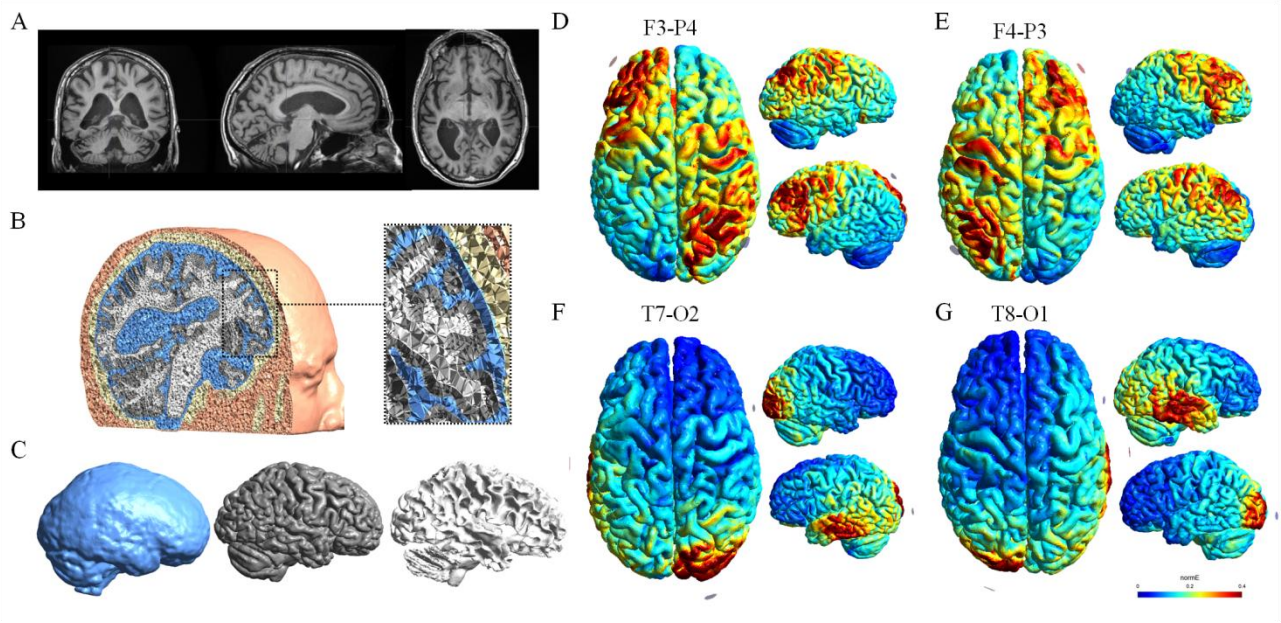


Figure 14. Details of biophysical modeling for one AD participant. Left panels. Image processing and mesh creation diagram. We collected the T1-weighted (T1-w) anatomical scan for one AD participant (**Panel A**). We ran the *headreco+CAT* pipeline from SimNIBS (Saturnino et al., 2019) to segment the T1-w anatomical image into class types (skin, bone, cerebrospinal fluid or CSF, eyes, gray matter, and white matter). We computed the head volume 3D mesh composed of tetrahedral elements (**Panel B**). We show a 3D representation of CSF: blue; gray matter: gray; white matter: white (**Panel C**). **Right panels. Electric field resulting from different tACS montages.** We computed the E-field resulting from the different tACS montages: F3-P4 (**Panel D**), F4-P3 (**Panel E**), T7-O2 (**Panel F**), and T8-O1 (**Panel G**). The electric field (NormE) is presented in V/m.

4.1.2 Second Sub-study: Investigate differences in electric field strength in a TMS-EEG study on AD patients

A similar version of the present article has been submitted for publishing [Smeralda CL, Tautan A, Palmisano A, Cappon D, Menardi A, **Romanella SM**, Macone J, Paciorek R, Rossi S, El Fakhri G, Pascual-Leone A, Press D, Santarnecchi E. "*TMS-EEG perturnational metrics correlate with neurodegeneration and inflammatory blood biomarkers in Alzheimer's Disease patients*"].

The rationale of the study. Cortical hyperexcitability might represent an early distinctive feature of Alzheimer's Disease, which seems to be associated with poorer patients' cognitive functioning. Hyperexcitability has been shown to even precede AD causative pathophysiological alterations such as accumulation of amyloid plaque and inflammation. However, the relationship between *in vivo* cortical excitability, cognitive performance, and biomarker of AD pathology and inflammation has not been extensively explored yet. In this study we conducted TMS-EEG co-registration to explore the relationship

between cortical excitability, cognitive profile, neurodegeneration, and inflammation blood biomarkers in 14 AD patients. 120 single pulses of TMS were delivered over three different cortical sites: left primary motor area (L-M1), right dorsolateral prefrontal cortex (R-DLPFC), and right occipital cortex (R-OC). Patients underwent an extensive neuropsychological evaluation, and blood amyloid (Aβ40 and Aβ42), p-tau181, and inflammation (IL-6, IL-10, IL-17, and TNFα) biomarkers were collected prior to TMS-EEG registration.To correct for the spread cortical atrophy characteristic of AD neuropathology, we performed biophysical modeling from the neuroimaging data collected from each enrolled AD patient. We ran simulations of the TMS pulse on every subject, computing the strength of the induced electric field reaching each specific target region. This allowed us to control that the e-field following the TMS was strong enough to overcome individual cortical atrophy in each participant and induce a perturbation in the activity of the target area. These values were included in the statistical analysis and regression model as a covariate.

***Biophysical modeling of all the AD participants enrolled in the study*.** MRI data quality assurance (sample homogeneity), preprocessing, and analysis was performed with the CAT12 Toolbox (version 1727) (Gaser and Dahnke, 2016) (http://www.neuro.uni-jena.de/cat) within the SPM12 framework (Wellcome Department of Cognitive Neurology, London, UK), using Matlab R2019a (Mathworks, Natick, MA, USA). The induced E-field of the TMS was computed in SimNIBS v3.2, an open-source simulation package that integrates segmentation of MRI scans, mesh generation, and finite element model (FEM) E-field computations (Guilherme B. Saturnino et al., 2019; Axel Thielscher et al., 2015). The software provides a realistic volume conductor head model, created as default in FEM generated using the individual T1-weighted image. The finite element head model for each participant was reconstructed by applying the headreco pipeline to the subject's T1-weighted scans. In our simulation, we kept the isotropic conductivities given by default (Thielscher et al., 2015) here provided for the main tissue volumes, in S/m: gray matter: 0.275; white matter: 0.126; CSF: 1.654; bone: 0.01; scalp: 0.465. To create the final mesh, comprehensive of gray and white matter, scalp, bone, and cerebrospinal fluid, we doubled the default number of nodes and tetrahedral elements in an attempt to better encompass differences in cortical thickness and morphological changes in AD brains. The final mesh comprises approximately 400,000 nodes and 7 million tetrahedral elements. Segmentations were carefully examined slice-by-slice to ensure proper tissue classifications.

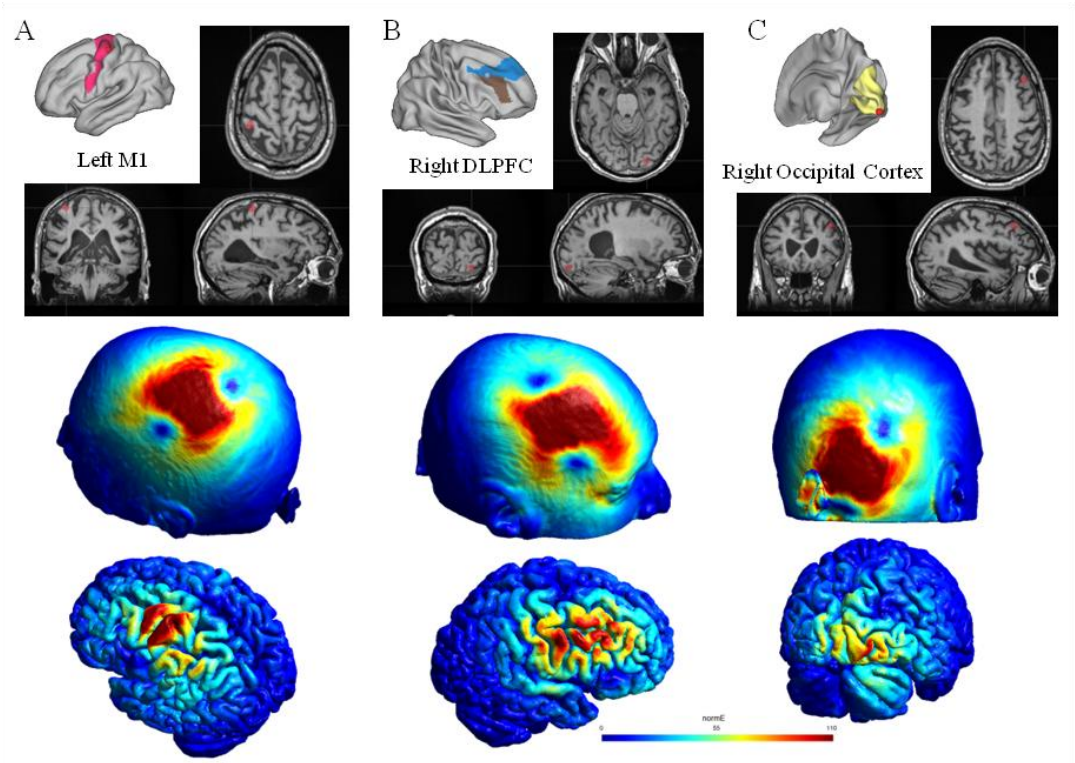


Figure 15. Details of MRI-guided TMS target selection and individualized biophysical modeling. **Panel A** shows MNI coordinates for each stimulation site according to standard targeting literature. **Panel B** reports projections of MNI coordinates onto individualized cortical surfaces. All the resulting target coordinates were visually inspected on the T1-w images to confirm their spatial correspondence to the target grey matter regions. In **Panel C** we depict the Finite element model E-field computations with E-field mapped on the scalp and the cortical surface (gray matter only). The e-field is reported in NormE (V/m) distribution for each stimulation. M1 – primary motor cortex; DLPFC- the dorsolateral prefrontal cortex.

TMS simulations and targeting. E-field distribution was computed within the SimNIBS (Guilherme B. Saturnino et al., 2019) model of the Magstim 70 mm figure-of-8 coil (P/N 9925-00, Magstim Co., Spring Gardens, Whitland, Carmarthenshire, UK). The coil has nine windings with outer and inner diameters of 8.8 and 5.2 cm, respectively (Thielscher and Kammer, 2002a) with a coil-to-scalp distance of 4 mm (by default in SimNIBS). As modeled in SimNIBS, the E-field input is in the form of dI/dt in units of A/us. The dI/dt is the speed of variation of the current through the coil. Its value depends on the coil model, stimulator model, and pulse intensity (for a detailed explanation see 19). For our simulations we assume to use a Magstim 200 stimulator (Vc|Max = 2800 V) and the inductance of the figure-8 70 mm coil is 16.35 uH. This would result in a max dI/dt value (at Max stimulator output, MSO) of 171.3 A/us. Assuming a Resting Motor Threshold (RMT) of around 40%, and knowing that variation with pulse is linear, we chose a dI/dt of 70 A/us (40.8% of the MSO 171.3 A/us). We then simulated the impact of TMS over the three cortical targets chosen in the study: left primary motor cortex (M1), right dorsolateral prefrontal cortex (DLPFC), and right occipital cortex. To do so, we chose the coordinates for each stimulation site according to standard targeting literature. leftM1 *[x=-37, y=-25, z=64]*. We chose the left DLPFC coordinates [*x=40, y=31, z=34]* from Cho and Strafella (2009), The coordinates corresponding to the visual cortex *[x=25, y=-92, z=-9]* were taken from Cocchi et al., (2016), For each participant, these MNI coordinates were converted to subject space in

SimNIBS. When choosing a target, we can enter coordinates within the brain and SimNIBS will automatically project them to the closest skin surface. All the resulting target coordinates were visually inspected on the T1-w images to confirm their spatial correspondence to the target grey matter regions. This was our set of coordinates for stimulation sites on the scalp, corresponding to the center of the coil. The coil handle was then manually moved on the simNIBS GUI and rotated according to the specified position and direction that is usually used in a real-life setting, according to the clinical experience of the authors.

The resulting NormE distribution for each participant on the three stimulation sites is shown in Gmsh v4.7.1 (Geuzaine and Remacle, 2008). The output is a mesh with nodes scattered in space forming tetrahedra with defined electric fields (and current density fields) in each element. To investigate specific changes in current strength generated in our target areas we extracted the mean value of the NormE field in the gray matter of the area stimulated for each individual. To do so we used the ROI spheres we previously created with coordinates in cortical relevant targets and masked them with the layer of gray matter within the mesh. SimNIBS will then get the center of the tetrahedral included in the GM layer inside the sphere and calculate the NormE in the ROI using a weighted average. The output is the average intensity as represented from NormE currently represented in V/m.

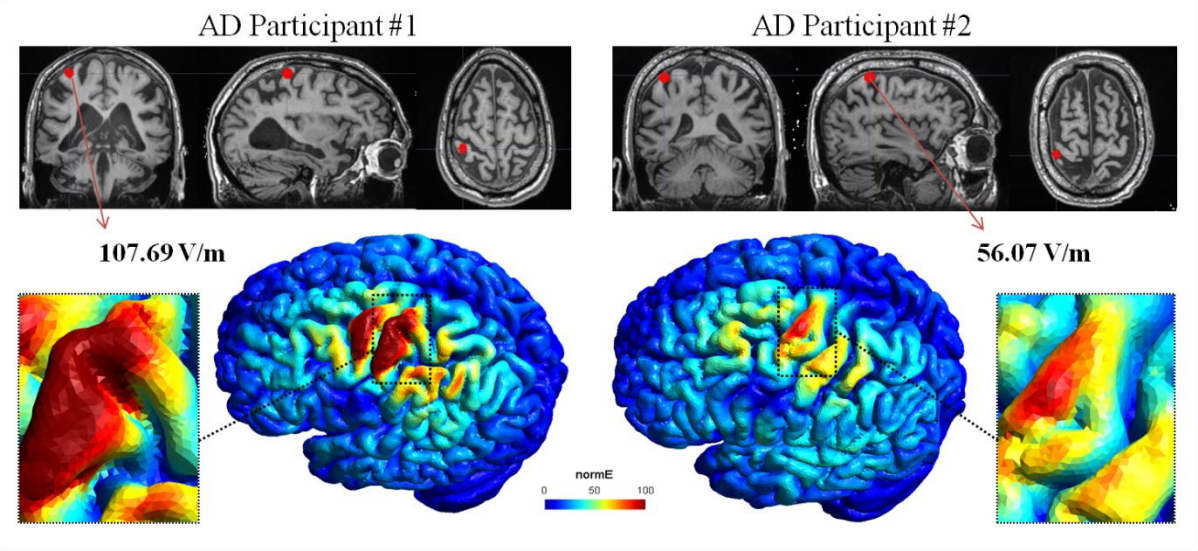


Figure 16. Biophysical modeling of electric field induced by TMS pulse in two AD patients enrolled in the study. The figure shows the position of the ROI sphere (red dot overlapped on the MRI scan) used to compute the average intensity of the e-field induced by TMS pulse on left M1 in two patients with AD enrolled in the study. As shown the strength of the electric field changes drastically due to CSF and morphological differences, local skull-to-brain, and cortical thickness modifications. The NormE is presented in V/m.

Results. The biophysical modeling result showed how the same TMS would result in electric fields different for propagation and current strength within the cohort of AD participants (see Figure 16). This is explained by the spread of cortical atrophy and morphological differences that characterized these patients. The general findings showed an inverse correlation between cortical excitability measures and cognitive performance. This further support the recently emerging concept of enhanced cortical excitability as causative of a worse cognitive performance in AD patients. Relative to AD pathology blood biomarkers, the analysis found a negative correlation between cortical excitability measures, cognitive performance, and

Aβ40 blood levels only after stimulation of the prefrontal cortex. Among the inflammatory biomarkers, only IL-6 positively correlated with cortical excitability after stimulation of the primary motor cortex. Our results suggest that TMS-EEG perturbation of the prefrontal cortex correlates with worse cognitive status and peripheral amyloid concentrations in AD patients. Moreover, we report the first evidence of an association between AD cortical excitability and peripheral pro-inflammatory biomarkers. Albeit preliminary, these findings represent the first evidence of a relationship between TMS-EEG cortical excitability measures and plasmatic biomarkers of AD pathology and inflammation *in vivo*.

4.1.3 Third Sub-study: Identify optimal targets for a tACS protocol to improve memory in AD patients.

The rationale of the study. With my colleague, Dr. Carmelo Smeralda, and the team at SiBIN-Lab, we are currently conducting a study aiming at investigating whether gamma-tACS intervention can improve cognition and enhance gamma oscillatory activity in patients with MCI and mild AD. We are testing whether different types of gamma- tACS stimulation might be equally beneficial in modulating memory performance in our patients' cohort. The study was planned to be a cross-sectional, randomized, double-blind, placebo-control study. We included biophysical modeling beforehand to identify the better target for gamma stimulation. Specifically, previous literature showed that cognitive deficits in AD and MCI patients significantly correlate with Aβ load and p-tau deposition (Bejanin et al., 2017; Ossenkoppele et al., 2016). Specifically, the network of inter-connected regions responsible for memory tasks seems to overlap with beta-amyloid deposition, as well as atrophy in cortical thickness and metabolic alterations reported in AD brains (Buckner et al., 2005; see Figure 17, Panel A). The typical distribution of Aβ in AD patients involves temporal, parietal, and prefrontal regions bilaterally, while p-tau deposition mostly affects the temporal lobe and its mesial part, in particular, Schöll et al., 2016; see Figure 17, Panel B), making the targeting maps with tACS more difficult from a computational modeling standpoint. It is important to take into consideration that given the safety recommendations for stimulation intensity in humans, stimulation of the entire cortical Aβa map would result in an average low current density likely not sufficient to reach the cortex. Following this reasoning, we identified a weighted map that encompassed regions with strong beta-amyloid and tau deposition. We ran a tES optimization algorithm on a head model of one AD patient to find the optimal electrode placement and intensity to target these regions with good focality and efficiency.

Biophysical modeling. The definition of the optimal electrode placement and montage to reach the interested targets in this protocol has been identified using customized biophysical modeling. In particular, the multielectrode tACS optimization was computed in SimNIBS v3.2. As aforementioned, the software provides a realistic volume conductor head model, created as default in FEM model generated using the T1- and T2-weighted images and segmentation from one AD patient previously enrolled in our studies with spread cortical atrophy. In our simulation we kept the isotropic conductivities given by default (Thielscher et

al., 2015), corresponding to gray matter: 0.276 S/m, cerebrospinal fluid: 1.790 S/m, bone: 0.010 S/m, scalp: 0.250 S/m (Opitz et al., 2011).

Multielectrode tACS optimization modeling. The tACS multielectrode solution is proposed as a result of the tES optimization algorithm targeting Aβ and p-tau deposition. In particular, we used the head model of the AD patient and we computed the leadfield thanks to the algorithm of tES optimization from SimNIBS. The leadfield is calculated by first placing electrodes in the head accordingly with a 10-10 EEG cap and afterward calculating the field caused by each electrode individually, keeping a constant return electrode (for a detailed explanation of the algorithm see Saturnino et al., 2019). Thanks to this first computational step, the software creates a matrix that can then be used to calculate the electric field with various measures (e.g., NormE, NormalE, E) caused by any combination of electrodes. In this case, we chose electrodes modeled as small cylinders (1 cm diameter, 4mm thickness) with homogeneous conductivity and added to a 0.5mm in height corresponding approximately to electrode gel. SimNIBS can optimize electric fields based on distributed targets as given by singular MNI coordinates or a file with a network map. We uploaded a map resulting from PET reporting regions associated with high Aβ and p-tau deposition. Because this is a weighted map, the optimization will compute greater intensity where values are higher within the physical limits set by the volume conductor. We set the minimum image threshold of 0.02. Every voxel in the targeted map with a lower value was discarded, focusing the stimulation on the higher values. We set the parameters as follows: maximum of the total current in the whole montage, 4 mA with a maximum of 2 mA individually for each electrode; maximum of 8 active electrodes. To maximize intensity within the target clusters, disregarding field focality, we set a large value for the target intensity (100 V/m). The algorithm will then use the matrix leadfield to find the combination of electrodes that will allow a higher peak value of intensity and mean field norm with good focality and the smallest possible error relative to non-intervention (ERNI). The optimization algorithm will suggest the optimal electrode placement and montage to reach bilateral temporal and parietal regions knowingly hit by tau and beta-amyloid deposition. The suggested tACS montage included 6 electrodes: T7 (1.76mA), TP7 (1.09mA), P3 (1.15mA), T8 (-1.76mA), TP8 (-1.09mA), and P4 (-1.15mA, see figure 17, Panel C). This electrode placement will be used during data collection in all tACS sessions.

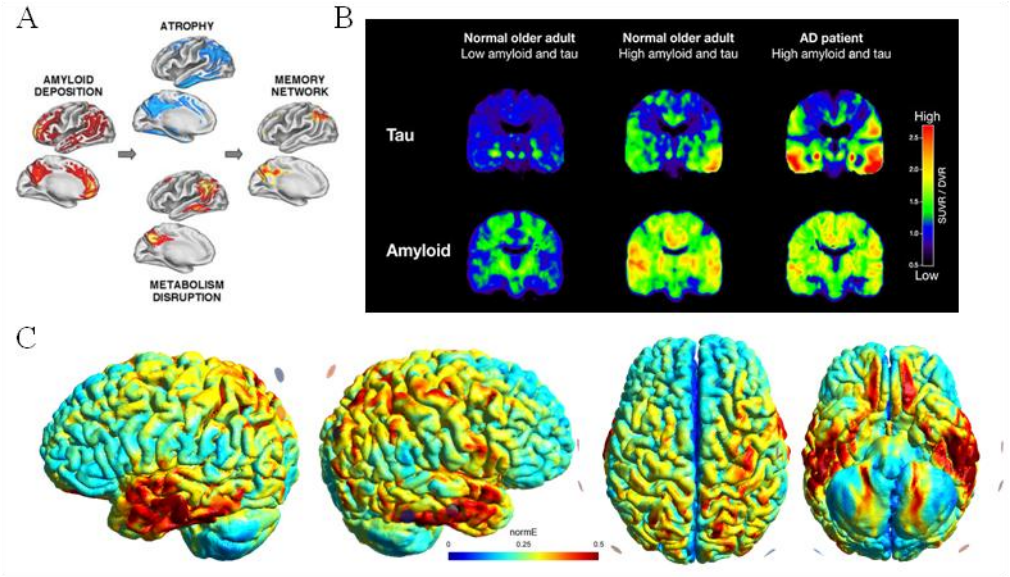


Figure 17. Optimized tACS targeting with tES optimization algorithm. **Panel A** shows the overlap between the amyloid deposition map, AD-related brain changes, and the network of regions involved in memory tasks. The same areas that show advanced atrophy and metabolic abnormalities at the early stages of AD progression, also belong to a network responsible for memory consolidation and retrieval. Image adapted by Buckner et al., 2005. **Panel B** shows Aβ and p-tau typical deposition patterns in the brain of a healthy elderly individual and AD patient. The image is adapted from Scholl et al. 2016. To target these regions associated with high beta-amyloid and p-tau deposition, we ran a tES optimization algorithm on the head model constructed from neuroimaging data from an AD patient previously collected. The simulation suggested the following tACS montage: T7 (1.76mA), TP7 (1.09mA), P3 (1.15mA), T8 (-1.76mA), TP8 (-1.09mA), and P4 (-1.15mA). **Panel C** shows the graphical representation of the induced electric field (NormE in V/m) resulting from this montage overlapped on the head model of the AD patient. This electrode placement and intensity will be the chosen montage for the tACS sessions in the data collection.

Experimental paradigm and methods. We are recruiting patients with a clinical diagnosis of memory impairment due to AD and: (i) Mini-Mental State Examination (MMSE) ≥ 20; (ii) Clinical Dementia Rating scale (CDR) ≤ 1; (iii) biological diagnosis of AD defined as evidence of AD pathology through CSF biomarkers or amyloid-PET imaging; (iv) presence of a caregiver available to escort patient for the study visits. The present study has been approved by the local ethical committee (Azienda Ospedaliera di Siena, Italy). Written informed consent is obtained from all participants before enrollment.

After being recruited, each eligible subject undergoes an extensive neuropsychological assessment evaluating several cognitive functions (memory, executive functions, language, and praxes). Subjects are then randomly assigned to receiving 5 different types of tACS conditions: 1) 40 Hz gamma-tACS; 2) 10 Hz (alpha)-tACS (active control); 3) sham (placebo); 4) random noise stimulation within the gamma band (30-60 Hz) (gamma-tRNS); 5) 40 Hz gamma-tACS stimulation with batches of high frequency (300 Hz) superimposed over each gamma peak (gamma-Pulsate). Conditions order is counterbalanced between subjects. At least 1 day of washout between each session has been left to avoid the potential carry-over effects.

Before and after each stimulation session, subjects are asked to perform a verbal episodic memory task (Rey Auditory Verbal Learning Task – RAVLT). During the task, the examiner reads a list of 15 words, at a pace of 1 second each, and then asks the subject to repeat as many words as he/she can remember. This

process is carried out five times in a row (Immediate Recall). After that, the examiner asks the subject to perform a "distracting", non-verbal task (i.e. find the differences) for the next 15 minutes, and then the examiner asks again the subject to recall as many words as he/she can remember from before without reading the list again (Delayed Recall). Every correctly recall word is 1 point. The score ranges from 0 to 75 for the Immediate Recall and from 0 to 15 for the Delayed Recall. Scores are adjusted for age and years of schooling. To avoid the subjects' learning effect, 10 different lists of words have been created and are randomized within and counterbalanced between subjects. tACS is administered using a 32-channel device (Starstim, NE) which is also capable of recording EEG. Five minutes of eyes-closed and eyes-open resting state EEG are recorded before and after each stimulation session, to assess the degree of entrainment of gamma oscillations during each tACS stimulation session. Stimulation is slowly ramped up/down at the beginning/end of each stimulation session to minimize skin sensation. Sham stimulation is delivered according to current standards. Stimulation intensity will be increased up to the intensity used for real stimulation, held active for 2', and then lowered down to zero. Participants are asked to report any discomfort or subjective feeling during the session. After each stimulation, they are asked to fill out a tACS side-effects questionnaire.

Results. 10 patients (8 male; median age 73 years; all right-handed; 1 MCI) have already completed the study. To assess whether differences in subjects' RAVLT scores before and after (Δ= post-pre) each stimulation session were already noticeable, we first looked at a qualitative change of memory performance across experimental conditions, separately for Immediate and Delayed recall. Afterward, we conducted a preliminary statistical analysis consisting of repeated measure ANOVA with CONDITION as a between-subjects factor. A Bonferroni *post-hoc* test has been applied to correct for multiple comparisons ($p<.05$). We reported a qualitative effect on RAVLT Immediate Recall for gamma-tACS, gamma-tRNS, and Gamma-Pulsate. Interestingly, gamma-tACS determined a 5-fold memory performance improvement compare to both alpha-tACS and sham. A repeated measure ANOVA revealed that there was no statistically significant difference in Δ score between conditions. To detect any significant different between means, we further performed paired sample t-test comparing stimulation conditions between each other. The only significant difference reported was between gamma-tACS and alpha-tACS, but not yet with sham. Delayed Recall: we reported a qualitative effect on RAVLT Delayed Recall for gamma-tACS and Gamma-Pulsate, but not for gamma-tRNS. A repeated measure ANOVA revealed that there was a statistically significant difference in Δ score between conditions. Post-hoc comparisons using Bonferroni correction showed a significant difference between gamma-Pulsate and sham. Despite preliminary, our results showed a significant effect of optimized gamma-tACS stimulation to boost memory performance in AD patients.

SIGNIFICANCE.

Focusing on NIBS protocols involving AD, we showed that field calculations using anatomically detailed head models help in the neurobiological interpretation of NIBS effects and aid the localization of the

stimulated area that underlies the researched physiological or behavioral effect. In the future, this process should also be implemented in data collection to ensure that every subject will be administered a precise amount of stimulation reaching the threshold needed to induce changes in activity/excitability. NIBS could therefore be individually personalized thanks to biophysical modeling and neuroimaging data.

4.2 Fourth Study: Optimize TMS Applications for Space Exploration.

A similar version of the present article has been accepted in Nature Microgravity [**Romanella SM**, Mencarelli L, Seyedmadani K, Jillings S, Tomilovskaya E, Rukavishnikov I, Sprugnoli G, Rossi S, Wuyts F, Santarnecchi E. "*Optimizing Transcranial Magnetic Stimulation for Space-flight Applications*"].

As previously mentioned, NIBS applications in space exploration need to take into consideration the brain adaptation to space stressors, such as microgravity and cosmic radiation. Changes in brain morphology, specifically, are frequently observed in long-term space missions, and they may impact NIBS efficacy. In this study, we investigated how to optimize TMS for space-flight-associated brain changes. Magnetic resonance imaging T1-weighted scans were collected from 15 Roscosmos cosmonauts and 14 non-flyer participants before, after 6 months on the International Space Station, and at a 7-month follow-up. Using biophysical modeling, we show that TMS generates different modeled responses in specific brain regions after space-flight in cosmonauts. Differences are related to space-flight-induced structural brain changes, such as those impacting cerebrospinal fluid volume and distribution. We suggest solutions to individualize TMS to enhance its efficacy and precision for potential applications during long-duration space exploration.

4.2.1. Methods

Subjects and data collection. A total of 29 male subjects were enrolled in the study: 15 cosmonauts and 14 matched controls. The two groups did not significantly differ in age. Three cosmonauts were first-time flyers, while the others had previously performed at least one space mission. Experienced flyers spent around 7 months prior in space. No participant took CNS-acting drugs during the time of the study. All subjects provided written informed consent before they participated in the study. The study was approved by the Institutional Review Board of Antwerp University Hospital (13/38/357), the Committee of Biomedicine Ethics of the Institute of Biomedical Problems of the Russian Academy of Sciences, and the Human Research Multilateral Review Board (HRMRB).

All cosmonauts were scanned at 3 time-points: approximately 3 months before launch (pre-flight), around 9 days after return from their 6 months duration space-flight (post-flight), and on average 7 months after their return (follow-up). In the control group, there was an interval of 7 to 8 months between the first two scans and an interval of 16 months between the second and the third scans (see Table 1). When collecting data at follow-up, we had a smaller sample of space travelers and control participants due to voluntary

discontinuation of the study (final follow-up count for cosmonauts: n = 11 and controls: n = 8; see Table 2 for the total final sample size).

We collected high-resolution T1-weighted magnetic resonance imaging (T1-w MRI) data on a 3T MRI GE Discovery MR750 scanner equipped with a 16-channel receiver head coil located at the National Medical Research Treatment and Rehabilitation Center of the Ministry of Health of Russia in Moscow. Imaging parameters include a repetition time (TR) of 8ms, echo time (TE) of 3ms, flip angle (FA) of 12°, 1mm isotropic voxel size, and a field-of-view (FOV) of 240x240x180 mm^3.

	Age	Prev Mission	T1 (pre)	Mission	T2 (after)	Interval T1-T2	Interval T2-T3
	years	*days*	*days*	*days*	*days*	*days*	*days*
Cosmonauts	46.06 (4.94)	206.26 (182.3)	86.5 (31.75)	184.46 (48.98)	9 (2.87)	278.26 (54.89)	228 (54.4)
Controls	43.16 (6.31)	-	-	-	-	237.85 (52.53)	495.75 (137.95)

Table 1. Characteristics of the sample. We show characteristics of cosmonauts and controls, such as age and length of previous missions. We then report the duration of the current missions and the time when the MRIs were collected before (T1) and after the space-flight (T2). We also add the interval between baseline and post-flight (Interval T1-T2), as well as the gap between post-flight and the follow-up (Interval T2-T3). Every measurement is reported with the average, standard deviation (in parenthesis).

	Cosmonauts			Controls		
	Pre-flight	Post-flight	Follow-Up	Pre-flight	Post-flight	Follow-Up
TMS Simulations	15	15	11	14	14	8
Total CSF Volume	15	15	11	14	14	8

Table 2. Final sample size for each analysis. The table presents the final number of MRIs collected and used for the study in different analyses for the group of cosmonauts and controls. Note: TMS: Transcranial Magnetic Stimulation. CSF: Cerebrospinal Fluid.

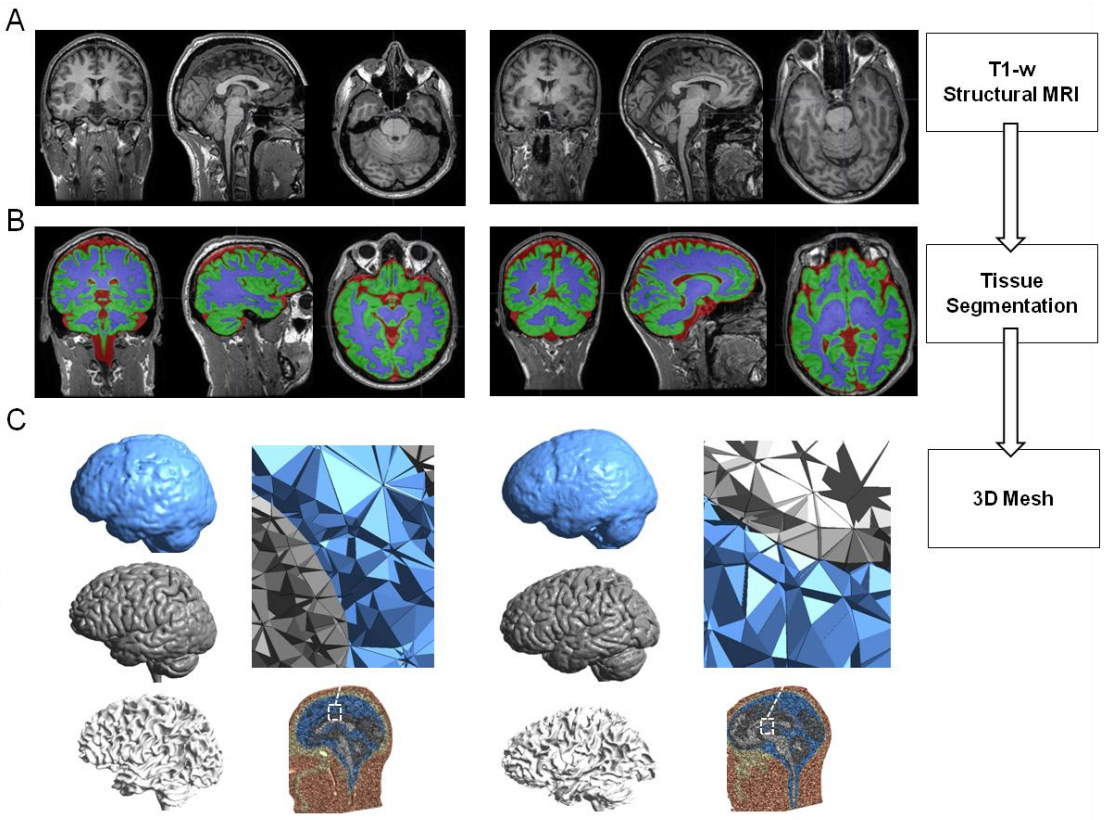


Figure 18. Image processing and mesh creation diagram. We show the pipeline of MRI processing to create a 3D mesh to run the simulations for two participants in the study, for example, one cosmonaut (left) and one control

participant (right). **Panel A.** We collected the T1-weighted (T1-w) anatomical scan for each participant at three-time points (pre-flight, post-flight, and follow-up). In the figure, we show MRIs collected pre-flight for both participants. **Panel B.** We ran the *headreco+CAT* pipeline from SimNIBS (Saturnino et al., 2019) to segment the T1 anatomical image into class types (skin, bone, CSF, eyes, gray matter, and white matter). For better visualization, we show segmentation of CSF (red), gray matter (green), and white matter (blue). For better visualization, we show segmentation of CSF (red), gray matter (green), and white matter (blue). **Panel C.** We then computed the head volume of 3D meshes composed of tetrahedral elements (CSF: blue; gray matter: gray; white matter: white). Thanks to this process we can enter coordinates in MNI and the software will convert them to personal subject space to ensure accuracy in targeting.

Individualized biophysical modeling. MRI data quality assurance (sample homogeneity), preprocessing, and analysis were performed with the CAT12 Toolbox (version 1727) (Gaser and Dahnke, 2016) (http://www.neuro.uni-jena.de/cat) within the SPM12 framework (Wellcome Department of Cognitive Neurology, London, UK), using Matlab R2019a (Mathworks, Natick, MA, USA; see Figure 18, Panel A). The induced E-field of the TMS was computed in SimNIBS v3.2, an open-source simulation package that integrates segmentation of MRI scans, mesh generation, and finite element method (FEM) model E-field computations (Saturnino et al., 2019; Thielscher et al., 2015). The software provides a realistic volume conductor head model, created as default in FEM generated using the individual T1-weighted image. The finite element head model for each participant was reconstructed by applying the *headreco+CAT* pipeline to the subject's T1-weighted scans. In our simulation, we kept the isotropic conductivities given by default (Thielscher et al., 2015) here provided for the main tissue volumes, in S/m: gray matter: 0.275; white matter: 0.126; CSF: 1.654; bone/skull: 0.01; scalp/skin: 0.465. The final mesh, comprehensive of gray (GM) and white matter (WM), scalp tissue, bone, and cerebrospinal fluid, comprises approximately 200,000 nodes and 3.6 million tetrahedral elements (see Windhoff et al., 2013) for further modeling details) for each participant (see Figure 18, Panel B and C). Segmentations were carefully examined slice-by-slice to ensure proper tissue classifications.

TMS simulations and targeting. E-field distribution was computed within the SimNIBS (Guilherme B. Saturnino et al., 2019) model of the Magstim 70 mm figure-of-8 coil (P/N 9925-00, Magstim Co., Spring Gardens, Whitland, Carmarthenshire, UK). The coil has nine windings with outer and inner diameters of 8.8 and 5.2 cm, respectively (Thielscher and Kammer, 2002a) with a coil-to-scalp distance of 4 mm (by default in SimNIBS). As modeled in SimNIBS, the E-field input is in the form of dI/dt in units of A/us. The dI/dt is the speed of variation of the current through the coil. Its value depends on the coil model, stimulator model, and pulse intensity (for a detailed explanation see Kammer et al., 2001). Coils have different inductances (L in micro-henrys). The stimulator output (% of the maximum capacitor's charging voltage in the stimulator) will result in different max dI/dt values. The expression is dI/dt|Max = Vc/L, where Vc is the capacitor's charging voltage and L is the inductance of the coil. For our simulations we assume to use a Magstim 200 stimulator (Vc|Max = 2800 V) and the inductance of the figure-8 70 mm coil is 16.35 uH. This would result in a max dI/dt value (at Max stimulator output, MSO) of 171.3 A/us. Assuming a Resting Motor Threshold (RMT) of around 40%, and knowing that variation with pulse is linear, we chose a dI/dt of 70 A/us (40.8% of the MSO 171.3 A/us).

We then simulated the impact of TMS over four cortical targets potentially relevant for neuromodulation protocols in space travelers (S. M. Romanella et al., 2020): left primary motor cortex (M1), left dorsolateral prefrontal cortex (DLPFC), left angular gyrus, and right visual cortex (V1/V2). To do so, we chose the coordinates for each stimulation site according to standard targeting literature. The left M1 coordinates were taken from Mayka et al. (2006), a meta-analysis of 126 articles to locate different motor areas with high accuracy (Mayka et al., 2006). The coordinates were in Talairach *[x=-37, y=-21, z=58]*, and converted in MNI thanks to an online toolbox (https://bioimagesuiteweb.github.io/webapp/mni2tal.html) *[x=-37, y=-25, z=64]*. We chose the left DLPFC coordinates [*x=-40, y=31, z=34]* from Cho and Strafella (2009), a study showing that repetitive TMS (rTMS) on this neocortical target produced dopamine release in cingulate and orbitofrontal areas relevant for improving learning and depressive symptoms (Cho and Strafella, 2009). We extracted the coordinates for the stimulation on the angular gyrus *[x=-48, y=-64, z=30]* from an fMRI-TMS study indicating it as the center of the region pivotal for episodic memory (Thakral et al., 2017). The coordinates corresponding to the visual cortex *[x=25, y=-92, z=-9]* were taken from Cocchi et al., (2016), a study of neuroimaging, non-invasive cortical stimulation, and computational modeling to investigate the visual cortex (Cocchi et al., 2016). We kept these 4 sets of coordinates as our cortical targets (see Figure 19, Panel A).

When choosing a target, we can enter coordinates within the brain and SimNIBS will automatically project them to the closest skin surface. This can cause a shift of the stimulation site and differences among subjects due to variance in skull/brain structure. To overcome this, we created a set of ROI spheres with the center as the coordinates in cortical target areas and 3mm diameter (red spheres in Figure 19, Panel B). We overlapped them on the T1-weighted in an MNI standard brain used as example data set (Ernie) included in SimNIBS software (Windhoff et al., 2013a). All the sites' coordinates were visually inspected on the T1-w images to confirm their spatial correspondence to the target grey matter regions. We then moved 90 degrees oblique from the sphere toward the scalp until reaching it and saved the position on the skin as the new target. We saved these new sets of coordinates as stimulation sites on the scalp: left M1 *[x=-51, y=-25, z=81]*, left DLPFC *[x=-55, y=31, z=46]*, left angular gyrus *[x=-69, y=-65, z=32]*, and right visual cortex *[x=33, y=-108, z=-9]*. All the coordinates are presented in MNI space. For each participant, these MNI coordinates were converted to subject space in SimNIBS. This was our set of coordinates for stimulation sites on the scalp, corresponding to the center of the coil (green spheres in Figure 19, Panel B).

The coil handle was then manually moved on the simNIBS GUI and rotated according to the specified position and direction that is usually used in real-life setting. We added a set of MNI coordinates for the corresponding orientation of the coil handle, to ensure an accurate representation of the generated E-field: left M1 *[x=-41, y=-8, z=85]*, left DLPFC *[x=-44, y=44, z=56]*, left angular gyrus *[x=-57, y=-80, z=54]*, and right visual cortex *[x=14, y=-118, z=5]*. These coordinates were converted in subject space as well during the simulations (see Figure 19, Panel C).

The resulting NormE distribution for each participant, on any time-point (pre-flight, post-flight, follow-up) on the 4 stimulation sites is shown in Gmsh v4.7.1 (Geuzaine and Remacle, 2008). The output is a mesh

with nodes scattered in space forming tetrahedra with defined electric fields (and current density fields) in each element (See Figure 19, Panel D). To investigate specific changes in current strength generated on our target areas we extracted the mean value of the NormE field in the gray matter of the area stimulated for each individual at each time point. We used the ROI spheres we previously created with coordinates in cortical relevant targets and masked them with the layer of gray matter within the mesh. SimNIBS will then get the center of the tetrahedral included in the GM layer inside the sphere and calculate the NormE in the ROI using a weighted average (see Figure 19, Panel E). The process starts from the final mesh created from the individual segmented MRI scan including approximately 3.6 million tetrahedral elements. SimNIBS computes the precise volume of every single tetrahedron within the chosen ROI. It will then calculate the NormE within every single tetrahedron. Finally, the average of the NormE in all tetrahedral elements is computed by weighting the electric field values based on the volume of each tetrahedron. The output is the average intensity as represented from NormE currently represented in V/m.

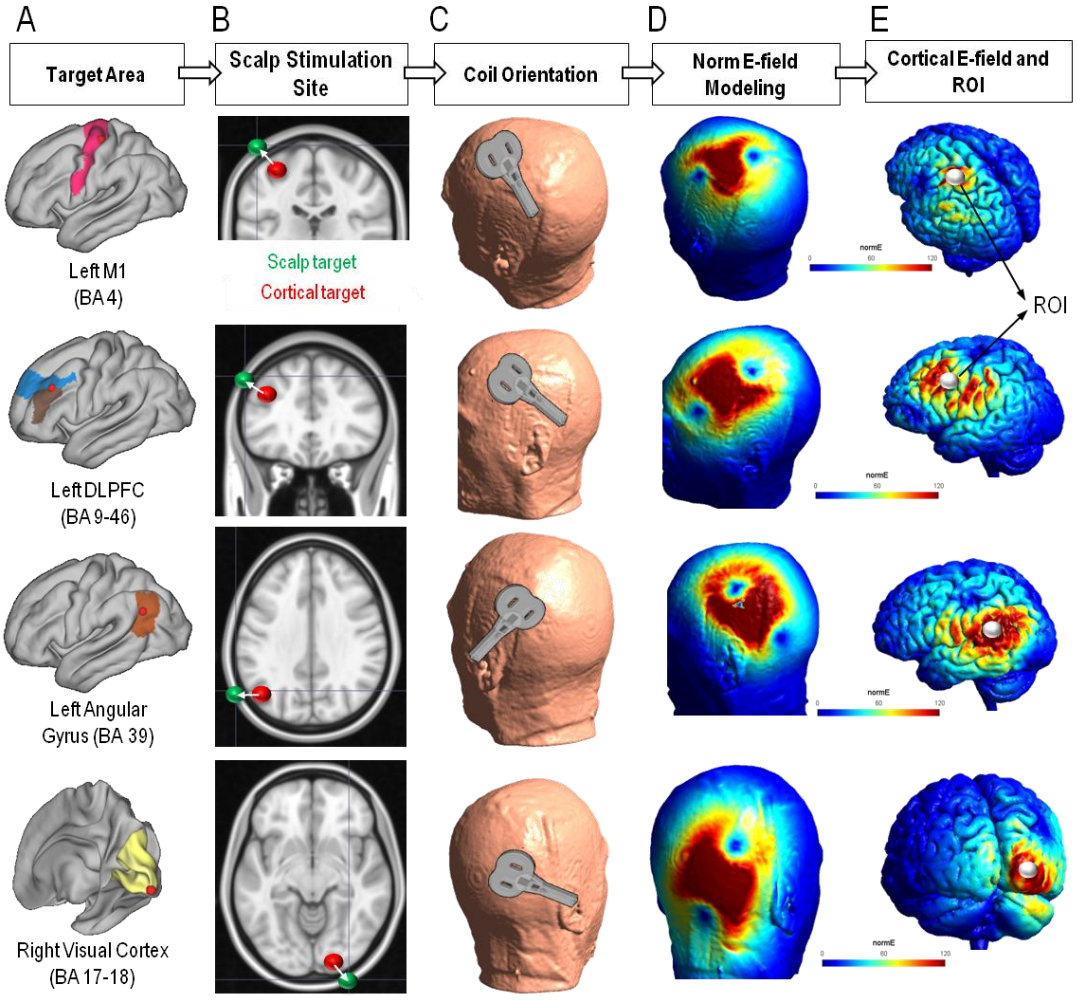


Figure 19. Process for TMS simulations and NormE extraction. The figure shows the process used for identifying the stimulation sites, TMS coil placement and orientation, and extraction of the resulting NormE. **Panel A.** We focused on four regions as potential stimulation targets for their relevance for neuromodulation protocols in space travelers: left primary motor cortex (M1), left dorsolateral prefrontal cortex (DLPFC), left angular gyrus, and right visual cortex. The set of cortical targets with the center in coordinates was chosen from up-to-date literature (see main text for details). The Panel shows the targets (red spheres) and the corresponding Brodmann Area (BA). **Panel B.** We created a set of spherical region-of-interest (ROI) with these coordinates (red spheres enlarged in the figure to allow visualization). The

ROIs were overlapped on the MRI T1-w in an MNI standard brain and moved 90 degrees oblique from the sphere toward the outside until reaching the scalp. We saved the position on the skin as a new target (green spheres: scalp targets). **Panel C.** We centered the coil on this new set of coordinates for stimulation sites on the scalp. The coil handle was then manually rotated to recreate the orientation normally employed in an experimental setting. In the main text, we also report the set of MNI coordinates for the corresponding orientation of the coil handle, to use the same precise orientation for each participant. All MNI coordinates were converted to subject space thanks to SimNIBS. **Panel D.** We then ran the simulation of TMS pulse computing the resulting NormE distribution for each participant, at each time-point (baseline, post-flight, follow-up) on the four stimulation sites. The resulting output from one of the cosmonauts enrolled in the study is shown in **Panel E.** To compute the current strength reached by the cortical areas we were interested in, the NormE was extracted in the gray matter of the area stimulated for each individual at each time point. The ROI spheres previously created with coordinates in cortical targets are here presented in white and still enlarged to allow visualization. We intersected them with the layer of gray matter within the TMS-generated electric field. The weighted average NormE in every tetrahedron of the mesh within the ROI was computed. The figure shows the NormE in V/m. Note = M1: primary Motor Cortex, DLPFC: Dorsolateral Prefrontal Cortex, BA: Brodmann Area, ROI: Region-Of-Interest.

Analysis of CSF volume. Automated segmentation of CSF volume was performed with Freesurfer software package Version 6.0 (http://surfer.nmr.mgh.harvard.edu/). Freesurfer volume-based subcortical segmentation pipeline has been extensively described in previous literature (Fischl et al., 1999). Briefly, Freesurfer uses a probabilistic atlas that is built by manually labeling a training dataset, which is then normalized to the MNI space to achieve a point-to-point correspondence between all the training subjects. The atlas provides the probability of each label at each voxel, the probability of each label given the classification of neighboring voxels (neighborhood function), and the probability distribution function of voxel intensities, modeled as a normal distribution, for each label at each voxel. The segmentation of a new image is achieved by normalizing the new subject to the common space and incorporating the subject-specific voxel intensities to find the optimal segmentation that maximizes the probability of observing the input data. We extracted CSF volume for each participant at each time point. Freesurfer separately extracts the volume of each ventricle (left and right inferior lateral ventricles, left and right superior lateral ventricles, 3rd ventricle, and 4th ventricle). We added the volume of the ventricles (filled with CSF) to the peripheral CSF volume to compute the total volume of the CSF and use the output for the analysis. The values are presented in mm^3.

Statistical analysis. All data were analyzed using SPSS version 22 (SPSS Inc., Chicago, USA). We ran separate analyses for every variable (generated NormE in four target regions, total CSF volume). Changes in NormE were computed separately for each stimulation site with repeated measure two-way analysis of variance (ANOVA), comparing cosmonauts and controls. We ran two ANOVAs for each variable for pre- vs post-flight, and pre-flight vs. follow-up. To be sure that significant differences in controls over time would not confound the effects seen in cosmonauts, multiple repeated measure one-way ANOVAs were performed exclusively on the control group for each stimulation site for pre- vs. post-flight, and baseline vs. follow-up. We report the p-values for the interaction group vs. time.

Linear regressions were then performed to assess associations between changes in NormE and modifications in brain anatomy. Specifically, we performed singular linear regression analysis for delta

(post-pre) in total CSF volume with the delta of NormE in each area. For every regression, we added Group as a second independent variable. A p-value lower than 0.05 was considered statistically significant.

TMS optimization. To show how the personalization of TMS parameters allows a more accurate stimulation, we provide solutions to resolve the difference in current strength between pre- and post-flight. The induced electric field distribution depends on multiple stimulation parameters such as intensity, location, and orientation of the TMS coil. For this example, we offer two potential solutions of personalization: i) changing the intensity of the TMS pulse and running a new simulation; ii) performing TMS optimization to find the best coil position and orientation. In both cases we ran these processes on post-flight scans, to account for the space-flight-induced brain structural modifications.

For the first solution, we started by normalizing the difference in NormE reached in TMS simulations over M1 at post-flight compared to baseline (100*(Post – Pre) / Pre) in two cosmonauts. This is the change of the current strength in percentage after the space mission. Knowing that pulse intensity and current are linear, we re-ran the TMS simulations on post-flight data over M1, modifying the dI/dT by lowering the score we used before (70 A/us) by the percentage change. The resulting NormE is shown in Gmsh v4.7.1 (Geuzaine and Remacle, 2008) with an output range in V/m. After calculating the strength of the field in the ROI with the process previously described, we compared it to the result in TMS simulation M1 on the same post-flight MRI of the same participant.

The second solution was performed by implementing a SimNIBS function (*TMSoptimize*) that computes the best TMS coil position and orientation to stimulate a certain target (Weise et al., 2020). We ran this analysis on the mesh of post-flight data for the same two cosmonauts with a target in the left angular gyrus (cortical coordinates as above: *[x=-48, y=-64, z=30]).* The software starts by searching coil positions in a grid around the target position and turning the coil at various angles for a total of 540 possible trials (Weise et al., 2020). SimNIBS returns with the position and orientation of the coil that induces the largest NormE at the target. At the end of the process, we compared the resulting NormE with the previous output in TMS stimulation over the same target on the post-flight MRI of this participant.

4.2.2. Results

Space-flight-associated changes. Comparing cosmonauts and controls, we found statistically significant differences in NormE under some of the stimulation sites post-flight (see Figure 20). Specifically, when compared to controls, cosmonauts showed a significant increase in intensity at post-flight when the stimulation site was left M1 [$F_{(1,27)} = 4.29, p = 0.048$]. Our results also show a statistically significant decrease in NormE when the stimulation was over the angular gyrus [$F_{(1,27)} = 10.37, p = 0.003$]. No significant differences in NormE were found at post-flight under the left DLPFC and right visual cortex (both p-values > 0.05). When comparing cosmonauts and controls at follow-up vs. pre-flight, the two groups showed no differences in NormE reaching any of the stimulation sites (all p-values > 0.05). We also analyzed NormE at pre-flight vs. post-flight in the control group alone. No changes over time in any area were found (all p-values > 0.05), suggesting that statistical differences in cosmonauts and controls seem to

be related to the time spent in space rather than variability in the cohorts. Total CSF volume change between baseline and post-flight was significantly higher in cosmonauts compared to controls [$F_{(1,27)}$ = 17.39, p < 0.001]. The ANOVA on CSF pre-flight vs. follow-up showed no significant difference (p > 0.05).

The linear regression revealed a significant negative correlation between the change in total CSF volume (post-flight – pre-flight) and the decrease of NormE reached in the angular gyrus [R^2 = 0.27, p = 0.004]. The analysis showed no relationship between CSF changes and NormE differences in M1, DLPFC, and visual cortex (all p-values > 0.05).

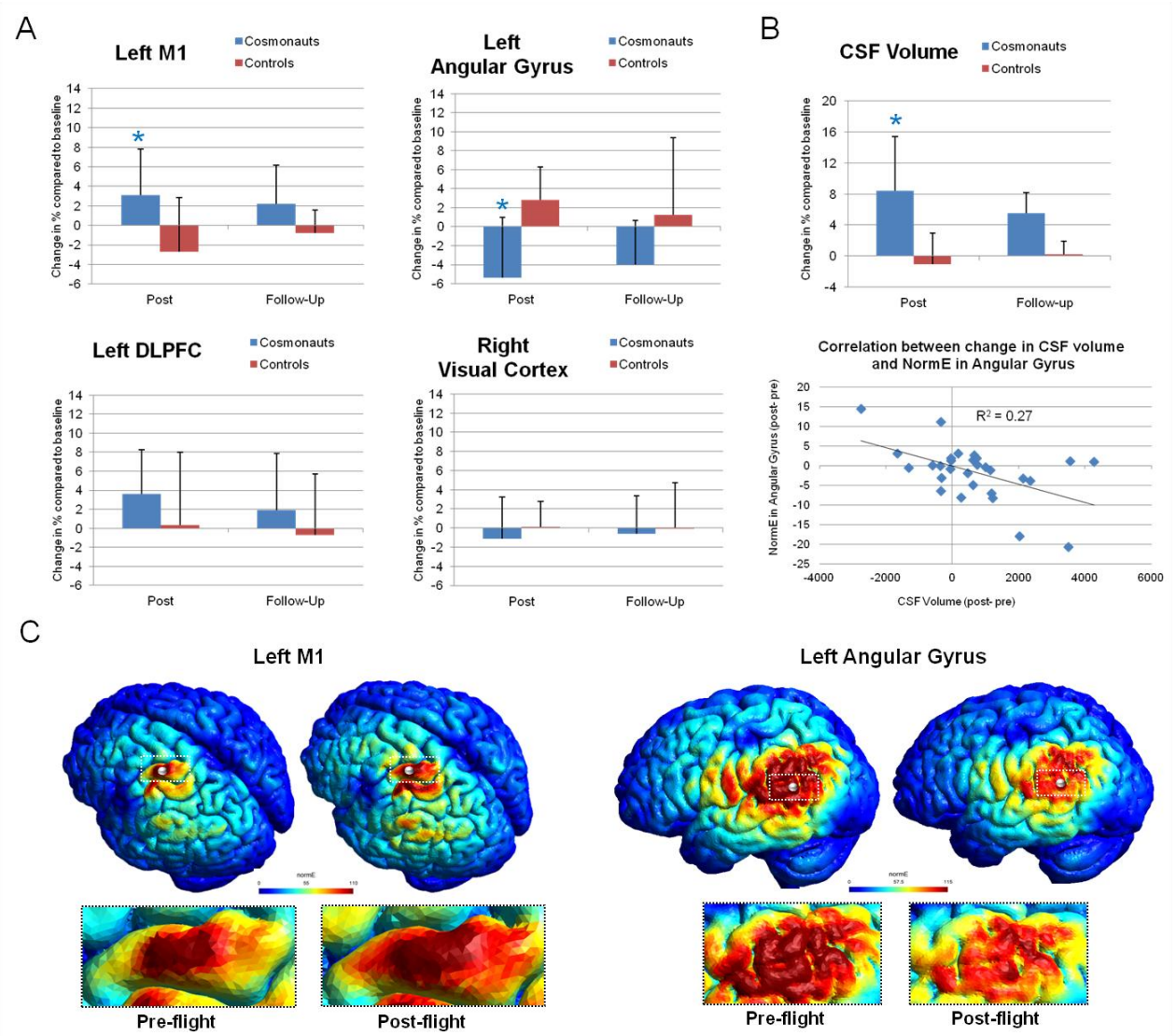


Figure 20. Changes in NormE and brain structure in cosmonauts. Panel A. Changes in NormE reaching the cortical regions in cosmonauts (blue bars) compared to controls (red bars) are presented. Graphs show the current strength of the E-field expressed in % difference of NormE from the baseline (pre-flight) in the target area for all cosmonauts/controls on each time-point. We found statistically significant differences in NormE under the stimulation sites in post-flight compared to baseline in M1 and angular gyrus. Asterisks indicate significant differences between cosmonauts and controls. **Panel B.** Significant differences in total CSF volume in cosmonauts compared to controls are also reported (left). Finally, the correlation between the change in total CSF volume and the decrease in NormE reached in GM in angular gyrus in cosmonauts is displayed (R^2 = 0.27, p = 0.004; right). The values are presented in mm^3. **Panel C.** Under the graphs, we also show the electric field (NormE) presented in V/m induced by TMS pulse in one cosmonaut as an example pre-flight and post-flight in M1 and angular gyrus. Note the difference in electric field strength as represented in NormE seen over the interested area. The white spheres represent the cortical ROI used to extract the NormE values.

TMS personalization. We offer two potential solutions to ensure more efficient brain stimulation (see Figure 21). As aforementioned, compared to controls, cosmonauts showed an increase of NormE in M1 and a decrease in the left angular gyrus after the space-flight. Therefore, we chose two different solutions to optimize stimulation for these two target sites. For stimulation over M1, we lowered the intensity proportionally to the post-flight change in NormE to reach levels similar to the baseline. We ran a new simulation on a post-flight scan using the adjusted intensity values and found the NormE values to reach baseline levels (see Table 3, left). On the other hand, the decline in NormE over the left angular gyrus in post-flight might affect TMS efficacy. On the other hand, the decline in NormE over the left angular gyrus in post-flight might affect TMS efficacy. We ran a TMS optimization algorithm and reported the resulting NormE values compared to the standard simulation (see Table 3, right). The TMS optimization suggested us the best coil position and orientation to achieve a more intense induced NormE in the left angular gyrus. For more information on the optimization, procedures see the Methods section.

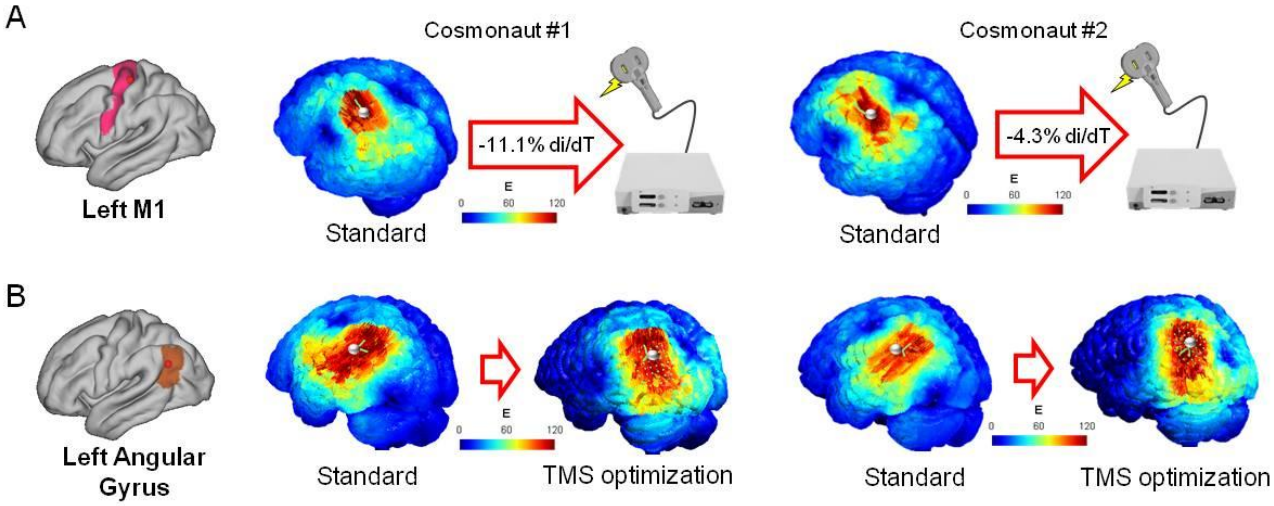


Figure 21. TMS optimization. The figure shows potential solutions to individualize TMS parameters tested on two cosmonauts (center and right). **Panel A.** For stimulation over left M1, we lowered the intensity of TMS pulse by the pre to the post-flight difference in E-field. **Panel B.** Over the left angular gyrus, instead, we performed TMS optimization to find the best-individualized setting. The TMS optimization algorithm suggested a coil position and orientation for both cosmonauts to induce the largest NormE (Cosmonaut #1: coil position *[x=-70.48, y=-74.28, z=29.95]*; coil orientation *[x=-72.1, y=-64.63, z=42.71]*; Cosmonaut #2: coil position *[x=-70.72, y=-67.42, z=43.03]*, coil orientation *[x=-76.07, y=-59.86, z=34.13]*. The output includes the position and orientation of the coil that induces the largest NormE (green line). We show the different current distributions resulting from the standard simulation and TMS optimization. Values are in V/m. The white spheres represent the cortical ROI used to extract the NormE values. Results in NormE can be seen in Table 1.

	Left Primary Motor Cortex			Left Angular Gyrus		
	Baseline	Post-flight		Baseline	Post-flight	
	Standard	Standard	Personalized	Standard	Standard	Personalized
Cosmonaut#1	71.60	79.98	70.61	79.08	71.94	80.16
Cosmonaut#2	63.69	66.44	63.59	77.41	64.79	78.58

Table 3. NormE values resulted from standard and personalized stimulations. We show the average NormE reached in left M1 and left angular gyrus in two cosmonauts. Values are extracted from standard simulations vs. personalized solutions and presented in V/m.

4.2.3. Discussion

We analyzed the electric field generated by TMS over four brain regions using MRI scans collected from crew members before and after long space missions, and at follow-up. When compared to controls, the cosmonauts exhibited significant differences in the modeled TMS-generated current after space-flight. We demonstrate that flight-induced alterations in brain morphometry are partially responsible for these findings resulting from computational modeling, while also suggesting that they are relevant for determining the safety and efficacy of TMS stimulation. We introduce two practical solutions based on individual neuroimaging data and simulation to personalize TMS intervention for space travelers. Finally, we discuss the potential implementations of TMS in space missions as well as the limitations of the study.

Differences in TMS-induced electric field. After the space mission, the cosmonauts showed a significant increase in the current strength over the left M1 and a decrease in current reaching the angular gyrus. The analysis showed no statistical differences in the control group alone, suggesting that changes in NormE were associated with space missions and not variability within the groups. At the follow-up, cosmonauts presented a return of all measurements toward the baseline level, suggesting Earth-based re-adaptation. Differences in TMS-induced electric fields in space travelers can be caused by a plethora of various functional and structural cortical changes. One of the most important is CSF volume and redistribution (Bijsterbosch et al., 2012). In our study, space travelers showed an increase in total CSF volume after space-flight, similar to previous studies (Jillings et al., 2020; Ombergen et al., 2019; Roberts et al., 2021, 2017). This is a well-known phenomenon and one of the most recognizable biomarkers of space-flight. As aforementioned, CSF redistribution will affect the location of the peak TMS-induced electric field due to its greater conductivity compared to other brain tissues. Our study seems to confirm its role, with the significant increase in total CSF volume accounting for over 25% of the variance in NormE in angular gyrus in cosmonauts.

Previous literature shows how changes in CSF are associated with an upward shift of the brain, consisting of a redistribution of the subarachnoid CSF that causes a reduced CSF volume at the vertex, coupled with an expansion at the bottom of the skull (Jillings et al., 2020; Ombergen et al., 2018). These findings have also been confirmed by studies using voxel-based morphometry (VBM) (Ombergen et al., 2018) and free-water analysis of diffusion MRI (dMRI) (Lee et al., 2019). However, high-induced electric fields are primarily found in grey matter regions adjacent to areas of reduced or thinning CSF thickness (Bijsterbosch et al., 2012). This would also reduce the distance between the brain and the coil. Therefore, an increase in the NormE in M1 following space-flight may be explained by the presence of a thinner regional CSF layer on the vertex and the upward shift of the brain. On the other hand, there is no significant correlation between changes in total intracranial CSF volume and NormE over the M1. The electric field in M1 may be affected by the upward brain shift, not only because of CSF redistribution but also following cortical thickness and MRI diffusion alterations. Therefore, it is not entirely surprising that we did not observe a significant correlation between specific, local E-field modifications and the mere total intracranial CSF volume.

The decrease in electric current reaching the angular gyrus seems to be influenced by an opposite modification of the CSF volume. The literature reports an increase in CSF volume after space-flight mostly

affecting the skull base, Sylvian fissure, and temporal lobes (Hupfeld et al., 2020). The angular gyrus, which is close to the Sylvian fissure, is the most inferior brain target region we chose. The CSF layer close to this area has been repeatedly found to be increased after space-flight (Jillings et al., 2020; Ombergen et al., 2018). This may explain the local decrease of NormE over the angular gyrus since a greater amount of CSF potentially causes widespread current shunting. We can speculate that the increase in total CSF volume explaining the variance in NormE in the angular gyrus may reflect the local increase in CSF. However, we did not assess the CSF variation on a region-by-region basis, therefore we cannot completely rule out the influence of other factors or confirm this hypothesis even if the present results are in line with the previous literature and proposed mechanisms. Finally, we did not observe significant variation in the NormE field simulated over the DLPFC and visual cortex at baseline versus post-flight simulation. The present investigation did not aim to assess the morphovolumetric changes that affect the brain after space-flight, so we cannot provide a definitive and certain explanation of the physiological process that may have influenced the tested brain regions and thus the electric field. Nonetheless, the findings could be related to the fact that these regions are less affected by the upward brain shift occurring after space-flight and by significant CSF redistribution following recent literature (Jillings et al., 2020; Ombergen et al., 2018).

At follow-up, total CSF volume exhibited a re-adjustment toward the baseline level in cosmonauts (see Figure 20). Because follow-up MRI scans were collected a considerable time after re-entry (7 months), this may signal homeostatic re-adaptation to Earth-based gravity, as previously observed and suggested (Hupfeld et al., 2020). However, the time required for the effects of space-flight on brain structure to reverse completely is currently unknown, as further follow-ups (one year, two years) have not yet been tested. Therefore, it is uncertain if the decrease toward baseline seen at approximately seven months after re-entry was reaching the plateau or continuing in the process of re-adaptation. Longer space missions, as required for Mars colonization, may also exponentially accentuate these modifications to brain structure. A longer period of Earth-based re-adaptation may be needed to return to values close to the baseline. In this situation, TMS may be a potential tool for investigating the neural process triggered by space-flight-associated adaptation. To overcome differences in morphology and volume due to space-flight and consequent re-adaptation, a call for individualization is needed.

TMS personalization. Considering the differences in NormE generated by TMS due to various concurring factors, great care must be taken when inducing electric fields at any stage of space missions. Space-flight-induced modifications in anatomy need to be considered, such as CSF volume and distribution, local skull-to-brain distance due to the upward shifting of the brain, and cortical thickness modifications. Along with a standard inter-individual variability, this may result in fundamental differences in the electromagnetic field exposure across subjects, even for an identical stimulation dose (for a review of the parameters and dose personalization, see *9*). Ignoring these modifications may result in various consequences, such as loss in the focality of the field. This is particularly relevant for the beneficial effect of TMS, which could fall under the threshold and consequently become inefficient. Furthermore, this argument must be addressed for its relevance in terms of safety. Structural brain changes may unexpectedly increase

the induced current strength reached in target cortical areas. Therefore, developing simulations that can mimic the generated E-field with high accuracy is crucial for TMS feasibility and future implementations in space missions.

We can personalize the setting by adjusting the parameters of the TMS pulse, correcting for changes in the brain structure. The induced electric field distribution also depends on multiple stimulation parameters, such as the location and orientation of the TMS coil. In this study, two potential solutions for providing a personalized TMS application are presented. The first involves adjusting the intensity of the TMS pulse (through the di/dT on the simulation parameters) to match the different current strengths reaching the relevant area. The TMS optimization algorithm, instead, compares a large number of potential coil positions and orientations to find the setting that generates the highest E-field in the target area. Furthermore, while using T1-w MRI provides valuable input for the creation of a model, recent literature has also suggested diffusion MRI as a tool to gather data for biophysical modeling (Wang et al., 2008). These techniques estimate tissue conductivities and can refine the precision of computational simulations.

While TMS may seem impractical on the ISS or space-flights owing to its weight and interference in the magnetic field, it is worth noting that potential TMS application during a space mission has already been explored. Space environments, such as the ISS, spacecraft, the Moon, and Mars will necessitate more innovative solutions than Earth-based non-laboratory settings. Such environments differ from Earth in several aspects, including temperature and pressure (Davis et al., 2021), and these may potentially harm stimulation devices. This will hence require a TMS device capable of functioning outside the experimental environment and in the absence of trained operators. A recent study of an individually tailored TMS helmet applied over M1 suggested it to be a feasible and reliable alternative to traditional laboratory settings (Badran et al., 2020b). The same group tested the helmet in 0G (Badran et al., 2020a). They recorded the resting motor thresholds (rMTs), stimulating M1 with single-pulse TMS on 10 participants before, during, and after a parabolic flight. They showed how zero gravity motor thresholds were lower than Earth rMTs at the baseline. This reduction was recovered immediately post-flight, with a level similar to the pre-flight one. They ascribed this to the physical upward shift of the brain within the skull. A lower scalp-to-cortex distance would require an electric field less intense to induce the same cortical activation. This is in line with our increase in the current strength in M1 at post-flight as compared to the baseline. While more investigation is required, this has proved how TMS can be implemented in non-laboratory settings with variable gravity. This solution may create opportunities for in-flight TMS implementations to support crew members in their daily work on the ISS and planetary surface installations.

Limitations. Although we analyzed a unique longitudinal dataset of MRI data from cosmonauts matched with a control group, the study has a few limitations. First, although our findings resulting from computational analysis are promising, empirical data is still necessary to confirm differences in TMS-induced electric fields due to morphological changes during space missions. Secondly, we must consider individual variability among space travelers due to previous training/education. Furthermore, the cosmonaut cohort contained a combination of first-time and experienced flyers. For space travelers who already

performed a space mission, the data at pre-flight may deviate from the baseline level similar to all first-time flyers. Although this may confound space mission-induced effects, it also confirms the necessity of adjusting TMS settings to personalize interventions in this special cohort. Another limitation involves the timeline constraints regarding the acquisition of neuroimaging data, driven by logistic and organizational constraints. Post-flight MRIs were performed after an average of nine days upon returning to Earth. In our study, we showed that time spent after being back on Earth can partially counteract the space-flight-associated changes in the brain. Although we do not think that the difference of a few days would be sufficient to trigger brain re-adaptation alone, we have to consider that an earlier scanning session may reveal more pronounced effects of space-flight on the brain. Similarly, Table 1 shows the missing MRIs of space travelers whose scans we were not able to collect on follow-up, limiting the sample size at this time point.

SIGNIFICANCE.

In this computational study, we demonstrated that the same TMS protocol generates different modeled current strengths in cortical targets simulated in cosmonauts after space-flight as compared to pre-flight. These differences are partly due to space-flight-induced changes in the CSF volume and distribution. Personalizing TMS via biophysical modeling can overcome differences in brain morphometry due to physiological adaptation induced by space stressors. This may increase its specificity and further enhance its beneficial effects.

My work on biophysical modeling also was included in different published studies in order to either identify potential optimal targets for NIBS data collection and/or analyzing the results correcting for e-field. A brief bibliography of the papers including biophysical modeling is shown below:

- Sergiou C. Santarnecchi E. **Romanella SM.** Franken I. Rassin E. van Dongen J. "*tDCS targeting the Ventromedial Prefrontal Cortex reduces reactive aggression and modulates electrophysiological responses: A HD-tDCS/EEG randomized controlled trial in a forensic population."* Biol Psychiatry Cogn Neurosci Neuroimaging**.** 2021 Jun 1; S2451-9022(21)00147-6. doi: 10.1016/j.bpsc.2021.05.007. **On the cover on the left.**
- Mencarelli L. **Romanella SM.** Di Lorenzo G. Rossi S. Santarnecchi E. "*Neural Correlates of Performance at the N-back Task and Proposal for Corresponding Neuromodulation Targets in Psychiatric and Neurodevelopmental Disorders*" (accepted in Psychiatry and Clinical Neurosciences).
- Benelli A, Neri F, Cinti A, **Romanella SM,** Giannotta A, De Monte D, Mandalà M, Smeralda CL, Prattichizzo D, Rossi S, Santarnecchi E. "*Frequency dependent reduction of cyber-sickness in Virtual Reality by transcranial oscillatory stimulation of the vestibular cortex*" (submitted).
- Sergiou C, Santarnecchi E, Tatti E, **Romanella SM,** Weidema A, Rassin E, Franken IH & van Dongen JD. *"The effect of HD-tDCS on brain oscillations and synchronicity in frontal electrodes during resting-state EEG in a violent offender sample"* (accepted in Clinical Neurophysiology).
- Rossi S, Cinti A, Viberti F, Benelli A, Neri F, De Monte D, Giannotta A, **Romanella SM**, Smeralda CL, Danniaucuo A, Prattichizzo D, Santarnecchi E, Mandalà M. "*Frequency-dependent tuning of the human "sixth sense" by transcranial oscillatory currents*" (submitted).

5. CONTROL FOR THE PLACEBO EFFECT IN NIBS STUDIES

While implementing modalities to optimize and personalize the stimulation, I came across a potential issue in experimental paradigms employing NIBS. It is well known that a placebo response can confound the main effect induced by NIBS intervention. Specifically, NIBS protocols frequently target cortical regions that may be involved in the emerge of the placebo effect per se, such as left DLPFC. An extensive body of literature, indeed, showed that left DLPFC is the prime NIBS target for FDA-approved treatment of different psychiatric diseases but also for cognitive enhancement (Downar et al., 2016). The issue arises from the fact that several lines of evidence support the modulating placebo effects via modulation of activity in left DLPFC as well. Specifically, a protocol of excitatory TMS over DLPFC has been shown to reduce pain, while inhibitory TMS in this area can inhibit and block placebo-induced analgesia. Although a control condition using sham stimulation is almost always included in clinical trials and research studies, the presence of a placebo effect is still difficult to clearly identify and exclude. Active stimulation might, in fact, just activate regions responsible to induce placebo effects per se.

To better investigate the potential overlap of placebo-associated neural correlates and NIBS targets, I conducted a meta-analysis investigating placebo effects in healthy volunteers, including both studies with emotional components or painful stimuli (First Study). The resulting Activation Likelihood Estimate (ALE) maps showed clusters of activation in the left prefrontal areas, left subgenual, and dorsal anterior cingulate cortex. A pattern of deactivation emerged with clusters in the bilateral insulae and right subcortical regions. In this light, placebo effects seem to emerge from an interplay of multiple cerebral regions working together to induce a behavioral effect across domains. The placebo effect is, indeed, mediated by diverse processes — including memories, emotional content, internal expectations, and appraisal. For this reason, I believed placebo effects may be better explained by a dynamic interplay of brain networks instead of discrete stand-alone clusters of activation/deactivation. As previously discussed in Chapter 2, research has shifted from the investigation of single brain regions to their connections by focusing more on the large-scale functional cortical networks than single regions (Fox et al., 2012; Lee and Frangou, 2017; Liégeois et al., 2019). In this study, I thus continued by mapping the functional connectivity (FC) profile of all meta-analytic clusters and computed the similarity coefficient with well-established resting-state networks. We found that the FC pattern of regions activated during placebo effects resembles networks subserving high-order cognitive, affective, and executive functions (default mode, fronto-parietal control, and limbic networks), while the connectivity profiles of deactivation areas align with somatosensory and ventral attention networks, associated with sensory processing. Placebo effects seem to emerge from a top-down increase in executive control, accompanied by a down-regulation of primary sensory signals.

These findings could offer new targets to harness the placebo effect via stimulation. NIBS techniques could manipulate the placebo effect by modulating the activity and excitability of placebo-associated regions. In this first study, thanks to biophysical modeling, as seen in the previous chapter, we finally offer practical NIBS solutions to manipulate the placebo effect by targeting either a single key region or multiple

connected areas identified from the meta-analysis. Following the network-oriented approach, we then suggest a multielectrode-optimized montage engaging the connectivity profile of placebo-associated clusters, to leverage the dynamic interplay of functional networks responsible for placebo response. These NIBS solutions provide a starting point to actively modulate placebo effects in future clinical studies.

Going further, while studying literature on placebo effects, we noticed that large placebo responses have been observed in many psychiatric treatment trials including depression, anxiety, and chronic pain (Kaptchuk and Miller, 2015) Treatment of depression and placebo effects, specifically, have a particularly longstanding and contentious history (Weimer et al., 2015). This discussion was accelerated in the early 2000s by two major studies: (i) Walsh and colleagues (Walsh et al., 2002) systematic review demonstrating very large placebo response effect sizes across depression RCTs, and (ii) Mayberg and colleagues (Mayberg et al., 2002) neurobiological work showing that placebo may activate similar areas of the brain as anti-depressants. Many debates persist regarding how much of the therapeutic response of anti-depressant treatments may be due to placebo response and whether or not there is a clinically meaningful difference above placebo responses. Different approaches to meta-analyzing trial data (published and unpublished) have yielded different interpretations and opinions (Kirsch, 2019). This is particularly relevant due to the use of rTMS in clinical trials for depression. Recent TMS trials have shown considerable clinical improvements in both active and placebo groups and this has yielded confusion about how to interpret such results. For example, a recent large multi-center RCT of TMS for treatment-resistant depression reported an impressive 41% remission rate in the active group, yet the trial was negative as they observed 38% remission in the placebo group (Yesavage et al., 2018) Similarly, a recent RCT of DBS for depression showed very promising overall results but failed to exceed surprisingly large sham responses (Holtzheimer et al., 2017) This has posed challenges for device regulators in interpreting potential efficacy, and the latter remains under consideration by the FDA. My second study tried to investigate the potential overlap with regions/circuits targeted by depression treatments and what the implications of this overlap would be on measuring efficacy in placebo-controlled clinical trials. We aimed to develop a map of brain regions implicated in placebo effects, compare this map with neuromodulatory targets of depression treatment, and model statistical impacts of potential overlap.

To do so, I performed another meta-analysis of neuroimaging studies involving placebo effects including both healthy subjects and patient populations. I also searched for interventional studies of TMS an DBS for depression and extracted target coordinates for comparative spatial analysis with the placebo effects maps. After identifying a common set of brain regions implicated in placebo effects across healthy individuals and patient populations, similar to the first study, we provide evidence that these regions overlap with depression treatment targets. Specifically, we identified three significant clusters of brain activation and two significant clusters of deactivation. This included the left dorsolateral prefrontal cortex and sub-genual anterior cingulate cortex. Comparative spatial analyses demonstrated an overlap of the above clusters with TMS and DBS depression targets respectively. Based on these findings, we suggest that these treatments may be

modulating the same regions/networks as placebo effects and this has major impacts on measuring and interpreting clinical efficacy. Below I show extracts from the two published studies.

5.1 First Study: Meta-analysis on Neural Correlates of Placebo Effect

A similar version of the present article has been pubslished [**Romanella SM**, Mencarelli L, Burke M, Rossi S, Santarnecchi E. "*Targeting neural correlates of placebo effects*" (Cognitive, Affective, & Behavioral Neuroscience - CABN).

As aforementioned, during the last decade, various functional neuroimaging studies have rapidly advanced our knowledge of the neural mechanisms involved in different placebo effects. The available studies vary substantially, mostly as a function of study design and technical details (e.g., sample size, functional magnetic resonance imaging –fMRI- scanner type). To perform the meta-analysis, we started by interrogating which kind of placebo effects should have been included. Placebo analgesia in healthy individuals has been the primary model and consistent changes across neuroimaging studies and has provided a foundation for conceptualizing a placebo effects brain network (Amanzio et al., 2013; Wager and Atlas, 2015). It is also the most robust and best-studied type of placebo effect. Experiments also differ in terms of important experimental features, such as the kind of nociceptive stimulation (e.g., heat, laser, or acupuncture) and types of placebo administered (e.g., drugs, creams, sham acupuncture, sham transcranial magnetic stimulation, or sham mindfulness). Despite these differences, some common placebo-inducing sets of loco-regional neural activations have been suggested (Wager and Atlas, 2015), suggesting an underlying mechanism able to modulate pain in different modalities. These activations are observed in the anterior cingulate cortex (ACC) and sub-regions of the prefrontal cortex (PFC; Wager and Atlas, 2015). Although these regions are associated with placebo analgesia, they may also be responsible for the placebo effect in other domains. Emotional relief, for example, can be triggered through placebo administration as well. Petrovic and colleagues (2005) showed activation in portions/sections of ACC and PFC during emotional modulation. This pattern is very similar to activation clusters in placebo analgesia (Atlas and Wager, 2014). Furthermore, the placebo effect seems to be transferred from analgesia to emotional relief (Petrovic et al., 2005). Placebo analgesia expectation can be transferred from the alleviation of pain to the reduction of anxiety (Zhang and Luo, 2009). This transferability from one domain to another suggests a common neural correlate. Several studies have reported this shared mechanism (Wiech, 2016; Zhang et al., 2011; Zhang and Luo, 2009). These results indicate a common cortical pattern for placebo effects, independent of the investigated domain. Therefore, to investigate and target neural correlates involved in placebo effects, we decided to include studies either investigating placebo analgesia or emotional relief with placebo administration.

We start by conducting a meta-analysis of the placebo-associated cortical activation/deactivation pattern across domains. We include updated literature on emotional placebo and analgesic paradigms employing fMRI and positron emission tomography (PET) neuroimaging. Then, we perform an analysis of the FC of the resulting clusters. We compute a network mapping analysis between these connectivity maps and RSNs to

investigate the profile of placebo effects compared to large-scale networks. Furthermore, investigating singular clusters associated with placebo effects and their connections could provide new perspectives to manipulate placebo effects thanks to non-invasive brain stimulation (NIBS) techniques. We offer potential optimized NIBS solutions to target the resulting clusters and connected regions to manipulate the placebo effect.

5.1.1. Methods

Literature search and coordinate identification. To identify potential neural targets to manipulate the placebo effect, we ran a meta-analysis with neuroimaging articles involving a placebo to modulate painful/unpleasant stimuli. We identified PET and fMRI studies investigating the placebo effect through literature searches in PubMed and Google Scholar (for a comprehensive flowchart of the selection see Figure 22). The terms "placebo", “analgesia”, and “expectation” were individually combined with "Functional Magnetic Resonance Imaging", "Position Emission Tomography", their acronyms, and “functional neuroimaging”. We screened the abstract of every resulting article published September 30th, 2021. We excluded (i) review papers, case reports, and re-analysis, (ii) studies in languages different than English, (iii) study reporting fMRI/PET activations coordinates in different spaces than MNI or Talairach/Tournoux, (iv) studies that used only predefined Regions of Interest (ROIs) or Volume of Interest (VOIs), (v) studies reporting results obtained only with Small Volume Correction (SVC), (vi) PET studies performed with μ-opioid receptor (MOR) tracer binding using [11C]-carfentanil, and (vii) studies that considered neurological or psychiatric patients. We also excluded articles with participants suffering from irritable bowel syndrome (IBS), knee osteoarthritis, and Low Back Pain. We then excluded (viii) experimental paradigms with placebo treatment given for a continuous period (e.g., fMRI performed before/after the treatment with 1-2 weeks of placebo). We focused on studies where neuroimaging was performed in anticipation and during the stimulation (online). For each study, the following information was extracted: (i) experimental paradigm (ii) sample size, (iii) average age of participants, (iv) demographic characteristics, (v) neuroimaging modality, (vi) MNI/Tailarach space, and (vii) type of contrast of analysis (Table 4 for activations and Table 5 for deactivations). Studies on the placebo effect on pain analgesia have been approached through two main experimental paradigms: i) by administering an inert treatment relying on the subject’s expectation (placebo paradigm; Amanzio et al., 2012; Benedetti et al., 2003), or ii) by covertly reducing the intensity of painful stimuli when the placebo is administered, to reinforce the belief during the learning phase (stimuli expectancy/conditioning paradigm; Wager and Atlas, 2015). We included both types of studies. Because the placebo effect is thought to be influenced by both preparatory processes and modulation during stimulation, our analysis also includes contrasts of activation during both anticipation and noxious/uncomfortable stimulation periods. Similarly, in the case of the division of responders and non-responders, we included both groups as two different contrasts, also adjusting the sample size. We computed maps including all the coordinates found in papers testing the placebo effect referring to (i) activation contrasts (n = 44) and (ii) deactivation contrasts (n = 37).

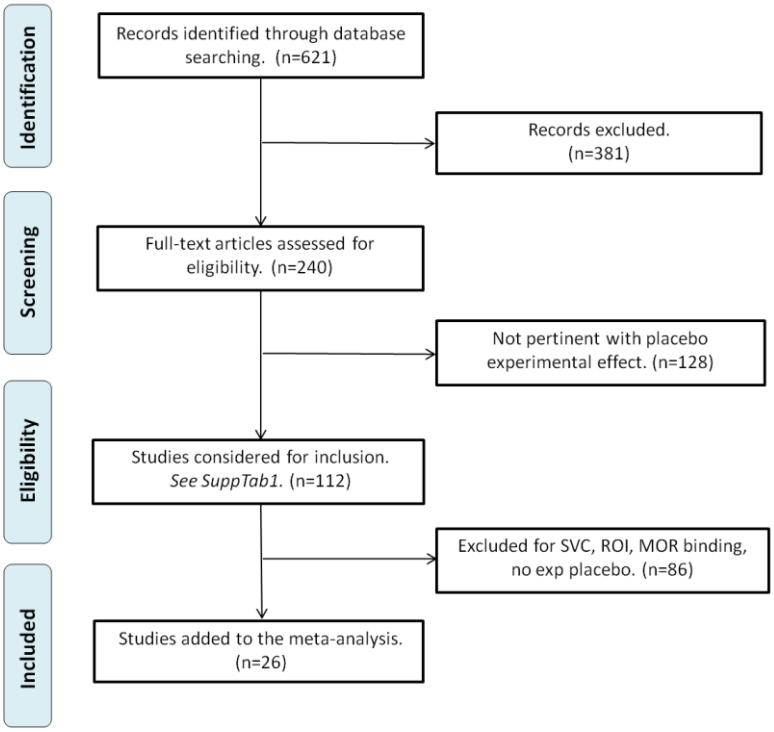


Figure 22. The figure shows the literature search for the identification of relevant publications included in the ALE meta-analysis (Liberati et al., 2009).

ALE maps computation. Specific activation and deactivation coordinates were collected and included in a quantitative Activation Likelihood Estimation (ALE) analysis technique implemented in the GingerALE software v. 3.0 (www.brainmap.org; Eickhoff et al., 2012, 2009). The method yields a statistical map that indicates the set of significant voxels while considering the magnitude of the effect, the number of studies, and the number of participants in each study. To do so, we extracted peak voxel coordinates from relevant contrasts. We applied the Tal2MNI algorithm implemented in GingerALE to convert Talaraich coordinates to MNI space (Matthew Brett; http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The reported foci for each study were modeled as Gaussian distributions and merged into a single 3D volume. Equally-weighted coordinates were used to form estimates of the probability of activation for each voxel in the brain, using an estimation of the inter-subject and inter-study variability, rather than applying an a priori full-width half maximum (FWHM) kernel. Therefore, the number of participants in each study influenced the spatial extent of the Gaussian function used. We first modeled the probability of activation overall studies at each spatial point in the brain, returning localized "activation likelihood estimates" or ALE values. Values were then compared to a null distribution created from simulated datasets with randomly placed foci to identify significantly activated clusters (permutations test= 1000 run). Corrections based on the false-discovery rate (FDR) at the cluster-level and voxel-level family-wise error (FWE) estimation were applied (Eickhoff et al., 2012a). Cluster correction for multiple comparisons with a $p < 0.001$ thresholds for cluster-formation and a $p < 0.05$ for cluster-level inference were set. We visualized ALE maps using MRICronGL on an MNI standard

brain. Each map resulting from the meta-analysis and GingerALE analysis is available for download as a nifti. nii volumetric file at (http://www.tmslab.org/netconlab.php).

MRI dataset and preprocessing. An fMRI dataset collected at Beth Israel Deaconess Medical Center that included 187 healthy participants was used for network mapping analysis. Characteristics of the cohort were: age; mean=29 (SD: +/-12), range=21-49; education; mean=15 (SD: +/-3), range=11-23. Neuroimaging data were acquired on a 3.0 T General Electric (GE Medical Solutions, Erlangen, Germany). For each subject, a three-dimensional T1-weighted MPRAGE image was acquired in the axial plane (TR/TE 2500/3.5ms; 192 slices; slice thickness 1mm; flip angle 8°; voxel size 1.0×1.0×1.0mm). Resting-state fMRI data were acquired using T2-weighted BOLD images (TR/TE 2500/30ms; 38 interleaved slices; slice thickness 3mm; 260 volumes; flip angle 80°; voxel size 3.0×3.0×3.0 mm). Participants were asked to maintain their eyes open in the scanner, fixate on a cross-hair and let their minds wander.

Preprocessing of the functional images was carried out using SPM12 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London; http://www.fil.ion.ucl.ac.uk/spm/) within the MATLAB scientific computing environment (http://www.mathworks.com, MathWorks, MA, USA). The first five volumes of functional images were discarded for each subject to allow for steady-state magnetization. EPI images were then stripped of the skull and other non-cerebral tissues, slice-timed using interleaved descending acquisition, manually realigned, and subsequently resliced. Structural images were co-registered to the mean volume of functional images and subsequently segmented using the NewSegment routine in SPM12. A Hidden Markov Random Field model was applied to remove isolated voxels. Moreover, to obtain a more accurate spatial normalization we applied the SPM12 DARTEL (Diffeomorphic Anatomical Registration Through Exponential Lie algebra) module, creating a customized gray matter template from all subjects' segmented images (Ashburner, 2007). A nonlinear normalization procedure to the Montreal Neurological Institute (MNI) template brain, and voxel resampling to an isotropic 3x3x3 mm voxel size, were then applied. Linear trends were removed to reduce the possible influence of the rising temperature of the MRI scanner and all functional volumes were band-pass filtered at 0.01 Hz<f<0.08 Hz to reduce low-frequency drifts. Finally, the potential contribution of nuisance sources of variability to grey matter BOLD time courses were controlled by regressing out the head motion parameters as well as the signal derived from four regions of interest (ROIs) placed in the white matter and cerebrospinal fluid, an approach that has been shown to significantly enhance within-subject and test-retest reliability (Behzadi et al., 2007).

Seed-based functional connectivity. We conducted a seed-based connectivity analysis looking at the spatial similarity of voxel-wise connectivity maps. The average BOLD time course during the resting state was retrieved by averaging the signal from all the voxels included in the resting-state map. Subsequently, the signal from each map was correlated with that of the remaining voxels in the rest of the brain, resulting in a 3D weighted volume where each voxel value represents the correlation coefficient between its BOLD activity and that of the seed map of interest. Results were computed applying a voxel-level threshold ($p< 0.05$, false discovery rate -FDR- corrected) and cluster size correction ($p< 0.05$, false discovery rate -FDR-

corrected) two-sided. The presence of similar connectivity alterations was also tested by comparing their respective seed-based connectivity maps via a functional clustering algorithm (Matlab 2016b, The Mathworks).

Network mapping analysis. To characterize the functional profile of each resulting network, functional labeling was performed by looking at the spatial similarity of each activation/deactivation map and those of RSNs. To do so we computed a weighted variant of the DICE coefficient (weighted dice coefficient, wDC; Dice, 1945). We decided to investigate the overlapping with the 7 RSNs of Yeo Atlas (Yeo et al., 2011). This included the visual network (VS), the ventral and dorsal attention (DAN and VAN), the somatosensory (SM), the limbic (LIM), the default mode (DMN), and the fronto-parietal control network (FPCN). Finally, we ran a network mapping analysis on another atlas proposed by Shirer et al., (2012; see Supplementary Material). The comparison of weighted, un-thresholded connectivity maps for activation/deactivation clusters in the placebo effect and RSN map at the single voxel level requires considering not only spatial similarity but also the similarity of connectivity signs (i.e., positive and negative connectivity). Therefore, the similarity index was obtained by computing the product of each voxel's value across two maps (e.g., voxel j in placebo maps and DMN maps), resulting in a map where positive values represent voxels with the same sign in both maps (i.e., positive connectivity in both placebo and DMN), while negative ones represent opposite signs (i.e., positive connectivity value in voxel j in placebo, negative in DMN). As a result, the magnitude of the wDC index represents the similarity of connectivity strength in any two given maps. This procedure allowed us to identify similar connectivity profiles between the main networks activated and deactivated in the placebo effect and known RSNs.

***Biophysical modeling*.** We propose different examples of how TMS, as well as more advanced optimized tDCS and tRNS multielectrode solutions, could target specific placebo-associated clusters and their connections. In particular, the induced E-field of the TMS simulations and multielectrode tDCS/tRNS optimizations were all computed in SimNIBS v3.2, an open-source simulation package that integrates segmentation of MRI scans, mesh generation, and finite element model (FEM) E-field computations (Saturnino et al., 2019; Thielscher et al., 2015). The software provides a realistic volume conductor head model, created as default in a FEM model generated using the T1-and T2-weighted images and segmentation from the SimNIBS example data set. The data sample was acquired from a healthy subject with the approval of the Ethics Committee of the Medical Faculty of the University of Tübingen (Windhoff et al., 2013b). The data corresponds to a healthy subject (Ernie), which includes white matter, gray matter, cerebrospinal fluid, bone, and scalp tissue volumes. In our simulation we kept the isotropic conductivities given by default (Thielscher et al., 2015), corresponding to gray matter: 0.276 S/m, cerebrospinal fluid: 1.790 S/m, bone: 0.010 S/m, scalp: 0.250 S/m (Opitz et al., 2011). The final mesh, comprehensive of gray and white matter, scalp, bone, and cerebrospinal fluid, comprises approximately 200,000 nodes and 3.6 million tetrahedral elements (see Windhoff et al., 2013 for further modeling details).

TMS on a single node. Due to its involvement in the placebo effect, we chose the left dorsolateral prefrontal cortex (DLPFC; activation cluster #3 from our results) as a potential single target for rTMS

simulation. In our biophysical modeling analysis, we investigated the electric field generated by single-pulse TMS. The electric field distribution was computed including the SimNIBS model of the Magstim 70 mm figure-of-8 coil (P/N 9925-00, Magstim Co., Spring Gardens, Whitland, Carmarthenshire, UK), which has nine windings with outer and inner diameters of 8.8 and 5.2 cm, respectively (Thielscher & Kammer, 2002) both for a coil-to-scalp distance of 4 mm. The center of the coil was positioned over the left DLPFC, expressed in MNI coordinates *(x: -38,2; y: 25,4; z: 37)*, as extracted from the peak of the third activation cluster resulting from our ALE map on the placebo effect. The coil handle was then manually moved on the simNIBS GUI and rotated according to the specified position and direction that is usually used in a real-life settings, according to the clinical experience of the authors. We added a set of MNI coordinates for the corresponding orientation of the coil handle, to ensure an accurate representation of the generated electric field: *(x=-44, y=44, z=56).* As modeled in SimNIBS, the E-field input is in the form of dI/dt in units of A/us. The dI/dt is the speed of variation of the current through the coil. Its value depends on the coil model, stimulator model, and pulse intensity (for a detailed explanation see Kammer et al., 2001). Coils have different inductances (L in micro-henrys). The stimulator output (% of the maximum capacitor's charging voltage in the stimulator) will result in different max dI/dt values. The expression is dI/dt|Max = Vc/L, where Vc is the capacitor's charging voltage and L is the inductance of the coil. For our simulations, we assume to use a Magstim 200 stimulator (Vc|Max = 2800 V), and the inductance of the figure-8 70 mm coil is 16.35 uH. This would result in a max dI/dt value (at Max stimulator output, MSO) of 171.3 A/us. Assuming a Resting Motor Threshold (RMT) of around 40%, and knowing that variation with pulse is linear, we chose a dI/dt of 70 A/us (40.8% of the MSO 171.3 A/us). The output is the average intensity as represented from NormE currently represented in V/m.

Multifocal tRNS optimization. Our meta-analysis showed three clusters of increased activity associated with the placebo effect. We propose a tES multielectrode solution simultaneously targeting all three clusters. Specifically, we suggest the application of tRNS to increase activity in the target areas. In particular, we used the head model of Ernie and we computed the lead field thanks to the algorithm of tES optimization from SimNIBS. The lead field is calculated by first placing electrodes in the head accordingly with a 10-10 EEG cap and afterward calculating the field caused by each electrode individually, keeping a constant return electrode (for a detailed explanation of the algorithm see Saturnino et al., 2019). Thanks to this first computational step, the software creates a matrix that can then be used to calculate the electric field with various measures (e.g., NormE, NormalE, E) caused by any combination of electrodes. In this case, we chose electrodes modeled as small cylinders (1 cm diameter, 4mm thickness) with homogeneous conductivity and added to a 1mm in height corresponding approximately to electrode gel. SimNIBS can optimize electric fields based on distributed targets as given by single or multiple MNI coordinates. We entered the coordinates in peaks of the three activation clusters resulting from our ALE map. We target the left subgenual ACC (MNI coordinates of peak activation in the main clusters: *x= -9.8, y= 19, z= -16.4),* left dorsal ACC with a peak in the second activation cluster (*x= 4.4, y= 41.9, z= 9.4*), and again the left DLPFC (*x= -38.2, y= 25.4, z= 37*). We set the parameters as follows: maximum of the total current in the whole

montage, 4 mA with a maximum of 2 mA individually for each electrode, with maximum of 8 stimulation electrodes. The algorithm will then use the matrix lead field to find the combination of electrodes that will allow a higher peak value of intensity and mean-field norm with good focality and the smallest possible error relative to non-intervention. The outcome as represented by NormE is reported in the Results section in V/m.

Multifocal tDCS optimization and experience. As a third solution, we suggest simultaneous stimulation and inhibition of macro-regions connected to placebo-associated clusters. To do so we offer an optimized multielectrode tDCS montage able to stimulate regions under the anodes and inhibit areas under the cathodes. As a target, we chose the profiles of FC of activation and deactivation clusters. As aforementioned, we extracted the FC maps separately from all activation and all deactivation clusters resulting from our meta-analysis. We ran the tES optimization algorithm for each FC map (see the previous paragraph for details). For each target, we uploaded the resulting file in NIFTI format. The montages obtained with tES optimization algorithm were then partially modified to favor stimulation in frontal/cognitive regions and inhibition in central/sensory-motor areas.

FIRST AUTHOR	YEAR	PARADIGM	SAMPLE SIZE	MEAN AGE	MODALITY	COO	CONTRAST
Atlas	2010	SE	18	25.5	fMRI	MNI	LT > HT
Bingel	2006	PA	19	24	fMRI	MNI	PL > CT (during)
Eippert	2009	PA	48	26.13	fMRI	MNI	PL > CT (early pain)
Fehse CTR1	2015	PA	30	32	fMRI	MNI	PL > CT
Fehse CTR2	2015	PA	30	32	fMRI	MNI	Original PL > Generic PL
Kong 2006 CTR1	2006	PA	24	28.4	fMRI	MNI	PL > CT (in post -pre)
Kong 2006 CTR2	2006	PA	24	28.4	fMRI	MNI	PL > CT (in post)
Kong (1)	2009b	PA	12	29	fMRI	MNI	PL group (Expected > CT)
Kong 2009actr1	2009	SE	12	26.4	fMRI	MNI	LT > HT in meridian side expect
Kong 2009actr2	2009	SE	12	26.4	fMRI	MNI	Post > Pre
Kong 2009actr3	2009	SE	12	26.4	fMRI	MNI	Main Expectancy LT > HT in Post-Pre
Kong 2013 CTR1	2013	SE	46	26.23	fMRI	MNI	LT > HT (antic)
Kong 2013 CTR2	2013	SE	46	26.23	fMRI	MNI	LT > HT (during)
Kotsis CTR1	2012	PA	36	18-45	fMRI	MNI	PL > CT (antic)
Kotsis CTR2	2012	PA	36	18-45	fMRI	MNI	PL > CT (during)
Leech	2013	PA	17	23.4	fMRI	MNI	PL > CT
Nemoto CTR1	2007	PA	5	23	PET	MNI	PL post - PL pre in resp
Nemoto CTR2	2007	PA	5	23	PET	MNI	PL Post > CT in resp
Nemoto CTR3	2007	PA	5	23	PET	MNI	Post PL > baseline in resp
Nemoto CTR4	2007	PA	5	23	PET	MNI	PL post - PL pre in Nresp
Nemoto CTR5	2007	PA	5	23	PET	MNI	PL Post > CT in Nresp
Petrovic CTR1	2002	PA	9	24	PET	TAI	PL > CT (during)
Petrovic CTR2	2002	PA	9	24	PET	TAI	[PL > CT] - [(warm+PL) > warm alone]
Sinke	2017	PA	42	25.4	fMRI	MNI	PosE > NegE (pain-control)(during)
Theysohn CTR1	2014	PA	15	36.9	fMRI	MNI	100% > 0% (PL>control) in Women (during)
Theysohn CTR2	2014	PA	15	36.9	fMRI	MNI	100% > 0% (PL>control) in Women (antic)
VanderMeulen CTR1	2017	PA	13	25.7	fMRI	MNI	PL > CT (antic)
VanderMeulen2 CTR2	2017	PA	13	25.7	fMRI	MNI	PL > CT (early pain)
Wager (a)	2004	PA	23	unknown	fMRI	MNI	PL > CT (antic)
Watson CTR1	2009	PA	11	27.5	fMRI	MNI	PL > CT (antic) in conditioning - pre
Watson CTR2	2009	PA	11	27.5	fMRI	MNI	PL > CT (antic) in post - pre
Wiech CTR1	2010	SE	16	24	fMRI	MNI	LT > HT (antic)
Wiech CTR2	2010	SE	16	24	fMRI	MNI	LT > HT (during)
Zeidan CTR1	2015	PA	75	27.84	fMRI	MNI	PL > baseline (antic)
Zeidan CTR2	2015	PA	75	27.84	fMRI	MNI	PL > CT (during)
Zeidan CTR3	2015	PA	75	27.84	fMRI	MNI	ShamMindfulness > Baseline (antic)
Zeidan CTR4	2015	PA	75	27.84	fMRI	MNI	ShamMindfulness > CT (during)
Zeidan CTR5	2015	PA	75	27.84	fMRI	MNI	PL > baseline (during)
Zeidan CTR6	2015	PA	75	27.84	fMRI	MNI	ShamMindfulness > baseline (during)
Zhang 2011 CTR1	2011	EP	27	20.64	fMRI	TAI	PL (unpleasant - neutral) > CT
Zhang 2011 CTR2	2011	EP	27	20.64	fMRI	TAI	PL (unpleasant) > CT (unpleasant)
Zhang 2011 CTR3	2011	EP	27	20.64	fMRI	TAI	PL (neutral) > CT (neutral)
Zhang 2013 CTR1	2013	EP	52	21.75	fMRI	TAI	PL (unpleasant-neutral) > CT
Zhang 2013 CTR2	2013	EP	52	21.75	fMRI	TAI	PL (unpleasant) > CT (unpleasant)

Table 4. List of contrasts included in the activation map (n=44). The table reports sample size, gender, and age of the sample, reference, foci, imaging modality, and types of contrast for each set of coordinates included in the activation map.
CTR: contrast. SE: stimuli expectancy. PA: placebo analgesia. EP: emotional placebo. COO: coordinates. MNI: Montreal Neurological Institute. TAI: Tailarach. PL: placebo. CT: control. During: neuroimaging performed during stimulation. Antic: neuroimaging performed in anticipation of stimulation. HT: high threat. LT: low threat. PosE: positive expectation. NegE: negative expectation. Resp: responders. NResp: nonresponders.

IRST AUTHOR	YEAR	PARADIGM	SAMPLE SIZE	MEAN AGE	MODALITY	COO	CONTRASTS
Atlas	2010	SE	18	25.5	fMRI	MNI	HT > LT
Eippert CTR1	2009	PA	48	26.13	fMRI	MNI	CT > PL (early pain)
Eippert CTR2	2009	PA	48	26.13	fMRI	MNI	CT > PL (late pain)
Eippert CTR3	2009	PA	48	26.13	fMRI	MNI	PL deactivations
Elsenbruch CTR1	2012	PA	36	18-45	fMRI	MNI	0 > 100% (antic)
Elsenbruch CTR2	2012	PA	36	18-45	fMRI	MNI	0 > 100% (during)
Keltner	2006	SE	27	19-27	fMRI	MNI	HT > LT
Kong	2006	PA	24	28.4	fMRI	MNI	CT (post-pre) > PL
Kong (a)	2009	SE	12	26.4	fMRI	MNI	HT > LT in meridian side expect
Kong (b)	2009	PA	12	29.00	fMRI	MNI	PL group (HT > CT)
Kong	2013	SE	46	26.23	fMRI	MNI	HT > LT (during)
Koyama	2005	SE	10	30.3	fMRI	MNI	LT > HT deactivation
Leech	2013	PA	17	23.40	fMRI	MNI	CT > PL
Nemoto CTR1	2007	PA	5	23.00	PET	MNI	PL pre > PL post in Nresp
Nemoto CTR2	2007	PA	5	23.00	PET	MNI	Baseline > PL during in Nresp
Nemoto CTR3	2007	PA	5	23.00	PET	MNI	PL pre > PL post in resp
Nemoto CTR4	2007	PA	5	23.00	PET	MNI	Baseline > PL during in resp
Nemoto CTR5	2007	PA	5	23.00	PET	MNI	Baseline > PL pre in resp
Schenk	2014	PA	32	25.60	fMRI	MNI	(Open > Hidden) > (PL > CT)
Theysohn CTR1	2014	PA	15	36.90	fMRI	MNI	0>100 in Men (antic)
Theysohn CTR2	2014	PA	15	36.90	fMRI	MNI	0>100 in Women (during)
vanderMeulen	2017	PA	13	25.70	fMRI	MNI	PL > CT deactivation (during)
Wager (a)	2004	PA	24	unknown	fMRI	MNI	CT > PL (in intense-mild shock) (during)
Wager (b)	2004	PA	23	unknown	fMRI	MNI	CT > PL (during)
Watson	2009	PA	11	27.50	fMRI	MNI	CT > PL deactivation (during)
Wiech CTR1	2010	SE	16	24.00	fMRI	MNI	HT > LT (antic)
Wiech CTR2	2010	SE	16	24.00	fMRI	MNI	HT > LT (during)
Wiech CTR3	2010	SE	16	24.00	fMRI	MNI	HT > LT in Pain > noPain (antic)
Wiech CTR4	2010	SE	16	24.00	fMRI	MNI	HT > LT in Pain > noPain (during)
Zeidan CTR1	2015	PA	75	27.84	fMRI	MNI	PL > Baseline deactivations (antic)
Zeidan CTR2	2015	PA	75	27.84	fMRI	MNI	CT > PL (antic)
Zeidan CTR3	2015	PA	75	27.84	fMRI	MNI	Deactivation ShamMindfulness > baseline (antic)
Zeidan CTR4	2015	PA	75	27.84	fMRI	MNI	CT > ShamMindfulness (antic)
Zeidan CTR5	2015	PA	75	27.84	fMRI	MNI	Deactivation PL > baseline (during)
Zeidan CTR6	2015	PA	75	27.84	fMRI	MNI	Deactivation ShamMindfulness > baseline (during)
Zhang 2011 CTR1	2011	EP	27	20.64	fMRI	TAI	CT > PL (unpleas + neutral)
Zhang 2011 CTR2	2011	EP	27	20.64	fMRI	TAI	CT > PL (unpleas)

Table 5. List of contrasts included in the deactivation map (n=41). The table reports sample size, gender, and age of the sample, reference, foci, imaging modality, and types of contrast for each set of coordinates included in the deactivation map.
CTR: contrast. SE: stimuli expectancy. PA: placebo analgesia. EP: emotional placebo. COO: coordinates. MNI: Montreal Neurological Institute. TAI: Tailarach. PL: placebo. CT: control. HT: high threat. LT: low threat. During neuroimaging performed during stimulation. Antic: neuroimaging performed in anticipation of stimulation. Resp: responders. NResp: nonresponders.

5.1.2. Results

ALE meta-analysis. Among 621 studies scrutinized, we initially identified 112 of them: 26 neuroimaging studies of placebo effects met the eligibility criteria for our meta-analysis (see Tables 1 and 2 above). We included all the coordinates in GingerALE to identify areas of increased and decreased activation. Figure 23 shows the placebo-associated activation and deactivation ALE clusters derived from data collected in placebo analgesia, during stimuli expectancy, or the placebo effect in a paradigm with emotional stimuli. We report the characteristics of each cluster in Table 3. We found 3 clusters of increased activity associated with the placebo effect. The first cluster includes various regions of the left subgenual ACC (BA 25; MNI coordinates of peak activation in the main clusters: *x= -9.8, y= 19, z= -16.4*). The second cluster encompasses the left dorsal ACC with a peak in BA 32 (*x= 4.4, y= 41.9, z= 9.4*). The third cluster lies in the left PFC (BA 8 and 9, *x= -38.2, y= 25.4, z= 37*). The ALE map of deactivation reports a decreased activation in the right subcortical structures part of the first cluster (*x= 20.2, y= 2.7, z= 7)*. Deactivation clusters also include the bilateral insulae (BA 13, MNI*: x= -32.2, y= 10.4, z= 10* and *x= 50.1, y= -4.7, z= 15.6*).

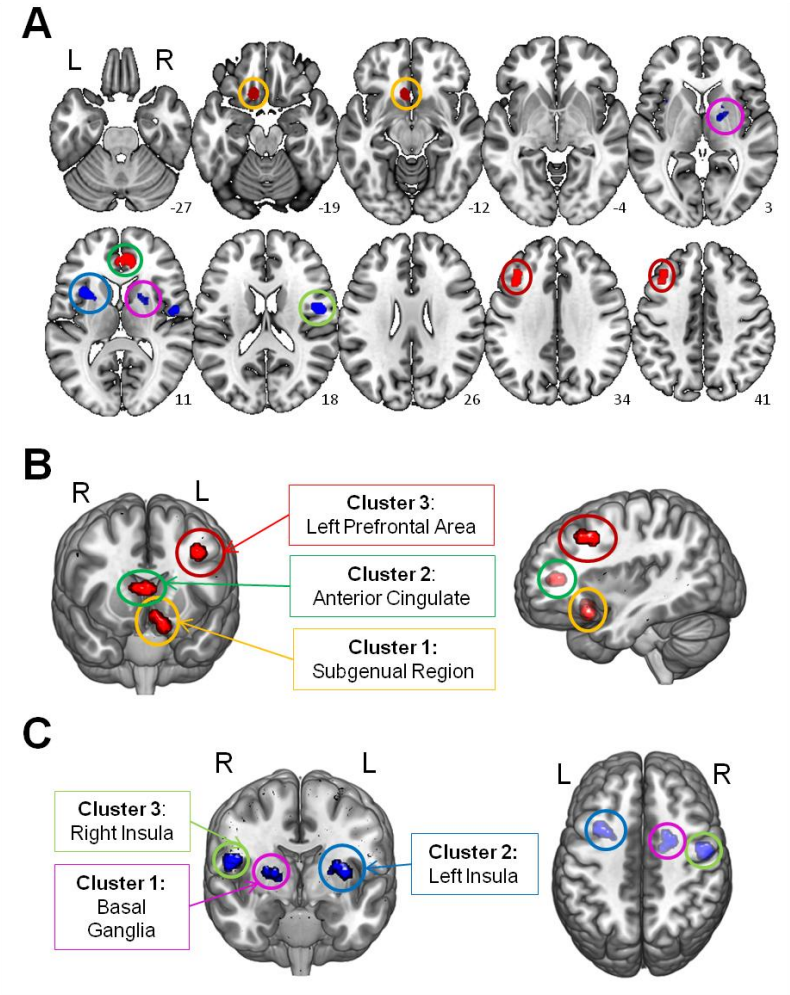


Figure 23. Map of activation and deactivation clusters associated with the placebo effect. The figure shows the activation (red) and deactivation (blue) clusters resulting from ALE analysis after including all coordinates from the chosen studies. The maps are presented together (**Panel A**), as well as separately to better identify singular clusters (**Panel B** for areas with activation and **Panel C** for regions with decreased activity). All the clusters are associated with placebo analgesia, stimuli expectancy, and emotional placebo in anticipation or during stimulation. The corresponding label for each cluster was found by entering the centroid of the cluster (see Table 6) in Neurosynth (https://www.neurosynth.org/) and looking for its strongest associated region.

ACTIVATION CLUSTERS

		Center			Extrema value coordinates						
Cluster	Volume (mm3)	x	y	z	Max Value	x	y	z	Hemisphere	Lobe	Label
1	1512	-9.8	19	-16.4	0.032	-12	18	-20	L	Limbic	Medial Frontal Gyrus
					0.021	-6	18	-12	L	Limbic	Anterior Cingulate
2	1256	4.4	41.9	9.4	0.024	2	42	10	L	Limbic	Anterior Cingulate
3	1136	-38.2	25.4	37	0.023	-38	22	36	L	Frontal	Precentral Gyrus
					0.021	-36	30	38	L	Frontal	Middle Frontal Gyrus

DEACTIVATION CLUSTERS

		Center			Extrema value coordinates						
Cluster	Volume (mm3)	x	y	z	Extrema Value	x	y	z	Hemisphere	Lobe	Label
1	1048	20.2	2.7	7	0.020	18	8	8	R	Subcortical	Caudate Body
					0.017	24	2	8	R	Subcortical	Lentiform Nucleus/Putamen
					0.015	16	-4	4	R	Subcortical	Thalamus (Ventral Anterior Nucleus)
2	952	-32.2	10.4	10	0.022	-34	12	8	L	Subcortical	Insula
3	944	50.1	-4.7	15.6	0.018	50	-4	16	R	Subcortical	Insula

Table 6. Characteristics of the activation/deactivation clusters associated with placebo effects. The table presents characteristics for each cluster of increased and decreased activation due to the placebo effect resulting from ALE maps. We report volume, center, coordinates, extrema value, lobe, hemisphere, and regional labels for each cluster.

Network mapping analysis. We analyzed the connectivity profile by grouping all activation clusters in one analysis and deactivation clusters in another. We then compared the resulting FC profile with RSNs from the Yeo atlas and computed the network mapping analysis (see Figure 24). The FC map of the activation clusters is similar to the default mode (DMN), the fronto-parietal control (FPCN), and the limbic (LIM) networks. The connectivity pattern of deactivation clusters resembled ventral attention (VAN) and somatosensory (SM) networks.

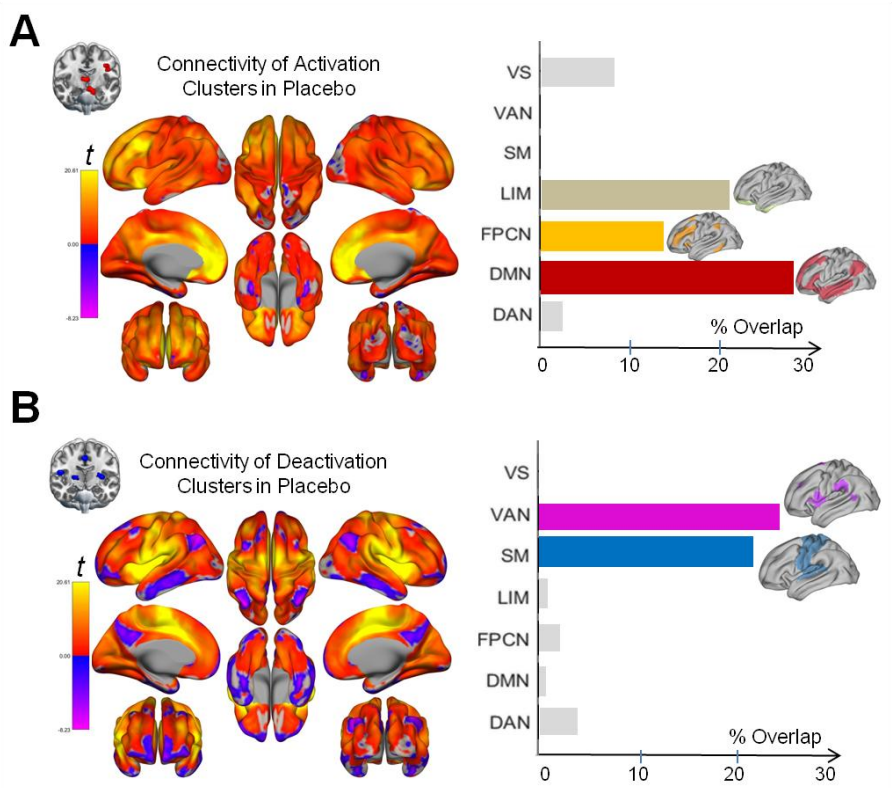


Figure 24. Network mapping of the connectivity profile of activation and deactivation clusters. The FC profiles for all activation clusters (**Panel A)** and deactivation clusters of interest (**Panel B**) are shown. Red and purple represent the intensity and polarity of correlations between activation/deactivation clusters and the rest of the brain. We computed wDC to investigate the similarity of the connectivity profile of clusters and networks mapped with Yeo atlas (Yeo et al., 2011). Horizontal bars represent the percentage of overlap with the different RSNs. VS: visual network. VAN: ventral attention network. SM: somatosensory network. LIM: limbic network. FPCN: fronto-parietal control network. DAN: dorsal attention network. DMN: default mode network.

Biophysical Modeling Results. Thanks to the findings from the meta-analysis and the network mapping analysis, we localized different regions implicated in placebo effects. These offer a foundation for future targeted NIBS interventions aimed to manipulate placebo effects. We used biophysical modeling and computational simulations to obtain optimized NIBS montages for placebo-associated targets. Figure 25 reports the targets, the optimized montages computed with biophysical modeling analysis, and the resulting electric field induced by those montages. In particular, we suggest three possible solutions: i) stimulation or inhibition of the left DLPFC as encompassed by activation cluster #3 with different protocols of repetitive TMS (rTMS; Figure 25, Panel A); ii) simultaneous stimulation of all three activation clusters resulting from our meta-analysis with multielectrode tRNS (Figure 25, Panel B); iii) simultaneous stimulation and inhibition of macro-regions located within the FC profile of activation/deactivation placebo-associated clusters with multielectrode tDCS (Figure 25, Panel C). The resulting electric field distributions are shown in Gmsh v4.7.1 (Geuzaine and Remacle, 2008).

We chose rTMS over left DLPFC as an example of an effective and simple solution due to its high focality and intensity. For the multielectrode tRNS optimization, the montage obtained through biophysical modeling to stimulate the three activation clusters was: Cz, AF7, F9, F5, F3, F2, F4, and C1 with intensity varying from -

1mA to 1mA. Given the current constraints, this solution represents the best fit of the NormE to reach all the targets obtained from the ALE meta-analysis. We then suggest an optimized multielectrode tDCS montage to target the average of the FC maps from the activation and deactivation clusters. Two montages were obtained through biophysical modeling with the tES optimization algorithm and then modified to better match the connectivity maps: F3: 2mA, F4: 2mA, C1: -1mA, C2: -1mA, T7: -1mA, T8: -1mA.

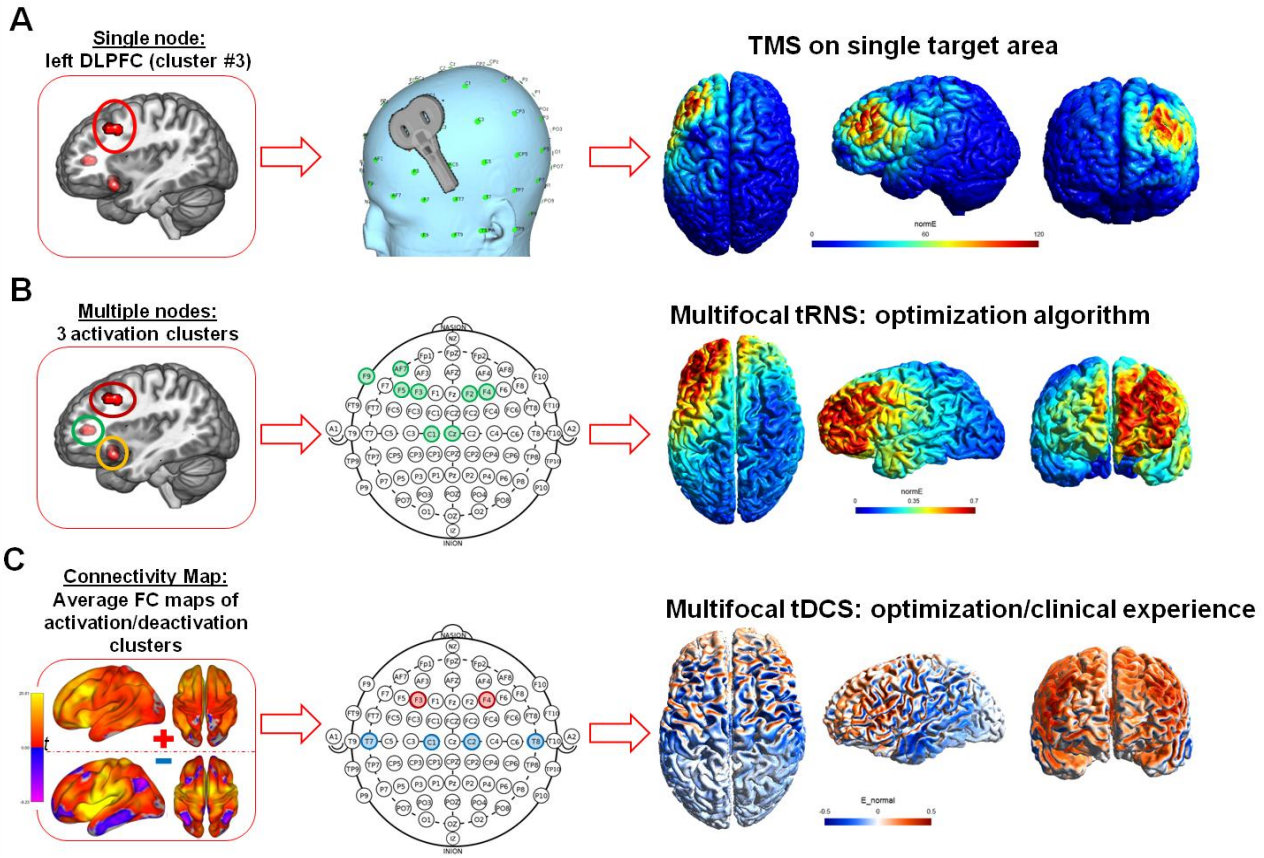


Figure 25. Potential targets and optimized NIBS solutions to manipulate the placebo effect. We offer three different NIBS solutions to manipulate placebo effects. Placebo-associated regions that could be used as targets for NIBS are shown on the left. The optimized montages and stimulation sites are represented in the middle column. On the right, we report the electric field distributions resulting from each solution in Gmsh v4.7.1 (Geuzaine and Remacle, 2008). In **Panel A** we suggest stimulating or inhibiting left DLPFC (encompassed by activation cluster #3) through rTMS. The NormE shows the strength of the electric field resulting from the TMS simulation of an output range from 0 to 120 V/m. In **Panel B** we present a multielectrode solution for tRNS to simultaneously stimulate the three activation clusters associated with the placebo effect. The resulting NormE field is shown with a range of 0 to 0.7 V/m. In **Panel C** the multielectrode tDCS montage is presented. For this solution, we separately ran an optimization algorithm targeting FC maps of all activation and deactivation clusters. We then adjusted the resulting montage to better match the FC profiles. To show the polarity for tDCS (red: anodes/stimulation; blue: cathodes/ inhibition) we present the field with NormalE with a range between -0.5/0.5 V/m.

5.1.3. Discussion

We performed a meta-analysis and a network mapping analysis of neural correlates associated with placebo effects. The results showed placebo-associated activation in nodes belonging to networks with high-order cognitive, affective, and executive roles. While the connectivity profile of deactivation clusters presents

similarities with networks involved in sensory processing. A dynamic interplay of networks seems to be the underlying common mechanism responsible for placebo effects. Below, we discuss the mapping of regions and networks associated with placebo effects. We then offer solutions for leveraging placebo effects via external manipulations such as non-invasive brain stimulation.

Specific clusters associated with placebo effects. Our meta-analysis showed significant activation in the left prefrontal cortex (BA 8 and 9; cluster 3) as well as hubs of the DMN and the FPCN. Prefrontal regions have been previously suggested to be responsible for initiating the analgesic effect during placebo administration (Amanzio et al., 2012; Colloca et al., 2013; Wiech et al., 2008). Specifically, our main activation resided in the dorsolateral prefrontal cortex (DLPFC; BA 9), a well-established region critical to the placebo effect. DLPFC has been consistently associated with cognitive control and maintenance of information, which is consistent with its expected role (Miller and Cohen, 2001). The relationship between the increased activity of DLPFC and placebo effects is one of the most consistently reported in analgesia studies (Craggs et al., 2008; Eippert et al., 2009; Geuter et al., 2013; Kong, 2006; Lui et al., 2010; Petrovic, 2002; Wager et al., 2004; Watson et al., 2009). Its connection to the periaqueductal gray (PAG) may also be partially responsible for placebo effects. PAG is responsible for activating the descending nociceptive control pathways (Amanzio et al., 2012; Bingel et al., 2006; Wager and Fields, 2013). The degree of the structural integrity of white matter pathways from DLPFC to the PAG is, indeed, directly related to the degree of individual placebo analgesic effect (Stein et al., 2012). Along with prefrontal regions, we found placebo-associated activation in the subgenual ACC (sACC, BA 25; cluster 1), part of the ventromedial PFC. The sACC plays an important role in regulating emotion, with various connections with relevant regions governing appetite, sleep, mood, and anxiety (Ramirez-Mahaluf et al., 2018). Degeneration in this area correlates with anhedonia (Rudebeck et al., 2014). It has been implicated in major depressive disorders and responses to anti-depressants (Konarski et al., 2009). Peciña and coworkers (2015) administered a receptor-selective radiotracer [11C] carfentanil to investigate the anti-depressant response to a placebo. They showed how increased μ-opioid neurotransmission in a network of regions including the sACC was associated with the anti-depressant effect induced by placebo treatment (Peciña et al., 2015). Moreover, intrinsic baseline connectivity between the left DLPFC and sACC has been demonstrated to predict the anti-depressant response to placebo/sham TMS (Wu et al., 2020). On the other side, deep brain stimulation (DBS) targeting sACC showed improvements in symptoms in depressed patients (Mayberg et al., 2005). We also found placebo-associated activation in the left dorsal ACC (dACC, BA 32; cluster 2). DACC is involved in the processing of cognitive stimuli and is interconnected with prefrontal areas and the PAG, which is responsible for endogenous opioid-mediated analgesic effects. This would explain its activation in the placebo response across different domains, as seen from this meta-analysis.

At the same time, the ALE map of deactivation showed corresponding to bilateral insulae. The insulae are generally involved in interoceptive assessments of physiological conditions as well as salience judgments, attention, and emotional awareness (Craig, 2009). They are also strongly connected to the rostral ACC (rACC;

Vogt, 2016). While the activation in these areas is associated with pain processing, its deactivation has been consistently reported during placebo analgesia (Atlas et al., 2010; Bingel et al., 2011; Eippert et al., 2009; Wager et al., 2004). This is also in line with lesion studies that indicate asymbolia for pain (i.e., loss of salience) as a hallmark of insular lesions (Berthier et al., 1988; Starr et al., 2009). New findings suggest that the deactivation of the insulae is involved in a wider range of placebo effects (Atlas et al., 2010). A reduction of insular activation has been reported in studies with an emotional placebo, where treatment with a placebo anti-nausea pill reduced ratings of disgust in effect to negative images (Schienle et al., 2014a, 2014b). Finally, another cluster of deactivation includes different subcortical structures, such as the right ventral anterior thalamic nucleus. This follows previous results of decreased activity in the thalamus, associated with the placebo effect (Geuter et al., 2013; Price et al., 2007).

The results from our study show consistencies with the previous meta-analysis of placebo effects (Amanzio et al., 2013; Atlas and Wager, 2014). Similar to our findings, Amanzio et al., (2013) reported meta-analytic clusters of activation involving both left and right medial and lateral prefrontal cortices and anterior cingulate cortices, as well as deactivation in the insulae, in the right thalamus, putamen, and caudate body. Results from Atlas and Wager (2014) also showed increased activity in the prefrontal cortex (including DLPFC), as well as the anterior cingulate. Reductions in activation were observed in the insulae, right thalamus, and striatum. Although our findings are in line with these results, these two previous meta-analyses reported clusters associated with placebo effects that did not appear in our analyses, such as activation in the left inferior parietal lobule and postcentral gyrus, as well as the hypothalamus and periaqueductal gray, and deactivation in left posterior cingulate cortex, superior temporal and precentral gyri. Some of these distinctions could be explained by differences in power due to the smaller sample size compared to this current study. However, the presence of other different meta-analytic clusters most likely emerges from one fundamental difference in the inclusion criteria. Both published meta-analyses included only experiments investigating placebo analgesia, while we also added placebo response in emotional relief paradigms. Some placebo-associated regions in previous meta-analyses could therefore reflect pain-related activity and nociceptive process, whereas the goal of the present study was to identify a neural substrate that was responsible for placebo effects across domains and modalities.

Brain networks involved in a placebo effect. Based on the activation/deactivation clusters from the meta-analysis, we mapped FC profiles and assessed their overlap with established RSNs. Activated regions, such as prefrontal areas and dACC, have FC similar to high-order cognitive, affective, and executive function networks, such as DMN and bilateral FPCN. The connectivity profile of deactivation clusters including the insulae resembles networks that are responsible for sensory perception and stimuli processing, such as SM and VAN. Our results corroborate the findings of a recently published meta-analysis on networks involved in placebo analgesia (Zunhammer et al., 2021). Zunhammer and coworkers performed a participant-level meta-analysis on 20 neuroimaging studies, investigating placebo administration during evoked pain. Similar to our results, they reported a strong correlation between placebo analgesia with reduced pain-related activity in SM and VAN.

They also showed a placebo-associated activity increase in frontoparietal regions, similar to our findings encompassed in the FPCN (Zunhammer et al., 2021).

The fronto-parietal network is responsible for engagement in attentive, goal-directed behavior (Vincent et al., 2008; Yeo et al., 2011). Specifically, the FPCN is involved in guiding decisions and performance adjustment, thanks to its role in integrating information from the external environment with stored internal representations (Miller, 2000), and controlling top-down attention during conflict processing of alternative responses (Corbetta and Shulman, 2002). Previous studies found that the activation of FPCN plays a crucial role specifically in endogenous pain modulation and analgesia. For example, Wager and colleagues (2011) reported how increased anticipatory activity in the FPCN predicted placebo effects. Going further, Kong and colleagues (2013) showed that resting-state FC between the FPCN and the rACC/mPFC was positively associated with cue effects on pain rating changes. FPCN could, therefore, play an important role in expectancy-induced modulation when a predictive cue is given and then anticipating the placebo effect. Our meta-analysis also shows an overlap of the activation map with the limbic network, which is an integral part of the well-known pain matrix (Apkarian et al., 2005). Similar to FPCN, previous investigators have hypothesized that this RSN may be crucial for the modulator effect of expectancy cues, thanks to its role in emotional modulation (Pessoa, 2009). The placebo-related activation overlapping with limbic and FPCN networks (and orbitofrontal connections) might also reflect learning effects. These two networks suggest that direct learning can shape expectations, via an interplay of limbic learning, relevant in the modulation of pain and emotional meaning (Koban et al., 2019).

While the FPCN is associated with cognitive control of external stimuli, the DMN is usually involved in self-related and internal control in a broad category of cognitive and affective processes (Buckner et al., 2008). The DMN seems also to be strongly involved in generating placebo effects through its involvement with introspective cognition (Buckner et al., 2008), prospection (Buckner and Carroll, 2007), representation of expected values (Hare et al., 2008), and generation of negative and positive emotions (Lindquist et al., 2012; Wager and Atlas, 2015). Moreover, DMN is strongly engaged during the appraisal processes, pivotal in modulating placebo effects (Y.K. Ashar et al., 2017). Appraisals, depending on personal cognitive beliefs, simulate potential outcomes and develop expectations about future events. Doing so influences precognitive learning and may enable a behavioral placebo effect. Appraisal processes are supported by a core brain system associated with the DMN (Y.K. Ashar et al., 2017). Increased engagement of DMN on expectation formation regarding treatment would generate the corresponding emotion/effect and facilitate a placebo effect.

Placebo effects also appear to be anchored to a widespread deactivation of networks processing sensory stimuli, such as SM and the VAN. The sensorimotor networks have critical nodes in the bilateral somatosensory cortex, supplementary motor area, and left posterior insula/superior temporal gyrus. Their deactivation may be related to a partial shut-down of the sensory circuitry. A decreased connectivity of the sensorimotor cortex implicates sensory and nociceptive modulation, likely reflecting a modulatory decrease of the early discriminative aspects of pain processing (Rossi et al., 2003). This shut-down in the early phases is also

temporally concurrent with a decreased detection of relevant stimuli, as explained by the overlapping deactivation in regions belonging to the VAN. The VAN is more active when detecting salient changes in the environment and acting as an alerting mechanism. Both auditory and visual oddball studies (Bledowski et al., 2004; Fichtenholtz et al., 2004) have commonly reported the involvement of ventral network regions, supporting the hypothesis that this network is a supra-modal "alerting" system (Corbetta et al., 2008). The deactivation of VAN may be explained by decreased attention to processing both pain and emotional external stimuli, enabling therapeutic benefits associated with the placebo effect.

Finally, the placebo effect seems to be mediated by a dynamic interplay of different RSNs working together. Wagner and coworkers (2019) investigated how placebo analgesia affected intrinsic network coupling on 99 subjects with resting-state fMRI study after pain processing. Although SM and Salience Network (SN) are already negatively coupled at rest, this coupling was even more negative following the placebo administration. The degree of inverse coupling between the networks was associated with lower individual pain intensity scores obtained during the preceding pain task. Negative coupling between the SN and SM might thus indicate an increased activation of descending pain modulatory processes after the placebo administration. This also corroborates our suggested model, where placebo effects are associated with the increased activation of descending cognitive modulatory networks and the deactivation of external sensory processing networks.

NIBS solutions to manipulate placebo effects. The present results shed light on neural correlates and networks involved in placebo effects. We propose that these findings can be applied to provide targets for neuromodulatory solutions to manipulate placebo effects. We used biophysical modeling to study the best montages based on our resulting placebo-associated ALE maps and their FC for different NIBS approaches.

Our first model is stimulation or inhibition of the left DLPFC, a pivotal node for placebo effects that we identified in our meta-analysis and already a well-established NIBS target. Up-to-date literature on DLPFC primarily includes the FDA-approved treatment of depression but also growing evidence for potential cognitive enhancement and pain relief (for a comprehensive review, see Downar et al., 2016). Interestingly, several lines of evidence support the modulating placebo effects via modulation of activity in DLPFC (Bingel et al., 2011; Borckardt et al., 2006; Krummenacher et al., 2010). Specifically, a protocol of excitatory TMS over DLPFC has been shown to reduce pain (Borckardt et al., 2006), while inhibitory TMS of this area can inhibit and block placebo-induced analgesia (Krummenacher et al., 2010). The increase of activity in lateral PFC, like the one induced by rTMS, is even directly correlated with the magnitude of reported analgesia (Atlas et al., 2012; Bingel et al., 2011; Geuter et al., 2013). Neuromodulation of the left DLPFC, specifically, might therefore benefit symptoms from a wide range of psychiatric/neurological disorders due to its involvement in mediating placebo effects. On the other side, a previous tDCS study investigated the involvement of right DLPFC in placebo analgesia (Egorova et al., 2015). Thanks to 20 minutes of anodal vs. cathodal tDCS they were able to manipulate the excitability of the right DLPFC on conditioned placebo cue response to heat pain. The authors reported an induced placebo effect during anodal stimulation of the right DLPFC. the cathodal inhibitory condition failed to

induce any placebo response, effectively blocking placebo analgesia, as seen in TMS studies (Egorova et al., 2015).

Although these findings are already promising, a multifocal network-oriented view may help optimize treatment protocols by manipulating multiple nodes implicated in placebo effects. We offered two tES protocols in this regard. First, we showed a tRNS-optimized montage to simultaneously stimulate all three activation clusters resulting from our meta-analysis. Second, we suggest an approach with simultaneous stimulation and inhibition of neural correlates of placebo effects which could be even more effective. To do this, we analyzed the FC profile of the ALE regions resulting from our meta-analysis and used them as targets. We suggest a final optimized tDCS montage able to stimulate and inhibit macro-regions associated with activation clusters and deactivation clusters. In a similar approach, Schambra and colleagues (2014) discussed how "functional targeting" tDCS could boost placebo effects in anti-depressant trials. TDCS, as a technique able to polarize a bigger portion of the network and significantly alter FC to deeper subcortical areas, may reinforce brain networks activated by the expectation of therapeutic benefit. This stimulation could recruit additional but distinct connected neural substrates when combined with other sources of expected benefit, such as a placebo pill in a clinical trial (Fabrizio Benedetti et al., 2011). As an example, the authors suggest a complementary approach to help investigate anti-depressant drug treatment. TDCS could be combined with the medication to reinforce placebo network activity arising from the expectation of medication benefit and associated affective learning (Schambra et al., 2014).

Limitations. These findings should be interpreted in the context of some important limitations. Firstly, while running the meta-analysis, we included experiments that investigated placebo effects across distinct modalities (emotional relief and placebo analgesia), employing unrelated experimental paradigms (stimuli expectancy and placebo analgesia), and separate timing (anticipation vs. during administration of painful/emotional stimuli). It is worth noticing that previous extensive literature showed how the placebo effect across different modalities and experimental paradigms emerges from the same neural correlates (Wiech, 2016; Zhang et al., 2011; Zhang and Luo, 2009). Similarly, a previous meta-analysis reported overlap between placebo-associated regions during placebo for painful or emotional stimuli and in anticipation of therapeutic benefit, as both reflect modulatory mechanisms (Amanzio et al., 2013). By combining studies with distinct modalities, timing, and experimental paradigms, we followed previous literature showing a common neural substrate of placebo effects across domains, as well as the method, chosen from the previous meta-analysis investigating placebo-associated regions (Atlas and Wager, 2014; Zunhammer et al., 2021). Although the goal of this study is to start from a substrate responsible for all placebo responses that could be actively manipulated with NIBS techniques, it would be interesting to investigate potential differences in neural correlates involved in distinct modalities, timing, and paradigms. Unfortunately, ALE maps based on small sample sizes are more susceptible to impacts of study heterogeneity (Eickhoff et al., 2012a). Indeed, a sample of at least 17 studies is required for solid results with enough statistical power (Eickhoff et al., 2017). Because of the small number of studies of each sub-group, we

could not run separate ALE maps. Hopefully, future meta-analyses will reach a sufficient sample size thanks to the growing neuroimaging experiments to test placebo responses with separate paradigms. Secondly, because we chose to investigate the placebo effects in healthy volunteers, our result may not be generalizable to a wider clinical setting. We did not find a sufficient number of neuroimaging studies for different diseases (e.g., AD, depression, Parkinson's disease) to compute a statistically relevant placebo effects map on different pathologies. Future studies should focus on how placebo network activity may be impaired in diseases with relevant differences in cortical structure and function. Furthermore, we included studies on immediate, short-term placebo effects, but the behavioral response to placebo may persist for longer periods. For example, in clinical trials for neuropathic pain, Parkinson's disease, and depression, placebo effects can be observed for weeks after initiating placebo treatment (Khan et al., 2008; Quessy and Rowbotham, 2008; Tuttle et al., 2015). A better understanding of the durability of placebo effects may help shed light on related mechanisms and how to manipulate them with neuromodulation.

SIGNIFICANCE.

The present study sheds light on neural correlates responsible for placebo effects. Our network mapping analysis suggested that placebo effects may emerge through a complex dynamic interplay of different functional networks. These findings offers an opportunity to either control for placebo effects, by trying not to engage activity in the relevant area, but they also provide targets for future neuromodulatory solutions to actively tuning placebo effects. We suggest new and likely more efficient neuromodulatory solutions to manipulate placebo effects for potential clinical benefits, to be verified in dedicated interventional studies.

5.2 Second Study: Similarities in Placebo Effect and Neuromodulation for Depression

A similar version of the present article has been published [Burke MJ **& Romanella SM***, Mencarelli L, Greben R, Fox MD, Kaptchuk T, Pascual-Leone A, Santarnecchi E. "*Placebo effects and neuromodulation for depression: A meta-analysis and evaluation of shared mechanisms*". **Mol Psychiatry**. 2022 Mar;27(3):1658-1666. doi: 10.1038/s41380-021-01397-3. Epub 2021 Dec 14.

As previously introduced, neuromodulatory treatments of depression may essentially be stimulating the brain's intrinsic placebo network and this explains why, for example, left DLPFC stimulation has shown therapeutic promise for at least 29 distinct neurological and psychiatric disorders. In the open-label setting, this has limited repercussions. However, in the context of a placebo-controlled clinical trial, if placebo effects are large, competing shared therapeutic mechanisms would limit the ability to detect a significant difference between active and placebo groups. This explains recent trends observed in the literature and sheds light on the importance of developing new protocols for measuring efficacy in this field.

In the present study, I created a brain map of placebo effects by synthesizing neuroimaging data from a healthy subjects and patient studies of placebo effects. I then aimed to use the results of this meta-analysis to compare areas of the brain implicated in placebo effects with neuromodulatory targets of depression treatment and examine the implications of potential shared mechanisms on measuring efficacy in clinical trials. Finally, I explore the hypothesis that if such overlap exists then stimulating a shared placebo effects target should be effective for a wide spectrum of disorders beyond depression.

5.2.1 Methods

Systematic Review and Coordinate Identification. Neuroimaging studies of placebo effects were identified using literature searches in PubMed/Medline and Google Scholar, the authors' libraries, and hand-searching references from recent review articles (see Figure 26 for the study selection flowchart). The primary search aimed to identify neuroimaging articles on placebo analgesia, the most widely studied paradigm in placebo neuroimaging. The terms "placebo", "analgesia", and "expectation" were combined with "functional magnetic resonance imaging", "position emission tomography", their acronyms, and "functional neuroimaging". This search included placebo analgesia studies enrolling both healthy volunteers and chronic pain disorders (musculoskeletal and visceral) and included both contrasts of activation during anticipation and noxious/pain stimulation periods. We then performed six additional literature searches of patient populations that have been studied under experimental placebo effects protocols and have established literature on placebo effects neuroimaging (Wager and Atlas, 2015). This included Parkinson's disease, depression, migraine, addiction, Alzheimer's disease, and schizophrenia. Search terms of "Parkinson", "depression", "migraine", "addiction", "Alzheimer's" and "schizophrenia" were independently combined with "placebo" OR "expectation", and then individually combined with "functional magnetic resonance imaging" OR "position emission tomography", their acronyms, OR "functional neuroimaging". We included articles published until April 25th 2020 and screened the title and abstract of every identified article. We excluded (i) review papers, case reports, and re-analysis of published data collection, (ii) studies not in the English language, (iii) studies not reporting fMRI/PET activation coordinates in MNI or Talairach/Tournoux space, (iv) studies that used only predefined Regions of Interest (ROIs) or Volume of Interest (VOIs), (vi) studies reporting results obtained only with Small Volume Correction (SVC), (vii) PET studies with specific tracers, e.g. μ-opioid receptor tracer. We also excluded experimental paradigms with placebo treatment administered for an extended period of time (e.g. neuroimaging performed before/after the weeks of placebo), focusing only on studies where the neuroimaging was performed in anticipation and during the relevant placebo-related task (online). We avoided multiple reports of single data sets across articles to ensure that only one report of a study contributed to the coordinates for the present meta-analysis. For each study, the following variables were extracted: (i) experimental paradigm, (ii) sample size, (iii) mean age, (iv) characteristics of participants, (v) imaging modality, (vi) MNI/Tailarach coordinates, and (vii)

contrast. In studies that reported a division of responders and non-responders, we used the coordinates as two different contrasts. We computed two different placebo effects neuroimaging maps: (i) activation contrasts (n=54) and (ii) deactivation contrasts (n=43).

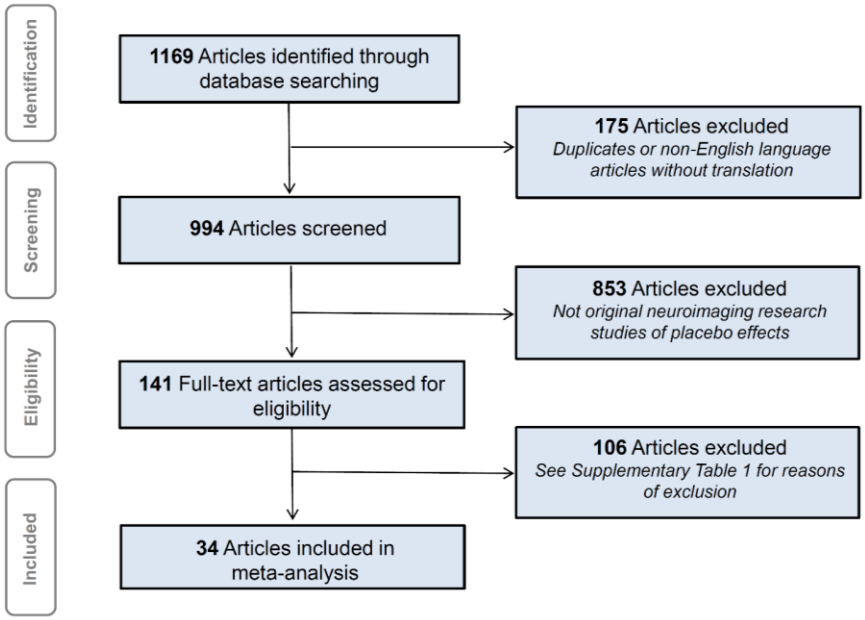


Figure 26. **Flowchart outlining selection of placebo effects neuroimaging studies included in the meta-analysis.**

Generation of ALE Maps. Specific activation and deactivation coordinates were collected and included in a quantitative Activation Likelihood Estimation (ALE) analysis technique implemented using GingerALE software v. 2.3 (www.brainmap.org). This method yields a statistical map that indicates the set of significant voxels while considering the magnitude of the effect, the number of studies, and the number of participants in each study (Eickhoff et al., 2012b; Turkeltaub et al., 2002). To do so we extracted peak voxel coordinates from relevant contrasts and applied the Tal2MNI algorithm implemented in GingerALE to convert Talaraich coordinates to MNI space (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The reported foci for each study were modeled as Gaussian distributions and merged into a single 3D volume. Equally-weighted coordinates were used to form estimates of the probability of activation for each voxel in the brain, using an estimation of the inter-subject and inter-study variability, rather than applying a priori full-width half maximum (FWHM) kernel. Therefore, the number of participants in each study influenced the spatial extent of the Gaussian function used. We first modeled the probability of activation over all studies at each spatial point in the brain, returning localized "activation likelihood estimates" or ALE values. Values were then compared to a null distribution created from simulated datasets with randomly placed foci to identify significantly activated clusters (permutations test = 1000 run). Corrections based on false-discovery rate (FDR) at the cluster-level and family-

wise error (FWE) at the voxel-level were applied. Cluster correction for multiple comparisons with a $p < 0.001$ thresholds for cluster-formation and a $p < 0.05$ for cluster-level inference were set. For a detailed explanation of the process of creating ALE maps and specific parameters chosen in the analysis see Supplementary Method Section: ALE maps. We visualized ALE maps using MRICronGL on an MNI standard brain.

***Overlap Mapping of Neuromodulation Stimulation Sites for Depression Treatment*.** We imported the placebo effects meta-analysis activation clusters to Connectome Workbench (Marcus et al., 2011) to assess for potential overlap between the clusters and proposed rTMS and DBS targets for depression treatment. To do so, we converted the placebo activation clusters in the ALE-maps to a surface display. On a canonical brain morphed in MNI space, we then overlaid coordinates from proposed targets of rTMS/DBS treatment for depression. We identified targets based on recent studies on this topic[14,15] and a search of the literature to date. We included clinical trials of rTMS targeting left DLPFC for depression, clinical trials of DBS targeting the subgenual anterior cingulate cortex (sgACC) for depression, and neuroimaging studies investigating antidepressant responses relevant to these targets. We included 11 coordinates from the TMS literature and 11 coordinates from the DBS literature. If studies presented coordinates in Talairach space, they were converted to MNI space. For DBS studies, due to the close localization of target sites in both hemispheres adjacent to the midline, for display purposes, we flipped the right-sided coordinates to enable visualization on a mid-sagittal slice.

Systematic Review of Non-depression TMS Trials Targeting the Left DLPFC. To further explore relationships between brain stimulation and placebo effects, we attempted to identify non-depression clinical treatment applications of left DLPFC-targeted TMS. This is based on the rationale that if the left DLPFC is also critically implicated in placebo effects then stimulating this target should benefit a broad spectrum of disorders beyond depression. We conducted a literature search of clinical trials in PubMed/Medline with search terms including "left dorsolateral prefrontal cortex or left DLPFC" and "transcranial magnetic stimulation or TMS". The search included articles published until April 25, 2020. We also hand-searched relevant review articles. We included TMS studies targeting the left DLPFC (which could also stimulate the left DLPFC and another region – e,g. bilateral DLPFC) for the treatment of a medical disorder or symptom. We excluded trials investigating depression, using technologies other than TMS (e.g. direct current stimulation), non-sham/placebo-controlled trials, and trials that demonstrated no significant benefit on relevant clinical outcomes. A total of 405 studies were identified and 65 met the eligibility criteria.

5.2.2. Results

Of the 1169 records identified, a total of 34 placebo effects neuroimaging studies met the inclusion criteria (Figure 27). The results of the ALE meta-analysis are shown at network-level volumes. The maps represent the entire cluster of increased and decreased activation computed by GingerALE. Figure 27 reports the coordinates and displays the activations and deactivations in all included placebo neuroimaging studies. There were three

significant clusters of activation: left dorsolateral prefrontal cortex (DLPFC) (BA 6, 8 and 9; x= -41, y= 16, z= 34), left sub-genual anterior cingulate cortex (sgACC)/ventral striatum (BA25; x= -8, y= 18, z= -15) and right rostral anterior cingulate cortex (rACC) (BA 32; x= 4, y= 42, z= 10). There were two significant deactivation clusters: right basal ganglia (x= 20, y= 2, z= 7) and right dorsal anterior cingulate cortex (dACC) (BA 24; x=1, y= -5, z= 45). For exploratory analyses assessing the potential overlap of depression neuromodulation sites with brain regions implicated in placebo effects, 11 TMS and 11 DBS targets were identified. Figure 28 shows the overlap of TMS target sites with the left DLPFC meta-analysis cluster and the overlap of DBS target sites with the sgACC cluster. To further explore relationships between left DLPFC stimulation and placebo effects, we identified 65 left DLPFC TMS treatment trials that demonstrated potential therapeutic benefits for non-depression indications (Table 7). The identification of 29 distinct disorders/symptoms showing response to left DLPFC activation supports a mechanism that may not be specific to depression but could be consistent with the activation of a non-specific placebo network.

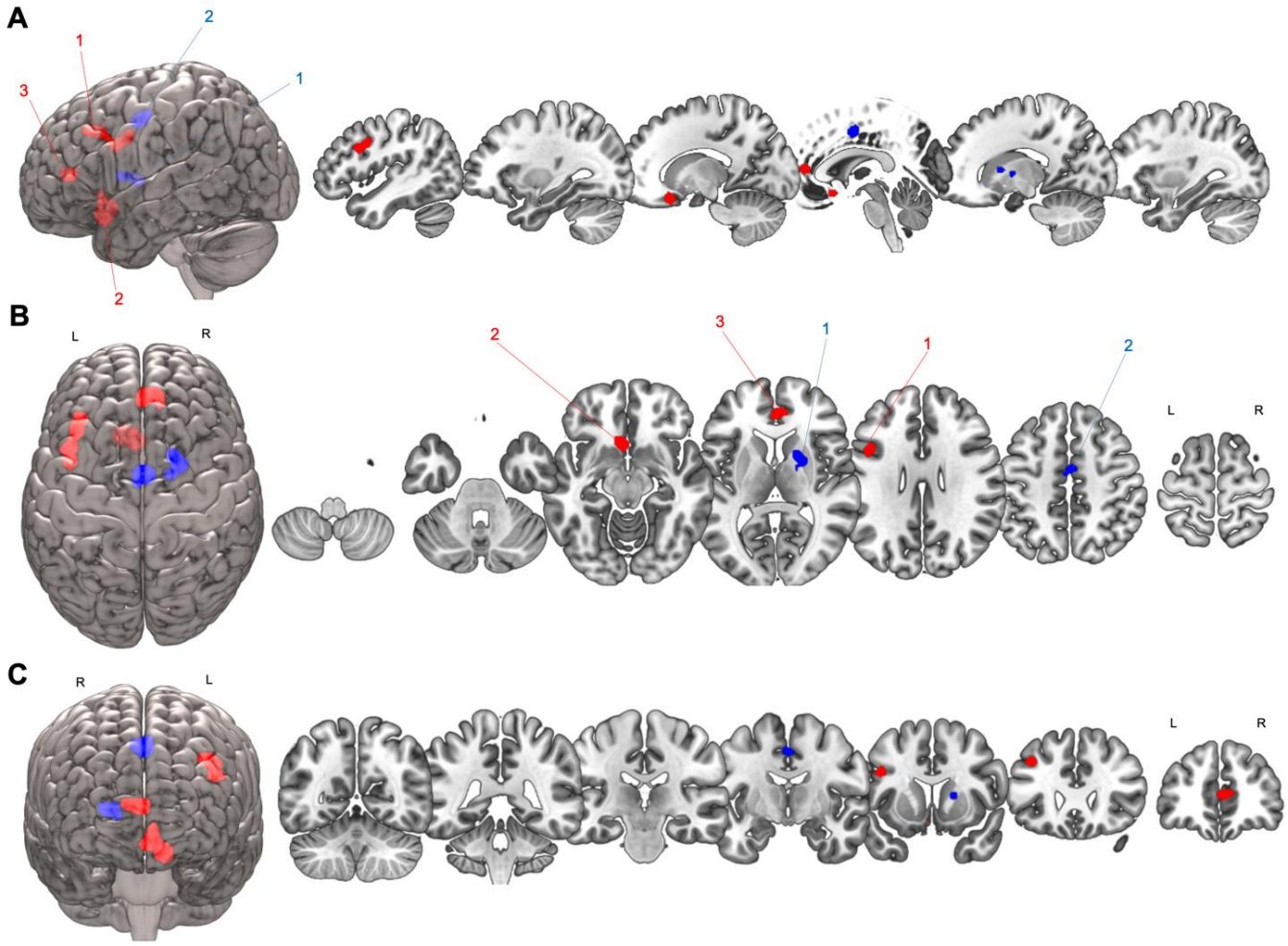
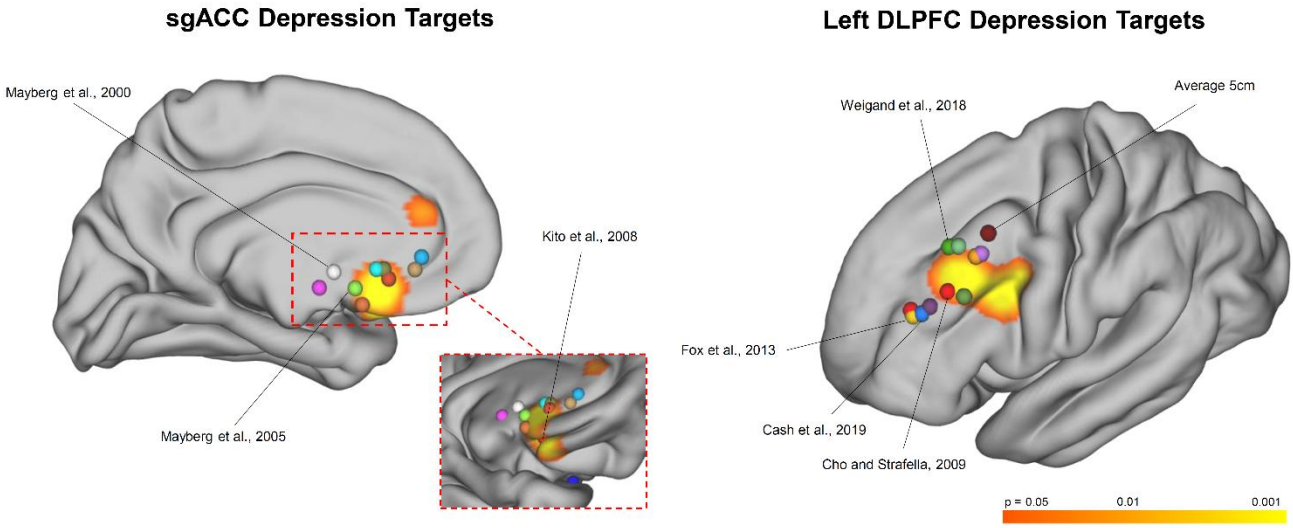


Figure 27. Map of brain activations and deactivations associated with placebo effects. Three activation clusters (red) from a meta-analysis with 58 contrasts and two deactivation clusters (blue) from a meta-analysis with 47 contrasts were identified. Glass brain representations and overlay with T1-weighted MRI slices in the sagittal (**Panel A**), axial (**Panel B**) and coronal (**Panel C**) planes are displayed. Note: Images are displayed in neurological convention.



Author	Year	X	Y	Z
Bewernick	2018	-5	-4	-9
Drevets	2002	3	32	-10
Hamani	2009	6	34	-6
Kito	2008	17	17	-16
Kito	2011	8	22	-9
Mayberg	2000	4	2	-5
Mayberg	2005	-2	9	-11
Mayberg	2005	10	21	-4
Nahas	2007	0	9	-19
Sani	2017	-52	0	-6
Wu	1999	7	18	-4

Author	Year	X	Y	Z
Average 5 cm		-41	16	54
Cash	2019	-43	46	32
Cho	2009	-40	31	34
Fitzgerald	2009	-46	45	38
Fox	2013	-38	44	26
Herbsman	2009	-46	23	49
Herwig	2003	-37	26	49
Paillère Martinot	2010	-44	20	48
Teneback	1999	-41	48	35
Weigand	2018	-33	30	50
Zrenner	2020	-50	30	36

Figure 28. Placebo effects and depression treatment. Proposed rTMS and DBS targets for treatment-resistant depression are overlaid on a surface representation of the meta-analytic placebo activation clusters associated with placebo effects (yellow-orange clusters). Left DLPFC TMS targets and sgACC DBS targets overlap with the placebo effects clusters. For the DBS targets, right-sided coordinates adjacent to the midline are flipped to enable display on the mid-sagittal slice. References for target coordinates for studies investigating TMS and DBS depression treatment are listed and color-coded with the brain maps. Coordinates are presented in MNI space. sgACC = subgenual anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex.

Disorder/Symptom	Treatment Trial
Alcohol Use Disorder	*Del Felice et al 2015*
Alzheimer's Disease	*Ahmed et al 2011, Cotelli et al 2011, Cotelli et al 2008*
Anorexia Nervosa	*McClelland et al 2016*
Attention	*Kim et al 2012*, De Raedt et al 2010**
Bipolar Disorder	*Yang LL et al 2018, Tavares DF et al 2017*
Bulimia Nervosa	*Guillaume et al 2018, Claudino et al 2010, Van den Eynde et al 2010*
Burning Mouth Syndrome	*Umezaki et al 2015*
Chronic Neuropathic Pain	*Borckardt et al 2009*
Cognitive Control	*Li et al 2017**
Fibromyalgia	*Atlas et al 2019, Fitzgibbon et al 2018, Cheng et al 2019*
Food Craving	*Uher et al 2005**
Opioid Use Disorder	*Shen et al 2016*
Dizziness	*Cha et al 2016*
Stimulant Use Disorder	*Liu et al 2017, Su et al 2017*
Mild Cognitive Impairment	*Drumond Marra et al 2015*

Obesity	*Kim et al 2019, Kim et al 2017*
Panic Disorder	*Deppermann et al 2017*
Parkinson's Disease	*Aftanas et al 2018, Lomarev et al 2006, Dias et al 2006*
Postoperative Pain	*Borckardt et al 2014, Borckardt 2008, Borckardt et al 2006*
Post-concussion Syndrome	*Koski et al 2015*
Posttraumatic Stress Disorder	*Boggio et al 2009*
Post-traumatic Headache	*Stilling et al 2019, Leung et al 2018*
Progressive Non-fluent Aphasia	*Cotelli et al 2012*
Schizophrenia	*Kamp et al 2018, Li et al 2016, Kamp et al 2016, Gan et al 2015, Dlabac-de Lange et al 2015, Wobrock et al 2014, Quan et al 2014, Wölwer et al 2014, Prikryl et al 2013, Barr et al 2012, Prikryl et al 2012, Schneider et al 2008,, Goyal et al 2007, Prikryl et al 2007, Mogg et al 2007, Rollnik et al 2000*
Social Cognition	*Hall et al 2018**
Suicidal Ideation	*George et al 2014*
Thermal Pain	*Taylor et al 2012*, Borckardt et al 2007**
Tobacco Use Disorder	*Sheffer et al 2017, Prikryl et al 2013, Li et al 2013, Amiaz et al 2009, Eichhammer et al 2003*
Working Memory	*Beynel et al 2019*, Hoy et al 2015**

Table 7. Left DLPFC TMS treatment trials demonstrating potential benefit for symptoms or disorders other than depression. **Legend:** Studies listed in alphabetical order. TMS = transcranial magnetic stimulation, DLPFC = dorsolateral prefrontal cortex, * = Recruited healthy subjects.

5.2.3. Discussion

In the present study, we identify common regions of brain activation (left DLPFC, sgACC/ventral striatum, and rACC) and deactivation (right dACC and basal ganglia) across neuroimaging studies of placebo effects. Comparative analyses revealed that many of these regions align closely with neuromodulatory treatment sites of depression, most notably the left DLPFC and sgACC. These results suggest that there may be an overlap in the therapeutic mechanisms of placebo effects and neuromodulatory treatments of depression. We use these findings to offer new insights into the complex interplay between depression and placebo effects and offer a new framework for interpreting recent trends in depression clinical trials.

***Placebo Neuroimaging Literature*.** The vast majority of neuroimaging studies of placebo effects have focused on placebo analgesia and administering a placebo to healthy individuals in the context of experimentally induced pain. It has been estimated that upwards of 80% of placebo studies concern healthy participants only (P et al., 2018) The results from our meta-analysis show consistencies with previous syntheses of placebo analgesia neuroimaging studies in healthy subjects (Amanzio et al., 2013; Wager and Atlas, 2015) In these analyses, many of the reported front-limbic regions were similarly highlighted across a variety of placebo analgesia contrasts and paradigms. Given that our analysis also included studies from patient populations (pain and non-pain-related), this supports models proposing that placebo effects may have common underlying cognitive-affective and reward-based substrates across different disease/symptom-states (Yoni K. Ashar et al., 2017) Indeed, core conceptual factors of placebo effects such as expectancies, motivation, and anxiolysis are broadly relevant across many clinical settings (Colloca and Barsky, 2020)

Neuroimaging research specifically investigating placebo effects in patients with depression is very limited and only one study met our inclusion criteria. This PET study of men with unipolar depression reported placebo-induced regional metabolic increases in many regions including prefrontal and anterior cingulate cortices and metabolic decreases involving the sgACC, parahippocampus, and thalamus (Mayberg et al., 2002) Interestingly, this study also included a fluoxetine arm and reported a common pattern of glucose metabolism changes in both placebo and fluoxetine responders. A more recent neuroimaging study using a mu-opioid receptor–selective radiotracer [11C] carfentanil found that anti-depressant response to placebo was associated with increased μ-opioid neurotransmission in a network of regions including the sgACC, nucleus accumbens, midline thalamus, and amygdale (Peciña et al., 2015) Further research is needed to corroborate these findings and establish a more robust signature of placebo effects in depression and how this may or may not vary across different clinical settings.

TMS and Depression. Neuromodulation with technologies such as TMS is one of the most promising recent advances in the management of medication-resistant depression. TMS is a noninvasive means of focally stimulating the brain via electromagnetic induction through the application of rapidly changing magnetic fields. TMS is safe if appropriate guidelines are followed (Rossi et al., 2009c) and the efficacy of repetitive TMS for treatment-resistant depression has been demonstrated in randomized clinical trials and has resulted in FDA-approval of multiple devices (Brunoni et al., 2017). Conventional TMS protocols for depression involve high-frequency repetitive stimulation of the left DLPFC for 3-5 days per week for 4-8 weeks (Brunoni et al., 2017) The main rationale for the left DLPFC target is that it may represent a superficial/accessible node of the depression network, particularly concerning its negative connectivity with the sgACC (Michael D. Fox et al., 2012) The sgACC has been relatively consistently reported to be hyperactive in depression and thus, given the direction of sgACC and DLPFC connectivity, stimulation that increases DLPFC excitability could potentially reduce and/or normalize sgACC hyperactivity, just like sgACC disruption by DBS may increase DLPFC activity (Mayberg et al., 2005)

Furthermore, the strength of functional connectivity between an individual's left DLPFC TMS target and the sgACC has been shown to predict the antidepressant response (Weigand et al., 2018) It is also important to note that despite the list of different TMS target localizations used for depression treatment - in reality, there is a range of errors in the intended target stimulated, particularly for TMS trials not using neuronavigation.

Our findings that the left DLPFC and sgACC are also critical nodes for placebo effects suggest that the previously proposed TMS anti-depressant mechanism may directly overlap with placebo effect mechanisms. Indeed, baseline connectivity to the sgACC has also independently been demonstrated to predict anti-depressant response to placebo/sham TMS (Wu et al., 2020) Thus, despite different labels, these circuits could represent the same or similar therapeutic pathways. However, given the complex functional neuroanatomy and connectivity of these regions and their sub-regions, the exact nature and extent of potential overlap require further research.

***Implications on Measurements of Efficacy*.** The potential shared mechanisms described above could provide new insights toward understanding trends of failed sham-controlled neuromodulation treatment trials of depression. Razza and colleagues recently conducted a meta-analysis of placebo/sham response magnitudes in TMS trials for depression (Razza et al., 2018) They reported a large overall placebo response effect size of 0.8 (Hedge g, $p < 0.01$), but more important to the present discussion, their meta-regression found a significant trend of increasing placebo responses with time to present ($\beta = 0.03$, $p < 0.02$). This increase could reflect multiple factors including increased therapeutic expectations from growing hype and media attention, more elaborate technological setups, changes in included patient populations, and improved blinding with more realistic sham coils (Burke et al., 2019)

Recent trials of TMS for depression have not failed because of a lack of patient improvement in the active arm, but because both active and placebo arms have yielded very large responses. To put this in context, in early randomized trials of TMS, the placebo responses were quite modest. For example, in the multi-site TMS depression trial that gave Neuronetics FDA-approval in 2007, they reported a 12.1% reduction of the MADRS depression score (their primary outcome) in the placebo group (baseline versus post-rTMS; O'Reardon et al., 2007b) However, in the most recent large multi-site sham-controlled trial of TMS, Yesavage and colleagues reported an extremely large 50% reduction in the MADRS in the placebo group (baseline versus post-rTMS; Yesavage et al., 2018) This trial's primary outcome was remission rate and despite achieving a 41% remission rate in the active TMS group, the trial was negative as they observed a 38% remission rate in the placebo group. Another recent TMS trial also reported very large responses in both active and sham groups (84% overall response rate), with no significant group difference (Valkonen-Korhonen et al., 2018) Other examples demonstrating this trend can be found elsewhere (Razza et al., 2018)

If placebo effects were mechanistically independent of the anti-depressant-specific effects of TMS, the trend of growing placebo effects should not impede measurements of efficacy. This scenario of adding large placebo effects to both trial groups, with no overlap in effect mechanisms, preserves the ability to demonstrate efficacy (Figure 29, panel B-1). However, with shared mechanisms, increasing placebo effects has a dramatic impact on the ability to detect differences between the active and placebo groups (Figure 29, panel B-2). In the latter scenario, placebo effects could be essentially consuming effect size that otherwise would have been attributed to the active TMS intervention (Figure 29, panel A). In this schematic, we depict that if placebo effects are large, the DLPFC circuit could be near maximally activated by placebo effects, and thus active DLPFC-targeted active TMS may have little ability to establish an incremental effect. The ceiling and dynamics of activating this circuit require further research and likely vary on an individual basis.

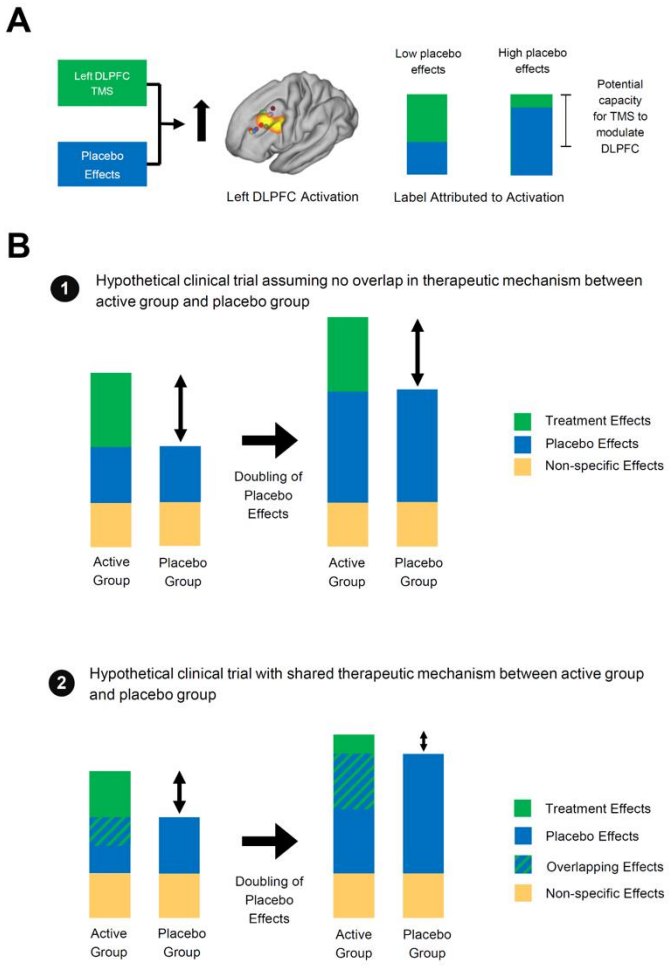


Figure 29. Implications of shared therapeutic mechanisms. Panel A. Placebo effects and TMS treatment for depression both increase the activity of the left DLPFC. In this hypothetical schematic, if placebo effects are elevated (right), the DLPFC circuit could be near maximally activated through placebo effect mechanisms (ceiling effect) and thus TMS may have little ability to establish an incremental effect. **Panel B.** Hypothetical clinical trials demonstrate the different impacts of doubling placebo effects when a treatment has a therapeutic mechanism independent of placebo effects (1) and a treatment that may have a shared mechanism with placebo effects (2). In the former, the effects are additive and the assay sensitivity to detect a difference between active and placebo is preserved. However, in the latter, increasing placebo effects effectively limits the ability to detect a significant difference between active and placebo groups. Non-specific effects include regression to the mean, spontaneous changes, Hawthorne effects, and other effects that have been held constant in the modeling above. Note: TMS = transcranial magnetic stimulation, DLPFC = dorsolateral prefrontal cortex

Implications for Other Depression Treatments. So far we have focused on TMS, however, the presented line of reasoning can likely also be extrapolated to other depression treatments. For example, Deep Brain Stimulation (DBS) is another neuromodulatory technology that has been investigated for the management of treatment-resistant depression. Based primarily on data from its use in Parkinson's disease, DBS also yields very high placebo responses that may be greater than other less intensive treatments (Mestre et al., 2016) Though no head-to-head comparisons are available, principles of differential placebo effects would suggest that DBS could potentially induce even larger placebo effects than TMS (Burke et al., 2019) The primary DBS target for

depression is the sgACC; the deep node of the depression network that TMS attempts to indirectly modulate via the DLPFC. In an initial open-label series of DBS targeting the white matter adjacent to the sgACC, dramatic responses of sustained remission were reported in four of six treatment-resistant patients (Mayberg et al., 2005) However, in the subsequent multi-site sham-controlled trial, both groups showed improvement and there was no statistically significant difference in response during the sham-controlled phase (Holtzheimer et al., 2017) Similar to our models with TMS, it is possible that DBS didn't fail in this sham-controlled trial because the target was wrong or because it didn't effectively modulate the target, but because it could have been competing with placebo effects for modulating the same circuit. If placebo effects are high, the shared mechanism affords little further room to demonstrate additional benefit. These implications could also extend beyond neuromodulation and to some extent likely impact all depression treatments including pharmacotherapy. Though drugs such as SSRIs may influence a more widely-distributed set of brain regions than targeted therapies, their response has also been linked to this shared mechanism with placebo effects (Mayberg et al., 2002) Furthermore, evidence-based psychotherapies for depression specifically aim to boost skills and/or cognitive frameworks promoting positive expectation of recovery and hopefulness. Thus, this could be conceived as delivering the principles of placebo effects in an alternate form without the "placebo".

Implications Beyond Depression. Based on our data suggesting that left DLPFC TMS may be stimulating a common 'placebo' network, it would follow that such a stimulation protocol should be effective for many disorders beyond depression. Indeed, numerous studies have reported beneficial effects from DLPFC-targeted TMS across clinical neurosciences. Furthermore, this is paired with relatively limited disease-specific mechanistic rationales for the left DLPFC stimulation protocol. A summary of different disorders/symptoms suggesting a clinical benefit from left DLPFC stimulation is presented in Table 7. These studies represent signals of possible efficacy from sham-controlled trials; however, no indication for left DLPFC targeted TMS other than treatment-resistant depression has met standards for FDA approval at present. Other technologies aiming to activate the left DLPFC, such as transcranial direct current stimulation (TDCS), have shown a similar breadth of potential clinical application and thus provide further support for this placebo hypothesis.(Lefaucheur et al., 2017a) Further research interrogating the dynamics and implications of neuromodulatory devices facilitating intrinsic placebo brain networks is needed (Schambra et al., 2014)

Limitations and future directions. Many important limitations need to be considered in the present work. First, in our placebo effects meta-analysis, we synthesize neuroimaging data across different disorders and include both healthy control and patient populations. This heterogeneity was intentionally introduced by our search strategy and, though not ideal for syntheses, would bias us away from the present findings. Second, comparisons of our meta-analysis results with neuromodulatory treatment targets are descriptive and based on the overlapping of neuroimaging maps in MNI space. This comparative analysis does not involve quantitative statistical testing and should be considered exploratory and hypothesis-generating. Third, these analyses focus on shared neuroanatomical localizations; however, directions of connectivity in the implicated circuits may also be

relevant. High-frequency left DLPFC TMS induces an increase in cortical excitation in most subjects (Maeda et al., 2000b) and this matches the activation of the DLPFC mapped for placebo effects. However, the proposed mechanism for DBS of the sgACC is inhibition/disruption and this is opposite to the sgACC activation seen in our placebo effects meta-analysis. Unlike Mayberg and colleagues' study which showed placebo-induced deactivation of the sgACC in patients with depression (Mayberg et al., 2002) the majority of studies contributing to our meta-analysis recruited non-depressed individuals and thus different connectivity dynamics may exist in this region. Furthermore, the exact mechanism of DBS and relative activation/de-activation profile over time remains incompletely understood (Herrington et al., 2016) We should also note that our sgACC meta-analysis cluster extends to the ventral striatum and nucleus accumbens, a region associated with activation during placebo effects (Wager and Atlas, 2015) Finally, our study cannot delineate whether changes induced in the DLPFC or sgACC by placebo effects is truly the same as the changes induced by neuromodulatory devices. Even if the cortical target were to be identical, we do not know the extent to which the network connectivity to/from these regions in the given therapeutic context may or may not overlap.

To prospectively test the hypotheses generated by these analyses, we propose three important future lines of research for this field. First, prospective evaluation of whether neuromodulation such as high-frequency left DLPFC TMS can increase placebo effects independent from depression. For example, one could compare placebo analgesic responses following sham or active excitatory left DLPFC TMS. Interestingly, Krummenacher and colleagues found that low-frequency "inhibitory" bilateral DLPFC stimulation abolished placebo analgesia effects; (Krummenacher et al., 2010) however, no studies have assessed whether placebo effects can be independently amplified by TMS. Second, "open-hidden" paradigms (Benedetti et al., 2011) could be used to assess the impact of manipulating expectation (eg, removing the placebo effects associated with the expectation of therapeutic benefit) on the effects of neuromodulatory treatment for depression or other brain disorders. Third, and arguably most importantly, we need more neuromodulatory studies that include a no-treatment control group. Such three-armed trials can help delineate and quantify magnitudes of active effects, placebo effects, and non-specific effects (spontaneous improvement, regression to the mean, Hawthorne effects, and so on; Colloca and Barsky, 2020)

SIGNIFICANCE.

We identify a set of brain regions implicated in placebo effects across multiple paradigms and provide evidence that these regions map overlap with neuromodulatory depression treatment targets. This offers new insights into the complex relationships between placebo effects and depression and helps explain recent challenges of establishing efficacy for clinical trials in this field. Further research is needed to prospectively evaluate the extent of potentially shared neurobiology and corroborate proposed implications on clinical trial results.

6. INNOVATIVE CLINICAL AND RESEARCH NIBS APPLICATIONS

6.1 First Study: Induce Sleepiness with Optimized tACS.

A similar version of the present article will be submitted for publishing [**Romanella SM** & Benelli A, Palmisano A, Tatti E, Neri F, Cinti A, Rossi S, Santarnecchi E. "*Induce sleepiness with optimized Transcranial Alternating Current Stimulation: a preliminary EEG, tACS and modeling study*" (in prep)]

As aforementioned, sleep disruptions appears to be among the earliest observable symptoms of a wide range of neurodegenerative diseases, such as AD, Parkinson's Disease, and Multiple Sclerosis (Kay et al., 2018; Mattis and Sehgal, 2016). The opportunity to intervene on sleep-onset latency and sleep induction is therefore pivotal to to improve the quality of life of healthy elderly, detect individuals at risk, and slow down/prevent the progression of MCI/AD and other diseases. Over the last decade, tACS has been tested as a noninvasive intervention to manipulate sleep oscillations and restore sleep quality, while preserving or enhance physiologically-declining sleep-associated cognitive functions. We refer to sub Chapter 3.2 for a detailed discussions on the innovative approach to treat sleep-related disruptions during healthy and pathological aging with tACS. As extensively discussed in sub-chapter 3.1, growing old is associated with profound difficulties in falling asleep. The sleep-onset latency (time required to fall asleep) is almost twice as long as older than younger participants (Crowley, 2002), and after falling asleep elderly show a disrupted and shorter sleep pattern. Frequent arousals are a result of different concurrent factors. First, elderly individuals are more sensitive to the external environment, showing a lower arousal threshold to auditory stimuli (Zepelin et al., 1984). Furthermore, once sleep is interrupted, the transition from sleep to a fully awake state occurs more rapidly in older subjects without a subsequent increase in sleepiness, thereby delaying the start of sleep again (Dement et al., 1985).

In this framework, we designed a study aimed to investigate the potential ability to tACS to induce sleepiness. We decided to start with a cohort of young adults, in order to test the effective feasibility of this intervention in sleep-induction, before moving to healthy elderly participants and MCI/AD patients. Specifically, given the ability of tACS to create greater synchronization between endogenous brain frequencies in specific brain areas, we focused on entrainment with frequencies related to sleepiness, therefore promoting the induction of sleep during the waking state. Theta oscillations (4-7Hz), specifically, are identified as predominantly associated with sleepiness both in animals (Vyazovskiy and Tobler, 2005) and humans (Finelli et al., 2000). Theta activity in frontal areas, along with slow waves in the same regions, is associated with an increased pressure and need to sleep (Aeschbach et al., 1997; Cajochen et al., 2002; Finelli et al., 2000).

Therefore, we chose a protocol of tACS administered in theta frequency during a sleepiness-induced task while the participants were laying on a bed in a dark room. We focused on stimulating regions functionally connected to some sub-cortical areas responsible for sleep induction (i.e. preoptic area, suprachiasmatic nucleus, and pineal gland). We identified an optimized montage to successfully engage the activity of these structures

through a network effect. Our preliminary findings suggested the feasibility and success of theta-tACS with an optimized montage to induce sleepiness. The data collection is still ongoing, so the results here presented are only partial, although promising.

6.1.1. Methods

Participants. Fourteen healthy subjects (9 males and 5 females) aged between 20 and 31 (mean 26,57 ± 3,27 years) participated in the study after providing written informed consent. Participants were recruited at the hospital La Maria alle Scotte University Hospital of Siena, Italy. Each subject declared his willingness to participate in the study and signed a written informed consent; the research was approved by the Local Ethics Committee. All participants were medication-free. We excluded subjects with a presence or history of epilepsy, neurological or psychiatric disorders, and intracranial metal implants. We also excluded subjects with diagnosed sleep disorders.

Experimental Design. Participants were asked to not consume stimulants like coffee and nicotine, and not undergo intense physical training on the day before the session. They were also required to not drink any alcohol the night before and to try to maintain a sleep schedule as usual before and after any session. The protocol involved one baseline session and three experimental sessions. During the baseline session, the participant performed a cognitive assessment including Trial Making Test A and Trail Making Test B (Llinàs-Reglà et al., 2017) to test visual attention and task shifting, Attentional Matrix (Mesulam 2000) to investigate the interaction of working memory with visuospatial-attentive processes, and a free-recall (FR) task (Ciaramelli et al., 2015; Neri et al., 2021) memory task related to remembering a short tale to assess each subject's attentional and memory performance. Finally, subjects were asked to take notes of their sleeping rhythms and sleep quality after each session in a sleep diary. In addition, sleepiness data was collected for each subject regarding their ability to fall asleep, in order to obtain a personal sleepiness baseline. At each session, participants were required to come to the lab in the early afternoon (around 1:00 p.m.) and the session would start with a montage of EEG (and stimulation) electrodes. The session would start around 1:30 p.m. Each experimental session would start with the assessment of the self-reported measure of sleepiness (Karolinska Sleepiness Scale – KSS) and Simple Reaction Time (SRT). Three minutes of a resting state eyes-closed EEG were recorded pre-task. The participants would then perform a behavioral task to induce sleepiness lasting 20 minutes. To facilitate drowsiness, the subjects were lying with their eyes closed in a bed in a dark and quiet room. The participants were told that they could fall asleep at any point during the experiment, although they were asked not to stop responding deliberately while still awake. During the first session, considered the baseline, no stimulation was applied during the task. In the experimental sessions, tACS was administered for 20 minutes while the subject was performing the task. Post-stimulation eyes-closed EEG was then recorded without interacting with the participant, followed by the post-stimulation self-reported sleepiness measurement and SRT task. We are currently preprocessing and analyzing the EEG data, therefore we will not report the related results in this partial presentation of the study.

During the experimental sessions, participants were required to perform the task while undergoing 20 minutes of tACS. Each session had a different tACS condition, including i) theta stimulation, ii) beta stimulation, and iii) sham. Subjects were blinded to the type of stimulation (i.e. single-blind protocol) and the order of the conditions was balanced across subjects. We maintained at least three days of wash-out between each session, to avoid build-up sleep alterations that could influence daytime drowsiness. The room temperature was controlled for each session (average 24.5 ± 3.3 Celsius Degrees across all participants and all sessions). After each stimulation session, the subjects were asked to answer a questionnaire about the side effects of stimulation (Brunoni et al., 2011).

The behavioral task to induce sleepiness. The behavioral task consisted of around 20 minutes of audio stimuli presented through headphones using a PC controlled by Presentation software (Versions 13 and 14, NeuroBehavioral Systems, Albany, CA, USA). The task has been previously presented in the literature (Comsa et al., 2019). The stimuli included 150 spoken words chosen from the CELEX lexical database (Linguistic Data Consortium, University of Pennsylvania) translated into Italian. While half of the words named common animals, the other half denoted any type of object. The subjects had to classify each stimulus in its respective category (animal or object) by pressing one button for one group or a different one for the second. The stimuli were presented randomized with an average distance of 7.3s (minimum 6.5s and maximum 8s) between consecutive stimuli. Auditory volume to administer stimuli was determined after some trials in a silent environment by peer-subjects of our sample participants. To analyze this database, we took into consideration the response time to each stimulus. We computed the average response time divided into 3 blocks (1^{st} block: stimuli from 1^{st} to 50^{th}; 2^{nd} block: 51^{st} stimulus to 100^{th}; 3^{rd} block: 101^{st} stimulus to 150^{th}). This allowed us to compare the trend for all conditions during the 20 minutes of performing the task.

***Targets for Electrical Stimulation*.** The NREM1 phase is related to the activation of both cortical, such as the frontotemporal areas, and subcortical areas, particularly the hypothalamus. From previous literature, it has been observed how effective frontotemporal zone stimulation was in increasing sleepiness, specifically by placing electrodes between the F7 and T7 sites of the EEG system 10-20 (D'Atri et al., 2019). To define the stimulation montage according to the subcortical pacing areas to be targeted for stimulation, correlation analyses were made between the functional activation maps of the POA, PG, and SCN by Neurosynth (Yarkoni et al., 2011) and areas with the highest correlation index (r =.26) were selected. Based on these results, using the biophysical modeling, we were able not only to identify which brain regions to stimulate to reach both deep hypothalamic areas and cortical brain regions but also to define the 6 stimulation sites of the 10-20 EEG System: FT7, FT8, Fp1, Fp2, AF3, AF4.

***Biophysical Modeling*.** The definition of the optimal electrode placement and montage to reach the interested targets in this protocol has been identified using customized biophysical modeling. In particular, the multi-electrode tACS optimization was computed in SimNIBS v3.2 (Thielscher et al., 2015). As aforementioned, the software provides a realistic volume conductor head model, created as default in the FEM model generated using

the T1-and T2-weighted images and segmentation from the SimNIBS example data set. The data sample was acquired from a healthy subject with the approval of the Ethics Committee of the Medical Faculty of the University of Tübingen (Windhoff et al., 2013b). The data corresponds to a healthy subject (Ernie), which includes white matter, gray matter, cerebrospinal fluid, bone, and scalp tissue volumes. In our simulation we kept the isotropic conductivities given by default (Thielscher et al., 2015), corresponding to gray matter: 0.276 S/m, cerebrospinal fluid: 1.790 S/m, bone: 0.010 S/m, scalp: 0.250 S/m (Opitz et al., 2011). The final mesh, comprehensive of gray and white matter, scalp, bone, and cerebrospinal fluid, comprises approximately 200,000 nodes and 3.6 million tetrahedral elements (see Windhoff et al., 2013 for further modeling details).

tACS Optimization Algorithm. The tACS multielectrode solution is proposed as a result of the tES optimization algorithm targeting subcortical structures involved in sleep induction. In particular, we used the Ernie head model and computed the leadfield thanks to the algorithm of tES optimization from SimNIBS. The leadfield is calculated by first placing electrodes in the head accordingly with a 10-10 EEG cap and afterward calculating the field caused by each electrode individually, keeping a constant return electrode (for a detailed explanation of the algorithm see Saturnino et al., 2019). Thanks to this first computational step, the software creates a matrix that can then be used to calculate the electric field with various measures (e.g., NormE, NormalE, E) caused by any combination of electrodes. In this case, we chose electrodes modeled as small cylinders (1 cm diameter, 4mm thickness) with homogeneous conductivity and added to a 0.5mm in height corresponding approximately to electrode gel. SimNIBS can optimize electric fields based on distributed targets as given by singular MNI coordinates or a file with a network map. We set the minimum image threshold of 0.02. Every voxel in the targeted map with a lower value was discarded, focusing the stimulation on the higher values. We set the parameters as follows: maximum of the total current in the whole montage, 4 mA with a maximum of 2 mA individually for each electrode; maximum of 8 active electrodes. To maximize intensity within the target clusters, disregarding field focality, we set a large value for the target intensity (100 V/m). The algorithm will then use the matrix leadfield to find the combination of electrodes that will allow a higher peak value of intensity and mean field norm with good focality and the smallest possible error relative to non-intervention (ERNI). The optimization algorithm will suggest the optimal electrode placement and montage reach stronger intensity in the target regions and minimize the stimulation in other areas. The suggested tACS montage included 6 electrodes: FT7 (1.47mA), FT8 (-1.47mA), AF3 (1.02mA), AF4 (-1.02mA), Fp1 (0.51mA), Fp2 (-0.51mA); see figure 30, panel A). This electrode placement will be used during data collection in all tACS sessions.

Electrical Stimulation. The tACS protocol included one stimulation block (20 minutes). The visit was run via a battery-driven current stimulator-EEG monitor (Starstim 32, Neuroelectrics, Barcelona, Cambridge) through surface circular Ø 20mm PISTIM electrodes (Neuroelectrics, Barcelona, Spain) with an Ag/AgCl core and a gel/skin contact area of 3.14 cm^2. The electrodes were placed into holes of a neoprene cap corresponding to the international 10/20 EEG system. Gel was applied to optimize signal conductivity and lower impedance.

Electrode impedance was checked before each tACS block to assure the safety and efficacy of the stimulation. As aforementioned, experimental sessions included three conditions differentiated for tACS parameters: i) theta frequency, ii) beta frequency (20Hz), and iii) sham stimulation. The montage resulting from the biophysical modeling algorithm was adopted for all the conditions with locations based on the international 10-20 system: FT7 (1.47mA), FT8 (-1.47mA), AF3 (1.02mA), AF4 (-1.02mA), Fp1 (0.51mA), Fp2 (-0.51mA). The stimulation was followed by 30 seconds ramp-up and ramp-down periods. Given the specific patient population, the investigator constantly monitored uncomfortable sensations potentially experienced by the participant.

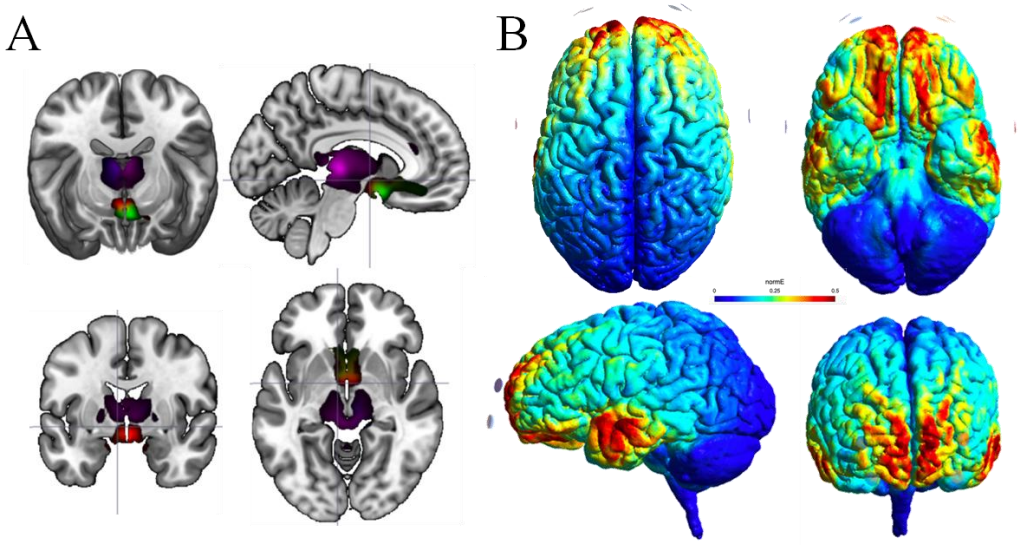


Figure 30. Targeting connectivity of subcortical structures responsible to induce sleepiness with biophysical modeling. The tACS multielectrode solution is proposed as a result of the tES optimization algorithm targeting the connectivity profile of subcortical structures involved in sleep induction. **Panel A** shows the overlap between the functional activation maps of the POA, PG, and SCN created in Neurosynth. **Panel B** is the graphical representation of the induced electric field (NormE in V/m) resulting from this montage overlapped on Ernie model. This electrode placement and intensity was the chosen montage for the tACS sessions in the data collection.

Sleepiness and Vigilance Measures. Subjective sleepiness was evaluated by the *Karolinska Sleepiness Scale* (Akerstedt and Gillberg, 1990) before the pre-stimulation EEG and following the post-stimulation EEG recording in each experimental session. KSS measures sleepiness on a rating scale with nine points, from 1 ("Very alert") up to 9 ("Very sleepy, fighting sleep"), and participants had to rate their sleepiness level considering how they felt at that moment. At the end of the session, each subject was asked how asleep they felt, without reminding them, what they had said before stimulation. Vigilance was tested with a Simple Reaction Time test before and after each session (Johnson et al., 1985). The test was administered by the subjects via a smartphone, through the PsychLab 101 platform (Leibo et al., 2018). SRT consists of 4 blocks of 2 minutes each. The target stimulus was represented by the letter A appearing in the center of the screen (inter-stimulus interval range between 1000-2000 ms), for a total of 8 minutes. The participant needed to touch the screen as soon as the target stimulus appeared.

Statistical Analysis. Behavioral data from the experimental sessions have been compared by repeated-measures ANOVA with Time (Pre vs. Post-Stimulation) × Condition (Baseline vs. Sham vs. Beta vs. Theta). When the ANOVA was significant we then continued with post-hoc analysis by performing the Tukey HSD test. This analysis was performed to investigate differences in self-reported sleepiness measured by KSS and the average time required to respond to stimuli in the Simple Reaction Time. To investigate differences in drowsiness and vigilance during the task, we took into consideration the average response time to auditory stimuli divided into 3 blocks (1^{st} block: stimuli from 1^{st} to 50^{th}; 2^{nd} block: 51^{st} stimulus to 100^{th}; 3^{rd} block: 101^{st} stimulus to 150^{th}). To compare different conditions, we performed repeated-measures ANOVA with Time (average response time in Block 1 vs. Block 2 vs. Block 3) × Condition (Baseline vs. Sham vs. Beta vs. Theta). To underline changes in drowsiness specifically induced by the stimulation, we then performed the post-hoc analysis with the Tukey HSD test.

6.1.2. Results

Feasibility. No participants reported any side effects, aside from a short moment of discomfort due to tingling and/or itchiness at the beginning of active stimulation (i.e. ramp-up, 30 seconds). 9 out of 14 participants spontaneously reported being more sleepy and relaxed after the theta stimulation. On the other side, 7 subjects out of 14 spontaneously revealed to be more impatient and activated after the session with beta stimulation. All subjects were blinded to the stimulation.

Post-stimulation changes in self-reported sleepiness and vigilance. Statistical analysis showed a significant increase in self-reported sleepiness, assessed by KSS, after active theta-tACS compared to beta and sham stimulation and baseline (Figure 31, panel A). Specifically, repeated measure ANOVA on KSS changes pre and post-stimulation reported a significant interaction of Condition and Time [$F(1,27) = 4.29$, $p = 0.0019$]. The post-hoc Tukey HSD test showed that only theta-stimulation induced a significant increase in self-reported sleepiness ($p = 0.0001$; other conditions: p-values > 0.05).

We then investigated differences in vigilance as assessed by SRT pre and post-task (Figure 31, panel B). Repeated measure ANOVA on changes in SRT response time did not show any significant difference in the interaction of Condition and Time (all p-values > 0.05). Even if the vigilance assessment failed to reach statistical significance, our finding showed that participants required a longer time (measured in msec) to answer to the stimuli post-theta stimulation.

Drowsiness and vigilance during the task. Repeated measure ANOVA performed on average response time to the auditory stimuli during the 20-minute task did not show any significant effect of Condition and Time although the p-value indicated a trend to significance [$p = 0.09$]. Upon visual inspection, we decided to perform the post-hoc test on the effect of interaction Condition and Time as an exploratory analysis (Figure 31, panel C). The post-hoc Tukey HSD test showed that only theta-stimulation induced a significant increase in response time to the auditory stimuli (comparison between Block 1 vs. Block 3: $p = 0.0003$; other conditions: p-values > 0.05).

The post-hoc Tukey HSD test also showed that the average response time during the first block was not significantly different comparing all conditions.

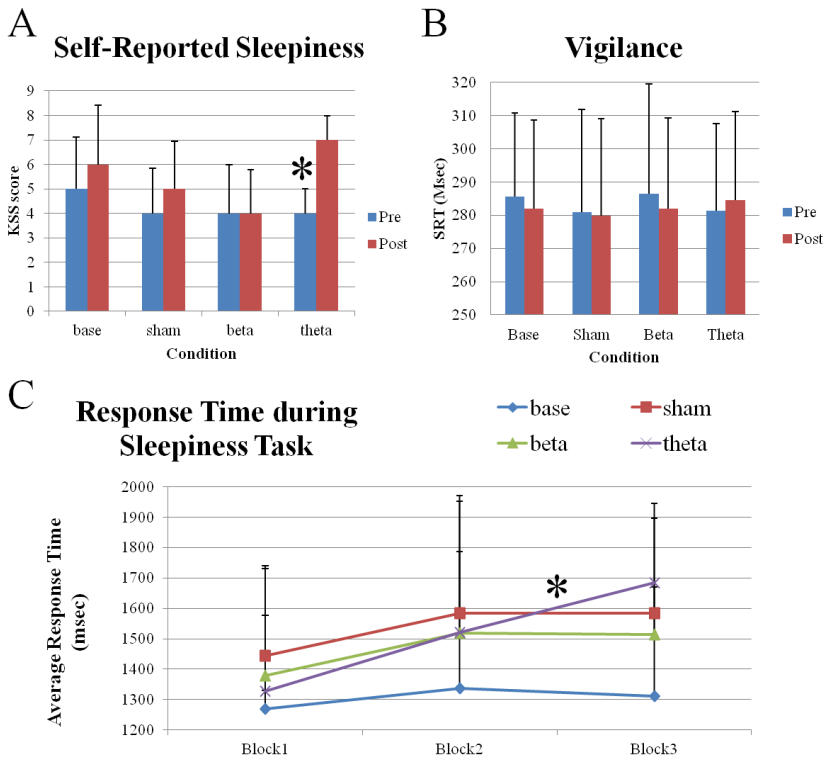


Figure 31. Behavioral results. The figure reports changes in behavioral data induced by tACS. **Panel A** shows pre and post-task scores in self-reported sleepiness as assessed by Karolinska Sleepiness Scale (KSS). Theta stimulation induced a significant increase in sleepiness comparing pre and post-task. The task alone (baseline) and within the sham condition induced increased non-significant sleepiness, whereas beta stimulation did not modulate sleepiness. **Panel B** reports the vigilance as assessed with the Simple Reaction Time. The graph shows modifications in average response time (assessed in msec). Although our findings did not show any significant effect of the condition on vigilance, raw scores indicate that theta stimulation is the only condition that induces a longer time required to answer to the stimuli post-task compared to pre-task. In **Panel C** we report the results collected during the sleepiness task, as measured in average response time to answer to auditory stimuli. Theta stimulation induces a longer response time during the task, compared to other conditions.

6.1.3. Discussion

In the current study we investigated how tACS could induce sleepiness in healthy young adults. Our results confirmed and expanded on previous evidence from the literature, showing theta tACS induces highly significant post-stimulation sleepiness at self-report measures such as the KSS, with no effects for stimulation in other frequency bands. Reaction times recorded for each stimulus during the task also showed a significant trend for increased drowsiness after 6Hz tACS.

This evidence confirmed the results of previous literature showing the success of tACS in promoting the EEG pattern distinctive of the wake-sleep transition, enhancing sleep propensity. The first explorative study testing this paradigm delivered different frequencies (0.8 Hz, 5 Hz) and polarities (anodal, cathodal, sham) in frontal

areas during resting wakefulness collecting sleepiness and EEG (Atri et al., 2016). The study confirmed the higher efficacy of the theta stimulation compared to the 0.8 Hz stimulation in increasing both theta and slow cortical oscillations, paralleled with a small enhancement of subjective sleepiness (Atri et al., 2016). However, the magnitude of the local effect was substantially small, raising doubts of the true efficacy of tES in inducing objective sleepiness. A second study from the same group showed that 5Hz-tACS with bilateral montage actively promote the synchronization process at sleep-onset before the cortex (Magnin et al., 2010; Sarasso et al., 2014), facilitating sleep propensity. Compared to the sham condition, 5-Hz tACS induced a posterior increase of theta activity, an EEG biomarker typical of drowsiness (Marzano et al., 2013). Unfortunately, no changes were found in subjective sleepiness (D'Atri et al., 2017), confusing the interpretation. No causal relation between sleepiness-associated electrophysiological pattern and subjective sleepiness was observed. Going further, the same group also tested the effect of theta-tACS on a following nap (D'Atri et al., 2019). Again, the direct comparison between active and sham conditions showed no differences in subjective sleepiness. The authors therefore categorized the cohort of participants in nonresponders and responders, subjects that actually exhibited a stimulation-dependent modulation of the EEG activity during wakefulness (i.e. an increase of theta activity during wakefulness after the active theta stimulation). Responders reported an enhancement of drowsiness following the stimulation (D'Atri et al., 2019). It is not clear what discriminates responders from non-responders since the baseline EEG did not show between-group differences (D'Atri et al., 2019). Even more, the small number of responders raises some doubts on the generalizability of the results. In this framework, our study could provide a step further in succesfully applying tACS to induce sleepiness in all participants, instead of a small sub-group of responders.

A partial explanation of the successful results of this study might lie in the new approach to optimize montage to target sub-cortical sleep-induction regions. Circadian rhythms and sleep induction are indeed regulated by a complicated network within the brain stem and hypothalamic nuclei, which is also affected by age on many levels (for a comprehensive review Rolls, 2012). Simplifying this intricate interrelationship the wake-promoting lateral hypothalamic area (LHA) and locus coeruleus (LC) help to maintain stable periods of wakefulness, while the preoptic area (POA) modulates LHA and LC function, sending inhibitory input to initiate and maintain sleep (Saper et al., 2010). The hypothalamic suprachiasmatic nucleus (SCN) is the endogenous clock promoting wakefulness during the day and permitting sleep (Mander et al., 2016; Wang et al., 2015). Age-related neuronal loss strikes these nuclei differently, disrupting the balance of sleep and wakefulness. The SCN age-related modifications involve alterations in neuronal network function, membrane properties, and modifications of components in cellular nuclei (for a complete review see Farajnia et al., 2014). Examinations post-mortem showed a decrement in SCN volume and cell number in the elderly (Swaab et al., 1985; Zhou, 1995). Specific neuronal subpopulations are particularly affected by this shrinking, including those expressing vasoactive intestinal peptide (VIP), receiving direct light input from the retina, and maintaining synchronicity between endogenous rhythms and the external light-dark cycle (Farajnia et al., 2014). Loss of VIP-ergic neurons

would lead to a lower influence from light to internal rhythms, leading to reduced circadian control from SCN (Wang et al., 2015), and therefore advanced phase shift, greater nighttime movements, and an increased number of awakenings. Impairment in SCN function also reflects a desynchronized melatonin secretion cycle. What makes the SCN so crucial in regulating circadian rhythms is that it contains neurons that present a circadian model of activity and regulate the secretion of melatonin by the pineal gland (PG) as a response to the light/dark environmental cycle (Benarroch, 2008a). This evidence provides a rationale for the alteration of circadian rhythms. Melatonin cyclical concentrations are indeed controlled by the SCN via a multisynaptic pathway (for a comprehensive review see Benarroch, 2008). The peak in endogenous melatonin is 2 hours before habitual bedtime and is correlated with the onset of evening sleepiness. The aging process attenuates melatonin secretion at night in older individuals, while diurnal secretion is similar in elderly and young subjects (Cooke and Ancoli-Israel, 2011; Copinschi and Caufriez, 2013; Münch et al., 2005). Its overnight decrement is linked to nocturnal light exposure in the elderly, mediated by the SNC. Light exposure during the night results in a dose-dependent suppression of melatonin secretion (Benarroch, 2008b). By contrast, insufficient daytime light exposure, often seen in the elderly due to social isolation and staying home-bound, elicits a desynchronization of the melatonin secretion cycle (Mishima et al., 2001), concurrent with a shift in the sleep-wake cycle. On the other side, the POA is formed by cells expressing inhibitory neuropeptide galanin (Saper et al., 2010), which undergoes a significant decline in aging. This results in abnormalities in overnight sleep consolidation. The degree of cell loss in the POA predicts the severity of sleep fragmentation and longer sleep-onset latency in older adults (Lim et al., 2014).

By targeting the functional connectivity maps of these three sub-cortical structures responsible for sleep induction, we were able to successfully manipulate sleepiness without categorizing them in responders and non-responders, a limitation seen in previous studies. This allows us to take a step further in applying tACS in sleep-induction paradigms and test this intervention in all subjects that would benefit from it (e.g. elderly at risk of developing MCI/AD, patients with a diagnosis of insomnia).

SIGNIFICANCE.

Our preliminary findings suggested the feasibility and success of theta-tACS with an optimized montage to induce sleepiness and potentially shorten sleep onset latency. We are now looking for testing this protocol on elderly at risk to develop AD (beta-amyloid positive or preclinical) and patients with a current diagnosis of MCI/AD.

6.2 Second Study: Improve Linguistic Skills with Repetitive TMS in Patients with Dementia.

A similar version of the present article has been published [Neri F **& Romanella SM***, Monti L, Santarnecchi E, Rossi S. *"Repetitive TMS Improves Verbal Fluency in a Patient with Primary Progressive Aphasia-Logopenic Variant (LPPA)"* **Clin Neurophysiol.** 2021 Jul 28;132(10):2481-2484. doi: 10.1016/j.clinph.2021.07.017. These authors contributed equally to the study.

As mentioned in Chapter 1, logopenic Primary Progressive Aphasia (lvPPA) is a rare neurodegenerative disorder characterized by a progressive deterioration of linguistic abilities (Marshall et al., 2018) with an estimated worldwide prevalence of 3/100,000 individuals (Grossman, 2010). In the beginning, the disease is associated with semantic and phonological paraphasia, isolated anomia, slow speech rate, phonological loop dysfunction, and frequent word-finding pauses. Difficulties in single-word retrieval and sentence repetition seem to be primarily due to phonologic short-term memory deficits (Gorno-Tempini et al., 2011). In fact, along with linguistic difficulties, symptoms include a disruption in short-term and working memory, associated with repetition impairments (Magnin et al., 2013; Butts et al., 2015). The progression of the symptoms is associated with a typical neurodegenerative pattern. LvPPA is characterized by perisylvian brain atrophy, particularly marked in left dominant temporoparietal distribution, as emphasized in many structural and metabolic neuroimaging studies (Gorno-Tempini et al., 2008; Rabinovici et al., 2008; Rohrer et al., 2009). Modifications in the white matter within the left superior longitudinal fasciculus and the arcuate fasciculus have also been reported along with the unavoidable progressive worsening of the symptoms (Galantucci et al., 2011).

No effective pharmacotherapy exists, and only supportive speech therapy (ST) is partially efficient to treat lvPPA and slow down the neurodegenerative process (Beeson et al., 2011), which cannot be halted. In the last decade, previous case reports suggested rTMS as a therapeutic approach to improve cognitive functions in patients with neurodegenerative diseases, such as AD (Cotelli et al., 2006b; Trebbastoni et al., 2013). The biological abnormalities in lvPPA may be similar to those of AD patients (Hu et al., 2010; Mesulam et al., 2008), thus opening an interesting link between the two disorders. Whole-brain post-mortem examinations confirm that alteration of Aβ amyloidosis, Tau, and p-tau is frequently present in patients with lvPPA (Rabinovici et al., 2008; Santangelo et al., 2014). Several clinical trials have tested different rTMS protocols for cognitive improvement in AD patients with encouraging results (Cotelli et al., 2008, 2006, 2012; Devi et al., 2014; Eliasova et al., 2014; Koch et al., 2018), especially regarding the enhancement of linguistic skills when the rTMS targets the left prefrontal cortex, as a reported improvement on naming (Cotelli et al., 2008, 2006a) and auditory sentence comprehension (Cotelli et al., 2011) in AD patients.

The first study of rTMS on a patient with PPA was with a patient diagnosed with the agrammatic variant of PPA. After only two rTMS treatments over the left prefrontal cortex, the authors reported a significant and lasting improvement in the patient's performance on verbs production (Finocchiaro et al., 2006). To date, rTMS was applied only in two cases of patients with a specific diagnosis of a lvPPA (Trebbastoni et al., 2013; Bereau et al., 2016). Trebbastoni and colleagues (2013) were the first to evaluate the effects of high-frequency (20 Hz)

rTMS over the left dorsolateral prefrontal cortex (dlPFC) in one patient with lvPPA. The patient underwent four stimulation sessions (two real and two sham conditions) combined with ST: after the active stimulation only, the patient showed a transient -one week- improvement in verbal phonetic fluency and writing language skills (Trebbastoni et al., 2013). Bereau and coworkers (2016) performed a similar rTMS protocol (same frequency and target) on another patient. The results showed an improvement in cognitive and language functions and a return to a non-pathological Mini-Mental State Examination score (MMSE) and verbal memory. The cerebral perfusion increased after treatment at the site of stimulation and was maintained at the one-month follow-up. Three months after the end of the treatment, the patient also maintained good verbal fluency with no paraphasia (Bereau et al., 2016). These findings suggest that rTMS may be an alternative therapeutic tool to slow down or transiently improve speech abilities in neurodegenerative forms of aphasia.

The neurophysiological mechanisms of these outcomes have yet to be investigated. Authors suggested that the direct activation of linguistic-associated areas by rTMS would increase synaptic plasticity and therefore lead to a facilitation of the frontotemporal network for language (Bereau et al., 2016). The clinical result may also rely on the association of rTMS with ST, thanks to a mutual potentiation of the two therapies. However, other authors suggested an elicitation of alternative functioning pathways of the language network. A single study investigating functional connectivity changes in PPA patients induced by neuromodulation of the left IFG, conducted with anodal transcranial direct current stimulation for three weeks, and showing a decrease in functional connectivity between the targeted region and posterior areas belonging to the language network (Ficek et al., 2018).

In this theoretical framework, rTMS could therefore compensate and partially restore functional plasticity within directly stimulated sites and interconnected brain areas. The language network includes numerous brain sites that are functionally related to productive and comprehensive linguistic abilities. A recent meta-analysis (Walenksi et al., 2019) found significant activation of brain regions in the left hemisphere, thus creating this language network during comprehensive and productive linguistic tasks. These brain sites include the inferior frontal gyrus (IFG), the insula, the medial temporal gyrus, the temporal pole, the precentral gyrus, the supplemental motor area, superior frontal gyrus. In the right hemisphere, the authors also showed some activated areas such as the temporal lobe and medial temporal gyrus. Beyond these cortical areas, specific cerebellum sites, such as the right crus II, seem to be usually recruited during a linguistic task and may be part of the large-scale language network (Starowics-Filip et al., 2017).

We attempted to stimulate high-frequency rTMS in the Broca's area in two patients with lvPPA, coupling the rTMS intervention with or without ST in two different cycles of treatment. The Broca's area was chosen as a target because in lvPPA it is spared by the neurodegenerative process, which mainly affects the temporoparietal junction (Sanches et al. 2021). Our aim was twofold: i) to investigate whether the stimulation of a still preserved hub within the language network, combined with ST, was effective in improving verbal performance, and ii) to disclose neural correlates in terms of functional connectivity of the eventual language improvement.

6.2.1. Methods

Procedure. Two right-handed male patients were recruited according to the criteria: having a diagnosis of lvPPA and a minimum score of 20 in the MMSE. At the first cycle of rTMS intervention, patient n.1 was 70yo, had a corrected MMSE score of 25, and performed ST once a week before and after the end of rTMS treatment, whereas, patient n.2 was 80yo, had a corrected MMSE score of 12 without any ST neither before nor after the rTMS intervention. Unfortunately, only patient n.1 participated in the second cycle of stimulation. Patient n.2 was unable to participate due to a worsening of his general health condition. Patient n.1 had an MMSE of 17 at the beginning of the second cycle. The study was previously approved by the Local Ethical Committee, and both patients signed the informed consent with information about the safety, common side effect, and potential benefits of an rTMS treatment. We only included patients that did not report epileptic seizures, the presence of a pacemaker, or other causes that would have fallen in the exclusion criteria (Rossi et al. 2021). For both cycles, Patients underwent a neuropsychological assessment with a focus on linguistic abilities and functional magnetic resonance imaging (fMRI) scans at T0 (before the treatment), at T1 (at the end of the treatment), and T2 (one-month follow-up).

rTMS Treatment. In the first cycle, both patients underwent 10 daily rTMS sessions lasting 20 min each. rTMS was administered with an air-cooling figure-of-eight coil, angled tangentially to the head, with the device STM9000 (Ates-EBNeuro). The stimulation site was real-time guided with a neuro-navigation system (BrainNET, EBneuro Ltd, Florence, Italy), targeting the anatomical localization of the left Broca's Area situated between the pars angular and pars triangularis of the Inferior Frontal Gyrus (IFG) (BA 44 and 45 respectively). Exact localization was found with the patient's structural image. Stimulation frequency was set at 10 Hz, in trains of 5s with an inter-stimulus interval (ISI) of 25s. In each session, a total of 2000 pulses at 100% intensity of the individual resting motor threshold (RMT) for the right first dorsal interosseous (FDI) were delivered. During the entire procedure patients and experimenters wore earplugs. The patients were asked to remain with their eyes open and not to fall asleep throughout the stimulation session. RMT measurement was used to set stimulation intensity before each visit, by using a device for electromyography (EMG) recording triggered by the TMS pulses (EEG NeMus 2, EBneuro Ltd, Florence, Italy). According to guidelines (Rossi et al., 2009, 2021), RMT was definite for the left primary motor cortex (M1) "hot spot", of the scalp where single TMS stimuli were able to evoke motor responses of ~50 μV in FDI muscle in at least 5 out to 10 trials. The muscular activity was recorded with the active electrodes positioned over the FDI muscle and the reference placed on the metacarpophalangeal joint of the index finger, while the ground electrode was positioned on the wrist. To evoke consistent responses, the coil was handled tangentially to the scalp and approximately at 45° respect to the midline inducing a flow of current directed from the back to the front of the scalp. Immediately after each rTMS session, patients underwent one-hour individualized ST with a speech therapist (see Supplemental Material for further details). After one year after the end of the treatment, patient n.1 was enrolled to undergo a second cycle

of rTMS, with the same design as the previous treatment, except for ST and MRI scans. Verbal interaction with the patient was minimized both before and after rTMS intervention, to verify a pure effect of the TMS on the linguistic abilities.

Linguistic Abilities Assessment. The neuropsychological tests that have been used to investigate specific productive and receptive aspects of patients' linguistic abilities were performed in Italian. In particular, common or less familiar visual object naming has been evaluated through the administration of the Italian Version of *Boston Naming Test (BNT)* (Kaplan et al 1983); *Token Test* (De Renzi, 1978) has been used to examine patients' auditory comprehension. The *Phonemic and Semantic Fluency Tests* were administered in order to evaluate the ability to access to the mental lexicon storage and the *Forward Digit Span Test* to assess verbal short-term memory skill. Specific subtests of Battery for the Analysis of Aphasic Deficit (BADA, Italian version: *Batteria per l'Analisi dei Deficit Afasici, Miceli, 1994*) were used to evaluate the linguistic abilities as the phonemes discrimination (*Acoustic Phonemic Discrimination Subtest*), visually naming of verbs and actions (*Verbs Naming Subtest*), auditory comprehension (*Grammar Understanding Subtest*), the production of phrases with a correct structure (*Oral Description of Images Subtest*), as well as the patients' transcoding skills throught the administration of these subtests: Repetition of *Words, No-Words and Sentences Words Writing, Words Delayed Writing, Words Reading and Sentences Reading.*

Percentages of improvement were calculated by dividing the difference in the score post- minus pre-, divided by the score at baseline (e.g., (T1-T0)/T0*100). A positive number meant that performance has been improved. A score differing at least 20% was considered representative of a significant change between evaluations.

MRI Data acquisition. The neuroimage acquisition was conducted on a Siemens Avanto Syngo VB17 scanner with a 12-channel head-coil (Siemens Medical Solutions, Erlangen, Germany). High-resolution T1-weighted axial images covering the whole brain were obtained using an 3D-MPRAGE sequence (TR = 1880ms, TE = 3.38ms, TI = 1100ms, flip angle (FA) = 15°, number of slices = 176, thickness = 1mm, gap = 0mm, imaging matrix = 256 × 256, acquisition duration: 5 minutes). Functional MRI images were acquire using standard echo-planar imaging (EPI) resting state (TR = 2000ms, TE = 20 ms, FA = 70°, number of slices = 37, thickness = 3.59mm, gap = 4.64mm, imaging matrix = 448 x 448, acquisition duration: 8' and36''). Subjects were instructed not to focus their thoughts on any particular topic, to do not cross their arms or legs and to keep their eyes open for the whole scanning session.

fMRI Data Preprocessing and Analysis.fMRI data preprocessing and statistical analyses were carried out using SPM12 software (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm/) and MATLAB 2013b (MathWorks, MA, USA). BOLD images underwent the following preprocessing steps: (i) discarding of the first three volumes to allow for steady-state magnetization and stabilization of participant status; (ii) slice timing correction using interval ascending acquisition criteria; (iii) realigning and reslicing to correct for head motion using an overall mean functional volume; (iv) co-registration with the T1-weighted structural images; (v) segmentation; (vi) nonlinear normalization to the Montreal Neurological Institute template brain; (vii) smoothing

with an isotropic Gaussian kernel (full-width at half maximum, 8 mm). To obtain a more accurate spatial normalization, the SPM8 DARTEL (diffeomorphic anatomical registration through exponentiated lie) module was applied, creating a customized grey matter template from all subjects' segmented images. Briefly, this approach is based on the creation of a customized anatomical template built directly from participants' T1-weighted images instead of the canonical one provided by SPM (MNI template, ICBM 152, Montreal Neurological Institute). This allows a finer normalization into standard space and consequently avoids under- or over-estimation of brain regions volume possibly induced by the adoption of an external template. A nonlinear normalization procedure with subsequent affine-only normalization to the Montreal Neurological Institute (MNI) template brain, and voxel resampling to an isotropic 3 × 3 × 3 mm voxel size, were then applied to functional images. Linear trends were removed to reduce the influence of the rising temperature of the MRI scanner and all functional volumes were bandpass-filtered at 0.01 Hz < f < 0.08 Hz to reduce low-frequency drifts. Resting-state functional connectivity (rsFC) change was evaluated between time points using the anatomic atlas CONN functional connectivity toolbox v.17f (www.nitrc.org/projects/conn, RRID:SCR_009550; Whitfield & Castanon, 2012) and MATLAB 2013 (Mathworks, MA, USA). A ROI-to-ROI analysis with a False Discovery Rate correction (p<.05; FDR; Benjamini and Hochberg, 1995) was conducted, and rsFC was calculated using the Pearson bi-variate coefficient between scanning sessions. Primarily, we were interested in verifying rsFC change between the TMS target area (reference ROIs: left IFG, specifically pars triangularis and pars opercularis) and the rest of the atlas ROIs.

6.2.2. Results

Safety and feasibility. The entire rTMS procedure and pre-post assessments were well tolerated by the patients and no side effects were reported, with exception of slight numbness of the skin area below the stimulation and occasional activation of ipsilateral face muscles.

Linguistic Abilities. Patient 1 showed improvement in a wide range of linguistic skills at the end of the treatment, which partially persisted for one month (see figure 32). At T1, the performance was higher than T0 in the following tests: the *BNT***,** the *Sentences Repetition*, the *Oral Description of Images*, the *Sentences Reading*, the *Phonemic Fluency*, the *Semantic Fluency*, and the *Forward Digit Span*. At T2 patient showed a better performance than T0 in the *BNT*, *Sentences Repetition*, *Oral Description of Images*, *Sentences Reading*, Phonemic Fluency, *Semantic Fluency*, and *Token Test.* Patient 2 had a higher performance at T1 in the *BNT*, the *Words Repetition*, *Verbs Naming*, *Grammar Understanding*, *Oral Description of Images*, *Words Reading*, *Phonemic Fluency*, *Semantic Fluency*, the *Forward Digit Span*. At T2 the patient still maintained a significantly higher performance in *Words Repetition*, *Verbs Naming*, *Grammar Understanding*, *Phonemic Fluency*, and *Semantic Fluency.* After the second cycle of rTMS treatment, patient 1 showed a significant improvement in *the BNT test*, with a reduction of no responses, misperceptions, semantic errors, and phonological errors. Moreover,

a higher score in the *Words Reading* and the *Words Writing* tests were also observed. The *Phonemic Fluency* was improved immediately after the end of the treatment. At T1, the patient showed the worst performance in the *Verbs Naming* and the *Grammar Understanding* tests.

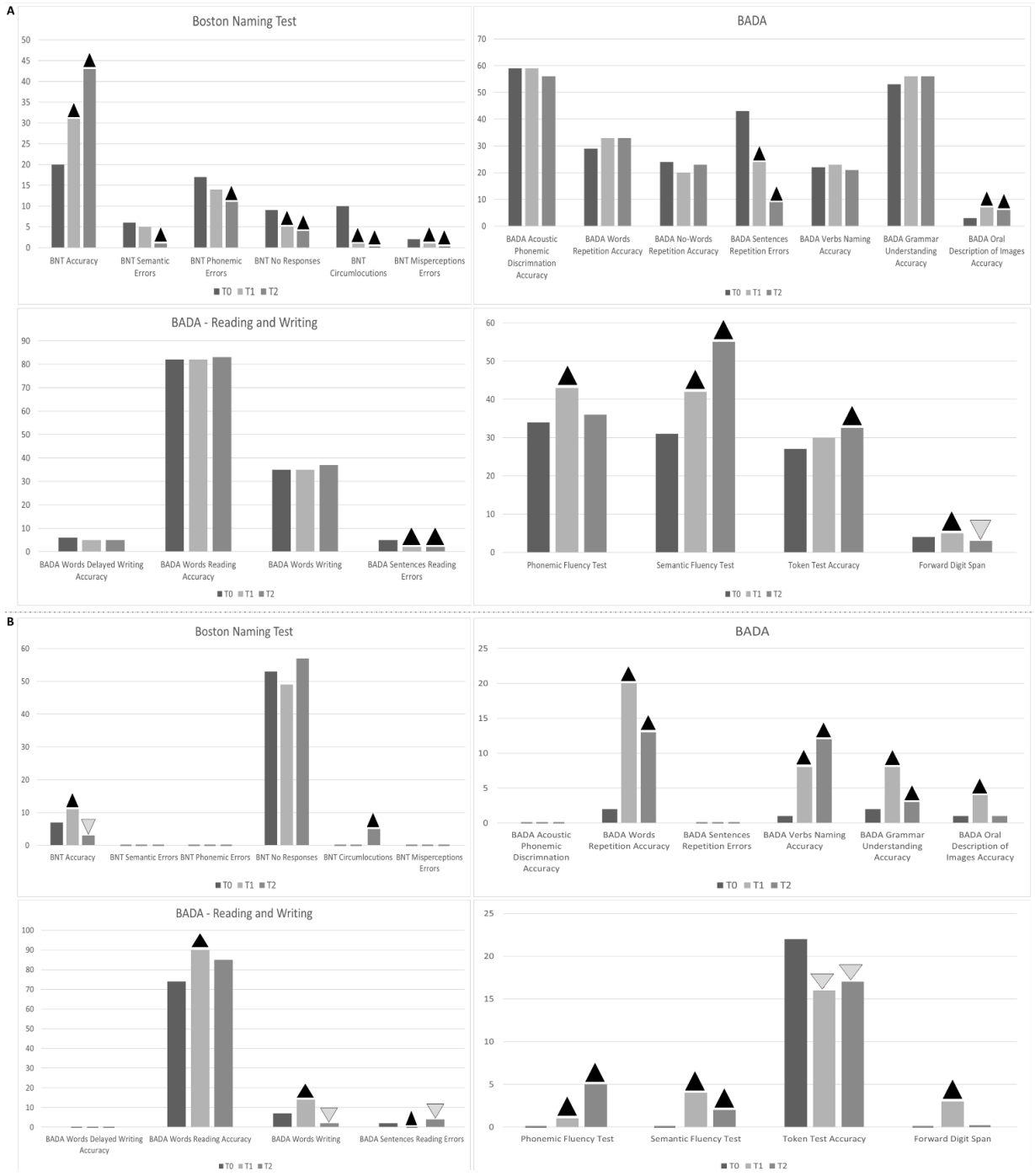


Figure 32. Results of Linguistic Performance after the 1st clycle of rTMS. lvPPA patient 1 **(Panel A)** and patient 2 **(Panel B)** at T0, T1, and T2**.** Asterisk: comparison between T1 or T2 and T0.▲ : improved performance from T0.▽ : decreased performance from T0.

Neuroimaging Results. Comparing T0 with T1, the ROI-to-ROI analysis (see Figure 33) revealed an increase of rsFC between the left IFG/pars opercularis and the right cerebellum/Crus II at the end of the treatment in both subjects (two-sided; p <.05 FDR; p< .05; FWE cluster level; see Figure 33-A). This interaction was not significant comparing T0 with T2 and looking at the rsFC value of these ROIs between sessions, an opposite pattern was highlighted in the two participants: in the patient 1, the rsFC at T2 was unchanged from T1, while in the patient 2 the connectivity strength between ROIs drop off from T0. (Figure 33-B). Moreover, comparing T1 with T0, significant rsFC increase between the left lateral occipital complex (LOC) with the right Putamen and between the Left Cerebellum 2 with the Brain Stem was detected at T1 (Figure 33-C). No significant interaction was detected at the follow-up evaluation.

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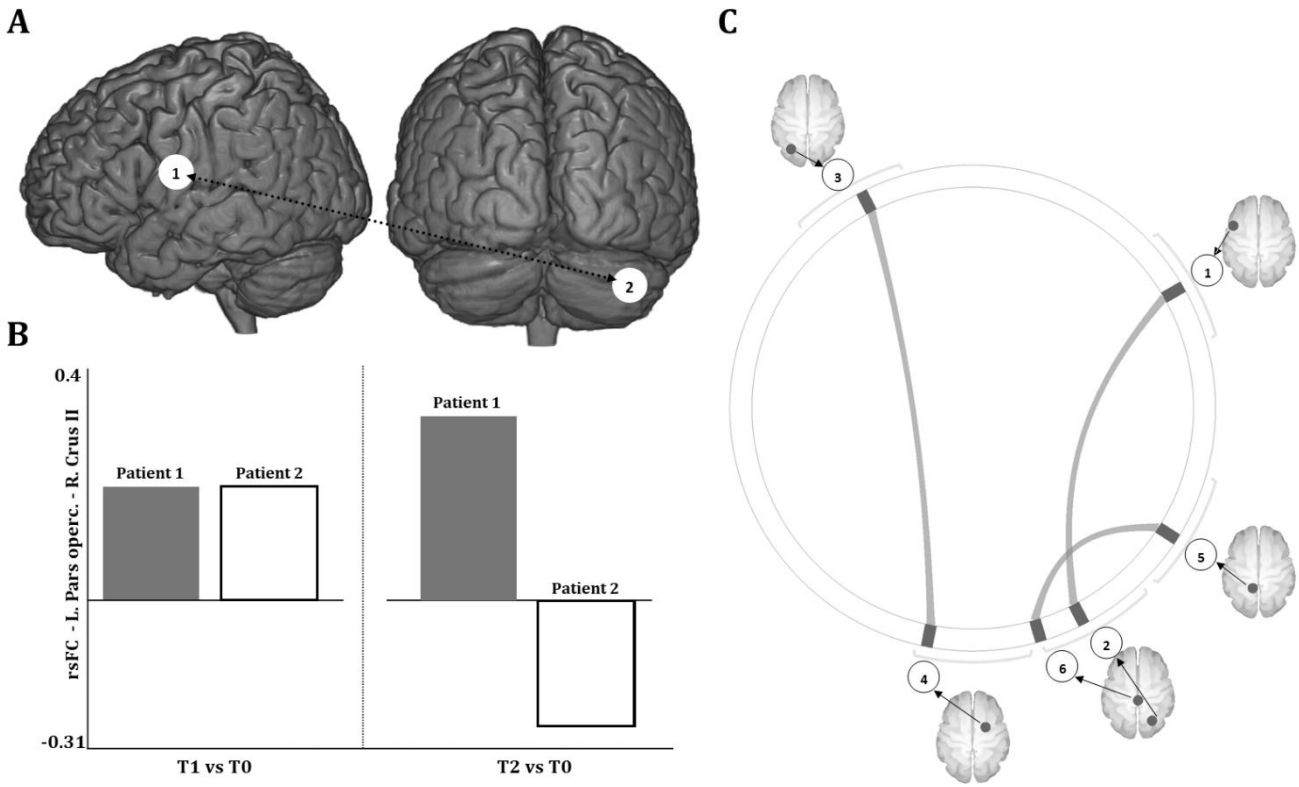


Figure 33. rsFC patterns within the Language Network. In the ROI-to-ROI analysis. a significant rsFC change between the of left IFG (pars opercularis) (1) and the right cerebellum (Crus II) (2) was detected comparing T1 with T0 **(Panel A)**. Both patients showed a similar augmentation of the rsFC value at T1 and an opposite pattern at T2 **(Panel B)**. Moreover, an increased connectivity was observed (**Panel C**) for: the left LOC (3) with the right Putamen (4) and the Left Cereb2 (5) with the Brain Stem (6)

6.2.3. Discussion

We administered 10 consecutive sessions of excitatory rTMS associated with ST to two patients with lvPPA testing differences in linguistic performance and changes in neural correlates with fMRI. This pilot study proved that rTMS of Broca's area, a language network hub generally spared by the neurodegeneration in the lvPPA

(Sanches et al. 2021), can be a noninvasive and efficient treatment for lvPPA. Moreover, the outcome demonstrates that the association between rTMS and ST might improve patients' language abilities, though it seems that rTMS alone can still bring short- and long-term cognitive benefits.

After the first cycle of rTMS; both patients benefited from the stimulation treatment, with significant common acute improvements in the objects naming, in the ability to describe images with a fluent and correct sentence, in the sentences reading skill, in the semantic and phonological fluency and in the verbal short-term span. The first patient also showed a significant improvement in word repetition, verbal naming, verbal comprehension, and word reading and writing. The data at the one-month follow-up, on the other hand, showed differences in the two participants. Patient 1 maintained the improvement in semantic fluency, naming objects, repetition, and reading of sentences, and in the description of images; compared to the data at the post he also reported a further reduction of phonemic and semantic errors, non-answers, circumlocutions. Patient 2, on the other hand, after an improvement following the treatment, showed a drop in performance at the follow-up. He maintained a significant increase in scores in phonological and semantic fluency, word repetition, the denomination of verbs, and verbal comprehension, but a worsening in the description of images, reading and writing, and object naming. The discrepancy between the two patients in the second follow-up data could result from a more severe clinical condition in patient 2 at enrolment and/or to differences in individual neuropathological progression. The tendency for patient 2 to return to the baseline performance after a month of wash-out may be explained by an individual faster progression of cortical dementia and personal environment differences. Patient 1 started from a less disintegrated linguistic ability and a more preserved general cognition. He was already following ST once a week that he maintained also after the rTMS treatment. Differently, patient 2 presented with almost any communication skill and an MMSE of 12 at the time of the first cycle of rTMS, indicating a very compromised cognitive situation. He stopped the ST right after the end of the rTMS cycle. Therefore, a worse prognostic and neurodegenerative disease trend could explain the difference between T2 and T1, and why improvement in linguistic skills has been only partially maintained.

It is worth noting that the continuative ST performed one a week before the rTMS intervention did not lead to significant improvements in none of the patients. Therefore, the 10-day rTMS intervention, coupled with intensive ST, was overall successful in improving linguistic abilities. However, treatment by means of TMS alone could be effective in bringing benefits to the linguistic skills. The preliminary results obtained in patient n.1, who had significantly worsened baseline compared to the previous year, showed that naming, verbal fluency, writing and reading skills increase after the rTMS, without the reinforce of ST. Previous studies using rTMS in lvPPA neither have targeted the Broca’s area nor have coupled rTMS with ST nor have used neuroimaging to investigate functional connectivity changes after this intervention. The target of left IFG is in fact well known for its pivotal role in the language production (Sahin et al., 2009) and comprehension processes (Rogalsky and Hickok, 2011). IFG corresponds to the BA 45, mainly involved in semantic processes, while BA 44 has a role in syntactic structure building (Friederici, 2011). A reduced cortical

thickness of IFG correlated to word fluency impairment and grammatical processing in sentence production (Rogalski et al., 2011). Left IFG has also been the preferential target in experimental paradigms administering transcranial direct current stimulation (tDCS), another method of NIBS, in cohort of patients affected by lv-PPA (see Sanches et al., 2021 for a detailed review of these studies). As an example, Tsapkini and colleagues (2014) and colleagues (2014), tested a mixed population of logopenic and agrammatic PPA patients stimulated with anodal current on the left IFG and reported lasting improvements in spelling for up to two months. In case of tDCS paradigms targeting language skills the stimulation is always combined with online oral naming and written spelling tasks, showing a more specificity in the improvements of language abilities than rTMS protocols.

Our goal was not only investigating the neuroimaging changes associated to TMS but also look for modifications in functional connectivity (FC) within the language network. Previous tDCS studies used fMRI to investigate if tDCS-induced language improvements could be explained by changes in FC. Ficek et al. (2018) showed a significantly lowered functional connectivity between the left IFG and other language network areas following the stimulation, also correlated with the language improvements. Interestingly, our analysis, even with methodological limitations due the small sample size, revealed a significant change of FC, but involving the cerebellum. Specifically, after the entire protocols we saw differences in the connectivity between the right cerebellum and left IFG. Each cerebral hemisphere receives and sends information to the contralateral hemisphere of the cerebellar cortex (Keser et al., 2015). The cerebellum is indeed a crucial brain structure that is recruited to regulate motor functions such as visuomotor coordination, maintenance of muscle tone, but the fact that it is also involved in higher cognitive functions, as the language, is not new (Leiner et al., 1993), though it was ascribed to be mostly recruited during the motor aspect of the linguistic function. Indeed, some evidences on ataxic dysarthria linked the role of the cerebellum in the articulatory control (Spencer and Slocomb, 2007). Specifically, verbal fluency task during fMRI, detected a coherent and simultaneous brain activation of the left frontoparietal cortex and in the right cerebellum (Schlösser et al., 1998) and different functional connections between the cerebellum and IFG including the Broca's area have been identified in humans (Sundermann and Pfleiderer, 2012) Moreover, by means of advanced tractography analysis, anatomical brain pathways between cerebellar and cortical areas have been revealed. Therefore, the cerebellum has also been suggested as being an active and relevant part within the functional language network (Shirer, 2012). In healthy subjects, the linguistic comprehension, production, and trans-coding are determined by consistent and timed activations between anterior/posterior cerebral structures and cerebro-cerebellar areas, communicating through both functional and anatomical networks (Starowicz-Filip et al., 2017). To further this framework, verbal fluency deficits and decreased naming recall performance have been observed in patients with cerebellum degeneration (Leggio et al., 2000; Stoodley and Schmahmann, 2009). Applying rTMS on the Crus II of the right cerebellum during a verbal fluency task, a decrease in performance in the task was detected (Arasanz et al., 2012). Just a single session of rTMS is capable of producing long-term modifications of synaptic connections (Esser et al., 2006).

In our study, a significant increase of rsFC between the left IFG and the Crus II of the right cerebellum has been demonstrated immediately after the end of the treatment. A month after, a substantial difference of rsFC pattern was observed in the two participants. The left IFG-right Crus II rsFC value of the Patient 1 was unchanged, while the patient 2 pattern was lower than the baseline. The explanation of this discrepancy follows the one advanced in the discussion section regarding the cognitive assessment, where two participants had a trend similar to that observed in the rSFC analysis: at T1 the two participants obtained better results in several linguistic tasks, compared to the baseline and the differences between the two patients were underlined at the follow-up assessement, with the participant 1 getting a performance similar to the post-assessment and the second person having a clear drop of performance. The plausible hypothesis seems to be ascribed to the gravity of the clinical disease at baseline. The excitatory stimulation of the area that the pathology has left partially preserved (the anterior area of Broca) may have activated a secondary linguistic pathway of the patients by enhancing the connectivity between the left lower frontal gyrus and Crus II of the right cerebellum, which does not involve the involvement of the posterior structures of language. We hypothesize that this increase in connectivity that was found between the stimulation site and the Crus 2 of the right cerebellum causes an increase in the performance of language tests in the immediate post-treatment. In the follow-up, the patient who was most serious at the neuropsychological evaluation at the baseline returns to very low-performance values and the same happens for the connectivity values between the two areas of our analysis.

Although out study showed promising results in the linguistic performance and of speech abilities in the framework of linguistic network, a few limitations should be addressed. This study firstly aimed to prove the feasibility and preliminary evaluation of clinical efficacy of rTMS and its ability to modify functional connectivity in the compromised brain.

SIGNIFICANCE.

rTMS over Broca's area combined with ST was successful to improve abilities in patients with lvPPA. The treatment led to significant improvement of verbal fluency, anomia, and reduction of both semantic and grammatical errors in both patients. It also helped revealing how potential modifications in connectivity within the linguistic network may play a pivotal role in the progression of the disease. Because there seems to be highly individual variability in clinical outcome after rTMS due to brain and neuropathological differences, our future clinical trials should will include the knowledge we developed while optimizing NIBS protocols to personalize the intervention on the individual.

6.3 Third Study: Investigate Brain Resilience in Response to External Perturbation: a TMS-EEG study.

A similar version of the present article has been submitted to Brain Stimulation [**Romanella SM** & Menardi A, Tatti E, Turrini S, Ozdemir R, Shafi M, Santarnecchi E. "*Manipulate Brain Resilience with Transcranial Magnetic Stimulation: a TMS-EEG Study]*.

Complex systems, like the brain, benefit from articulated structures capable of ensuring efficient information flow at minimum wiring costs. Across a diversity of complex networks, universal laws determine the principles beyond such efficient organization: physical proximity between the network's components, hierarchical modularity, and physical embedding (Bassett et al., 2010; Bullmore and Bassett, 2011). This results in a high degree of generalizability in the study of complex networks, allowing for the same principles to be applied for the understanding of the mechanisms of information flow across systems like the Internet, transportation, power grids, social networks, or, finally, in terms of neural interactions (Barabasi and Bonabeau, 2003; Watts and Strogatz, 1998). Indeed, graphical representations have the advantage of being of simple understanding and can be easily applied for the study of a variety of networks. Within the mathematical field of graph theory, the study of the brain's intricate topographical organization is approached by representing brain regions as nodes and their structural or functional coupling as edges (Albert and Barabási, 2002a; Erdos and Renyi, 1959). Knowledge of the network's topology is particularly valuable as it can also enlighten its degree of resilience to errors or attacks, for example in terms of the brain's ability to withstand acquired damage (Santarnecchi et al. 2015). In the literature, in silico lesioning is usually employed as a methodology to simulate brain resilience to damage (Achard et al., 2006; Joyce et al., 2013). In this approach, after estimating the individual network topology at baseline, the network is iteratively lesioned via the targeted or random removal of its nodes or edges based on their centrality or connectivity strength, respectively. The resiliency of a system is hence inferred by looking at the progressive reduction in the size of the largest connected component (LCC), i.e., a connected subgraph that is not part of any larger connected subgraph (Alstott et al., 2009), assuming that a more resilient system will show less reduction in its LCC size following an external attack and/or it will take a longer time for the networks to become completely disconnected (Menardi et al., 2021; Santarnecchi et al., 2015).

From a biological perspective, this translates into the evidence that a more resilient brain can sustain a higher degree of damage, and for a longer time, before displaying the same symptomatology as a less resilient individual (Satz, 1993). Similarly, a resilient brain can likely better compensate for or defer, cognitive consequences by capitalizing on intrinsic plasticity mechanisms (Stern, 2009). Importantly, the individual level of resilience is a dynamic measure, which can be strengthened as a function of individual exposure to favorable environmental stimuli (Barulli and Stern, 2013b; Stern, 2009). In this study, we asked whether changes in brain resilience could be achieved following exposure to noninvasive brain stimulation as well, as a stimulation proxy capable of temporarily altering the individual level of brain connectivity and hence its topographical organization (Ghazi and Soltanian–Zadeh, 2021; Shafi et al., 2014; Ueda et al., 2019).

Indeed, TMS offers the possibility to directly activate the underlying neural substrate using short magnetic pulses of high intensity. The induced neural activity can then be used to enhance or disrupt cognitive and behavioral outputs, detect abnormal response patterns via perturbation-based indexes and finally support cortical plasticity mechanisms for remapping and compensatory effects; thus overall proving useful in exploratory, diagnostic, and therapeutic applications (Valero-Cabrè et al., 2017). Although the effect of TMS on the underlying functional and structural connectivity has been widely assessed (Beynel et al., 2020; Esposito et al., 2020; M.D. Fox et al., 2012), relatively less is known about the induced changes in terms of topological measures, as this is a relatively new field of investigation (Bullmore and Bassett, 2011a). To fulfill this gap, we started by investigating the induced changes in topology following pulse delivery. Secondarily, we explored if changes in topology would also result in resilience alterations, possibly toward an enhancement of the network shielding toward external perturbations.

Given the limited literature on the matter, we were also interested in addressing if distinct brain networks are equally, if at all, susceptible to this type of intervention. We did so by comparing the induced changes in topology and/or resilience in two different brain networks: the Dorsal Attention (DAN) and the Default Mode (DMN) networks. The DAN and the DMN are well-known to be negatively correlated with one another, hence they present opposite functional profiles. They differ in the degree of inter-individual variability in their structure: indeed, task-positive functional networks, such as the DAN, are known to display higher inter-individual variability (Doucet et al., 2019). This was proven in a recent investigation, showing over the course of more than 10 hours of resting state and task functional magnetic resonance imaging, that the DAN is one of the networks with the highest inter-subject variability in its topology (Gordon et al., 2017). This depends on the fact that the DAN comprises highly associative regions, such as middle temporal regions (Fox et al., 2006; Van Essen et al., 2012), which tend to participate in multiple resting state networks (Doucet et al., 2019; Yeo et al., 2014). On the other hand, the DMN presents a more stable connectivity profile (Damoiseaux et al., 2006), which has been assessed across processing methodologies, for example via effective connectivity analysis (Almgren et al., 2018), as well as across neuroimaging modalities, for example via both resting state functional data and arterial spin labeling (Jann et al., 2015). In light of this, we were interested in assessing if TMS might have a different impact on networks at the opposite ends of the inter-individual variability scale.

6.3.1. Methods

Participants. The study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center. Twenty-three right-handed healthy volunteers (15 males, age = 32±10 years, range 19-49 years old) with no neurological and psychiatric diseases and no history of drugs were recruited. In line with the Declaration of Helsinki, each participant provided written informed consent before participating in the study and received compensation at the end of the entire study.

TMS-EEG Data Collection. Participants underwent two TMS visits, one month apart. During each visit, 120 single pulses were delivered at 120% of the individual resting motor threshold (RMT) on the left primary motor cortex. RMT was defined as the minimum intensity of the stimulator output inducing motor evokes potentials (MEPs) with an amplitude of at least 50 μV in 5 out of 10 consecutive trials in the relaxed first dorsal interosseus muscle (Rossini et al., 2015). MEPs were recorded by means of Ag-AgCl surface electrodes placed on the first dorsal interosseous (FDI) and abductor pollicis Brevis (APB) muscles of the right hand, with the reference electrode placed on the right ulnar styloid process. TMS was administered using a figure-of-eight shaped coil with dynamic fluid cooling (Magpro 75 mm cool B-65, Magpro A/S., Denmark) attached to a MagPro X-100 stimulator (MagVenture A/S, Denmark). Individual high-resolution T1w images were imported into the Brainsight™ TMS Frameless Navigation system (Rogue Research Inc., Montreal, Canada), and co-registered to digitize anatomical landmarks. This allowed precise online monitoring of coil positioning.

During the entire TMS session, concomitant electroencephalography (EEG) recording was performed. The EEG was collected with a whole scalp 64-channel cap connected to a TMS-compatible amplifier system (actiCHamp system, Brain Products GmbH, Munich, Germany) and labeled following the extended 10–20 international system. Digitized EEG electrode locations on the scalp were also co-registered to individual MRI scans using Brainsight™ TMS Frameless Navigation system. During recording, electrodes' impedances were maintained below 5kΩ and at a sampling rate of 1000 Hz, with Fp1 as the reference electrode. EEG signals were digitized using a BrainCHamp DC amplifier and linked to BrainVision Recorder software (version 1.21) for online monitoring. TMS pulses were delivered to two stimulation targets with randomly jittered (3000–5000 ms; Rothwell et al., 1999) inter-stimulus intervals over two repeated blocks, each consisting of 60 trials.

TMS Targeting. To investigate resilience changes, we chose to target two nodes belonging to two negatively correlated resting-state networks (RSNs): the DAN and the DMN. We started with group-level resting-state functional network maps, based on the Yeo 7 networks parcellation covering cortical and subcortical structures (Yeo et al., 2011). We then projected the 7-network atlas and their confidence maps onto the subject's cortical surface using the spherical registration implemented in Freesurfer software and then re-sampled it to native structural T1w MRIs. Based on such morphed confidence maps for each RSN— representing the confidence of each vertex belonging to its assigned network across a sample of 1000 healthy subjects—we targeted two of the most relevant nodes of the DAN and the DMN, respectively the right superior parietal gyrus (SPG) and the right angular gyrus (ANG; see Figure 34, Panel A). This resulted in personalized targeting sites for each network (for more information on preprocessing procedure see Ozdemir et al., 2020).

EEG Data Processing. We preprocessed EEG data based on a script running in Matlab 2017b (MathWorks Inc.), relying on EEGLAB (Delorme and Makeig, 2004) functions and TESA Toolbox for artifact removal (Rogasch et al., 2017). The two single blocks of 60 trials each were merged into a single block of 120 trials and then segmented into epochs of 1500 ms each (from − 500 ms (pre-pulse) to 1500 ms (post-pulse). EEG preprocessing steps included baseline correction considering the 500 ms preceding the pulse and removal of

noisy channels following visual inspection. The TMS artifact was removed using zero-padding (-2ms to 14 ms time window) and a fast independent component analysis (fICA) inspection. Noisy epochs were rejected based on the voltage (≥100 μV), kurtosis (≥ 3), and joint probability (single channel-based threshold ≥ 3.5SD). Before that, principal component analysis (PCA) was used to reduce the data into 60 components to minimize the risk of overfitting. EEG data were then interpolated around the zero-padding time window, band-pass filtered (1-100 Hz), notch filtered (57-63 Hz), and referenced to the global average. A second round of PCA and fICA were performed to remove additional sources of noise (eye movement/blink, muscle noise, single electrode noise, TMS evoked muscle twitches, cardiac beats, and auditory evoked potentials). A semi-automated artifact detection algorithm incorporated into the open-source TMS-EEG Signal Analyzer (TESA v0.1.0-beta; https://nigelrogasch.github.io/TESA/) was used during both fICAs. We chose three-time windows of 300ms each from which to compute connectivity matrices: pre-pulse (from −500 ms to -200ms before the pulse), post-pulse (from 1ms to 300ms after the pulse), and late (from 700ms to 1000ms after the pulse).

EEG Connectivity and Phase-Locking Value. We first computed the power and cross-spectrum by convolving the signal using Complex Morlet Wavelets at linearly spaced frequencies (1-100 Hz, 1 Hz bins steps) and a constant time window (-0.5 to -0.2 s before the TMS pulse). The number of wavelet cycles and length were progressively increased as a function of frequency to maintain a good frequency and time resolution trade-off (cycles: 3-10, length: 3 to 0.1s). For each time window (see above), we extracted EEG whole-brain connectivity over 63 electrodes in different EEG frequency bands: theta (5-7 Hz), alpha (8-12 Hz), beta (15-29 Hz), gamma1 (30-59 Hz), gamma2 (60-90 Hz).

Functional connectivity was estimated by computing the Phase-Locking Value (PLV, Lachaux et al., 1999), a phase synchronization measure that corresponds to the mean phase difference between signals from two electrodes. As a result, NxN connectivity matrices were derived from the PLV correlation between each pair of electrodes (N=63). The PLV matrices between visit 1 and visit 2 were averaged together to obtain a more stable representation of the individual brain coupling patterns irrespective of possible state-dependency effects (i.e., visit-specific). This allowed us to stabilize the connectivity matrix and all its derived measures.

Graph Measures. In the literature, graph and resilience metrics are usually computed at lower connection densities (top 10-40%) to ensure that only the most relevant connections are retained, thus decreasing the risk of false-positive edges (Bullmore and Bassett, 2011b; Menardi et al., 2021). For this reason, we thresholded our PLV matrices to retain only 10% of the original connection density (results estimates at different threshold values – 30% – are reported in the Supplementary Materials). A threshold of 10% was chosen because it has previously been associated with higher test-retest reproducibility for global metrics (Wang et al., 2011). Weighted adjacency matrices were then computed, where each node (N) represents an input in the square matrix: A = NxN, where the assigned value to the edge A_{ij} is equal to the PLV between node i and j when the connection exists, or zero otherwise. Graph theory and resilience measures were extracted from these matrices using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) functions running in MATLAB 2017b.

Five graph theory metrics were identified and extracted (for more details see Rubinov and Sporns, 2010): the *Characteristic Path Length*, as the average shortest path length between all pairs of nodes; the *Clustering Coefficient*, or the fraction of the node's neighbors that are also neighbors of each other; the *Global Efficiency*, as the average inverse shortest path length; *Local Efficiency* representing the inverse of the average shortest path connecting a node to all other nodes of the system, and the *Modularity* index, computed using the Louvain algorithm, expressing the tendency of the connectivity matrix to separate in distinct sub-modules.

Resilience Measures. We investigated resilience based on an *in silico* network lesioning of nodes and edges from the weighted adjacency matrix, as done in previous studies (Achard et al., 2006; Albert and Barabási, 2002b; Joyce et al., 2013b; Santarnecchi et al., 2015; Santonja et al., 2021). In this approach, nodes and edges are ordered based on their nodal degree and edge strength. One by one, they are removed from the adjacency matrix and the drop in size in the largest connected component (LCC) is recorded as a measure of the inferred damage. This measure refers to the biggest set of nodes whose pairs are connected by an edge. At each iteration, the nodes' degree is re-calculated and the order of removal is adjusted based on the effect of prior lesioning. This allows us to analyze two types of resilience: targeted, when the removal of nodes/edges progresses based on their nodal degree/connection strength - from strongest to weakest; or random, where the removal of nodes/edges happens in random order. The following resilience metrics were hence computed: *Targeted Node/Edge Removal* (the mean reduction necessary to bring the LCC to a value of zero following a targeted progression of node/edge removal) and *Random Node/Edge Removal* (as the mean reduction necessary to bring the LCC to a value of zero following the progressive random removal of nodes/edges). More resilient individuals will show greater robustness to the inferred damage before any decay in their LCC, represented by higher scores in these metrics. The code used for resilience measures extraction is available at http://tmslab.org/netconlab.php.

Statistical Analysis. All data were analyzed using SPSS version 22 (SPSS Inc., Chicago, USA). For both networks and each frequency band, Paired t-Tests were run to control for statistical differences in topography and resilience across time. In particular, we tested for differences in three-time windows around the time of pulse delivery: pre vs. post, post vs. late, and pre vs. late, to better capture quick differences in resilience and graph metrics induced by the TMS pulse. We refer to pre-pulse as the time window from 500ms before the pulse to 200ms, post-pulse as data extracted from 1ms after the pulse to 300ms after the pulse, and late as the window from 700ms to 1000ms after the pulse. Finally, we performed Pearson correlation analysis between all significant measures to detect possible meaningful associations between topographical and resilience indices. For all analyses, the significant threshold was set at $\alpha = 0.05$.

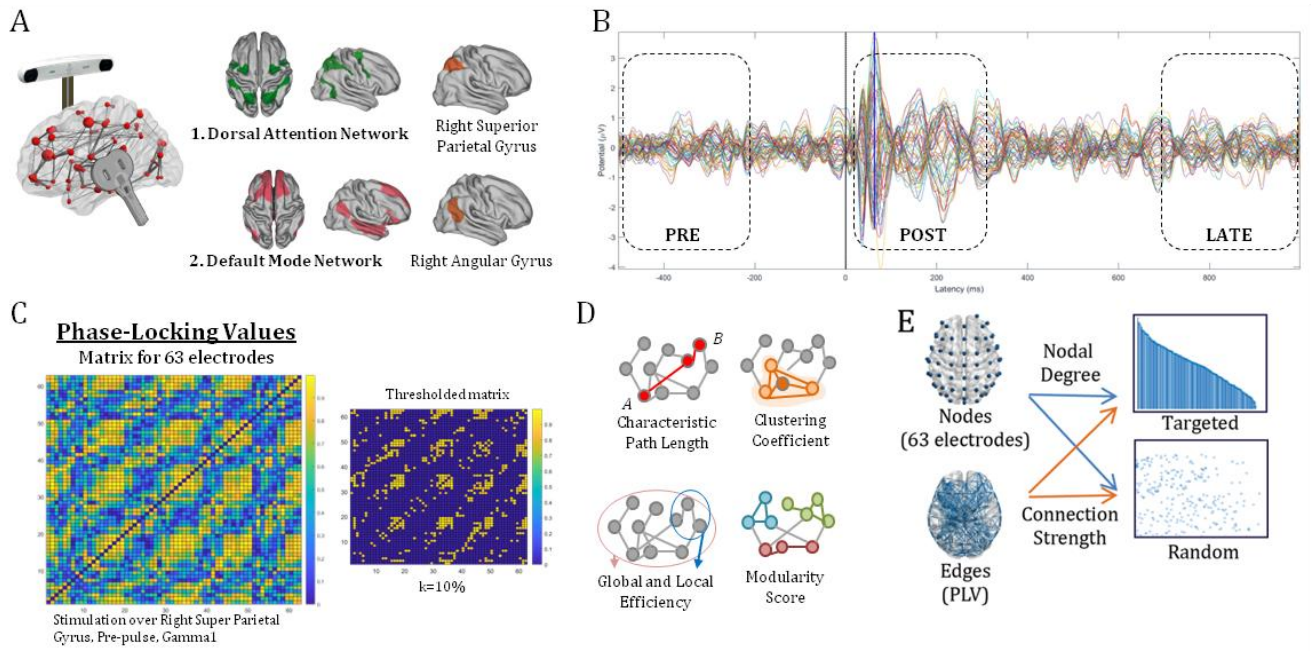


Figure 34. Methodological Workflow and Measures of Interest. Panel A. We administered single TMS pulses to the Right Superior Parietal Gyrus (Dorsal Attention Network – DAN node) and the Right Angular Gyrus (Default Mode Network- DMN node) in 23 healthy young volunteers during concomitant EEG recording. **Panel B.** We then extracted EEG whole-brain connectivity over 63 electrodes in each EEG frequency band (theta, alpha, beta, gamma1, gamma2) using a sliding window approach across three-time points concerning pulse delivery (pre, post, late). **Panel C.** For each frequency band and at each time window, we computed the Phase Locking Value (PLV), a phase synchronization measure that corresponds to the mean phase difference between signals from two electrodes. We thresholded each matrix to ensure that only 10% of the strongest connections were retained. **Panel D**. For our analyses, we first extracted measures of graph theory to determine if brain stimulation could induce significant changes in the functional topographical organization of the brain network. We focused on graph measures representing the integration and segregation of information flow, including *Characteristic Path Length, Clustering Coefficient, Global and Local Efficiency*, and *Modularity*. **Panel E.** Resilience to the Random or Targeted removal of either brain nodes or edges (connections) in the connectivity matrix was investigated using iterative *in silico* lesioning.

6.3.2. Results

DAN Stimulation. Following stimulation of the right SPG within the DAN, we found statistically significant changes in graph and resilience metrics within the gamma1 band (see Figure 35, Panel A). In particular, we observed a significant decrease in the measure of Modularity in the post- vs. pre-pulse contrast [t_{22} = 2.127, p = 0.045], followed by a significant increase in the late-pulse window compared to the immediate post-pulse window [t_{22} = 2.190, p = 0.039], but not significant when compared between late and baseline (p > 0.05), suggesting a homeostatic return to baseline. We also saw a significant increase in resilience as compassed by the measure of Targeted Edge Removal in the post-pulse vs. pre-pulse windows comparison [t_{22} = 2.190, p = 0.039]. This difference was however not present in the late-pulse window (p > 0.05). No other significant differences were observed for the remaining graph and resilience metrics in the gamma 1 band (all p > 0.05). We did not find any significant changes in resilience and graph scores in any other frequency bands (all p > 0.05).

Correlation analysis showed that Modularity and Targeted Edge Removal at baseline were strongly negatively correlated [$r_{(22)}$ = -0.886, p < 0.001] (see Figure 35, Panel B).

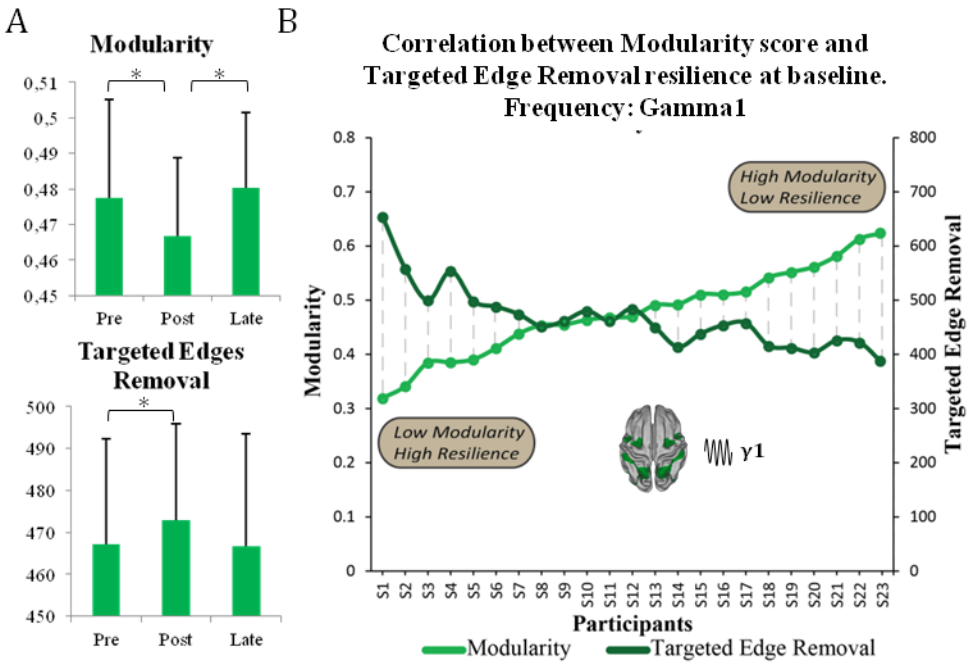


Figure 35. Graph theory and resilience metrics changes after TMS stimulation of the DAN. Panel A. Following stimulation of the DAN, we observed a decrease in the measure of Modularity in the post-pulse time window, followed by a return to baseline levels. This change in topology was mirrored by a significant increase in the degree of resilience to the Targeted Edges Removal in the post-pulse window compared to baseline. **Panel B.** Correlation analysis showed a negative correlation between the measures of Modularity and Targeted Edges Removal.

DMN Stimulation. On the other hand, stimulation of the right ANG, a node of the DMN, resulted in significant findings within the theta band (see Figure 36, Panel A). In particular, we observed a significant

increase in the measure of the Clustering Coefficient in the post-pulse window compared to baseline [t_{22} = 2.213, p = 0.038], followed by a return to baseline (p > 0.05). Stimulation of the right ANG also resulted in an increase in the measure of Local Efficiency compared to the pre-pulse window, both immediately after the pulse [t_{22} = 2.234, p = 0.036], as well as later on [t_{22} = 2.533, p = 0.019]. Similar to what was reported for the DAN condition, we also observed a statistically significant decrease in Modularity in the post-pulse time window compared to the pre-pulse time window [t_{22} = 2.173, p = 0.041]. This was followed by a progressive return to baseline in the late-pulse window, demonstrated by a non-significant difference in the Modularity values in the late-pulse vs. pre-pulse contrast (p > 0.05, see Figure 36, Panel A). In addition, we observed a significant increase in resilience to Targeted Edges Removal in the post-pulse window compared to the pre-pulse time window [t_{22} = 2.532, p = 0.019], followed by a return to baseline. No other significant contrast was observed in the theta band (all p > 0.05). We did not find any significant changes in resilience and graph scores in any other frequency bands (all p > 0.05).

In addition, our correlation analysis showed a negative association between the measure of Modularity and resilience to the Targeted Edge Removal [$r_{(22)}$ = 0.926, p < 0.001] (see Figure 36, Panel B), as well as a positive correlation between the latter and the measure of Clustering Coefficient [$r_{(22)}$ = 0.647, p = 0.001].

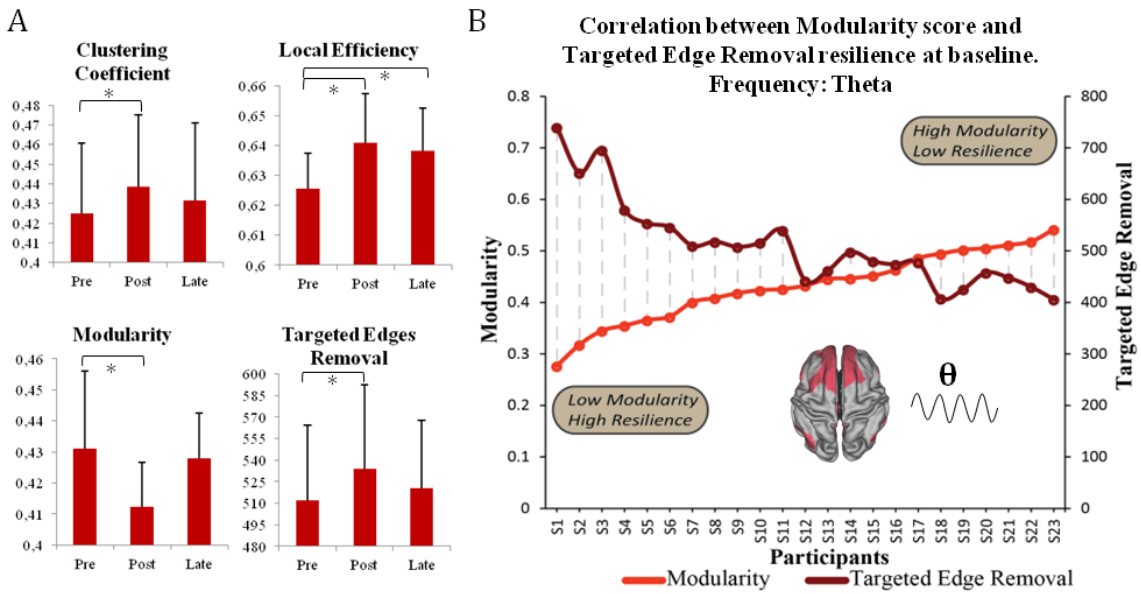


Figure 36. Graph theory and resilience metrics changes after TMS stimulation of the DMN. Panel A. Following stimulation of the DMN, we observed a decrease in Modularity, accompanied by an increase in the measures of Clustering Coefficient and Local Efficiency in the theta frequency band. In addition, we observed a significant increase in the degree of resilience to Targeted Edges Removal in the post-pulse period compared to baseline. **Panel B.** Correlation analysis showed a negative correlation between the measures of Modularity and Targeted Edges Removal.

6.3.3. Discussion

In recent years, the interest in the study of complex networks has favored the development of new mathematical frameworks aiming at understanding the relationship between a network organization and its degree of

efficiency. An example is represented by the field of graph theory, which deals with the representation of the patterns of information flow between the components of a system (nodes) and their interactions (edges) via the characterization of the graph's topological organization. Since its application to the neuroscience field, several studies have hence reported the association between brain topology and cognition, as well as a variety of neurological disorders (Farahani et al., 2019). As an example, the individual intelligent quotient (IQ) has been reported to correlate with the degree of global efficiency (van den Heuvel et al., 2009), i.e. the ability of a network to integrate information across its distant components (Rubinov and Sporns, 2010), which suggests that the individual level of intelligence is directly dependent on how well different regions of the brain communicate with one another, especially parietal and frontal nodes, as evidence by a short path length between them (van den Heuvel et al., 2009). Similarly, the ability of the network to sustain damage after a random or targeted attack on its hubs has also been correlated with the individual IQ, again highlighting the importance of distributed processing in cognitive functioning (Santarnecchi et al., 2015). Importantly, the brain network is a highly plastic system, which undergoes significant functional and structural reorganizations with age (Collin and Heuvel, 2013). Indeed, as a function of brain maturation, the brain graph increases its modularity and local efficiency (Meunier et al., 2009), resulting in better inter-modular communication (Betzel et al., 2014), as well as hub stabilization (Hwang et al., 2013) and strengthening of the "rich club" (Cao et al., 2014), i.e. the preferential attachment between highly connected nodes with each other's (van den Heuvel and Sporns, 2011). Although evidence indicates that genetic predispositions partially shape the association between brain topology and cognitive functioning (Bolken et al., 2014; Gu et al., 2021; Menardi et al., 2022), environmental stimuli still significantly modulate such interaction (Collin and Heuvel, 2013; Tooley et al., 2020). In particular, individual exposure to favorable environmental stimuli has been proven to have a positive impact on the brain network wiring capacity, making it more resilient to pathology, in terms of its ability to defer, offset and/or compensate for such insult (Barulli and Stern, 2013b).

Based on this notion, we decided to investigate if exposure to noninvasive brain stimulation could also lead to meaningful changes in the brain topology and hence alter, at least temporarily, one's level of resilience. This is a necessary knowledge step to verify the possibility to capitalize on such an effect for future neuromodulatory therapeutic purposes. In this work, brain resilience was tested via an *in silico* network lesioning procedure, whereby nodes and edges are iteratively removed and the reduction in the graph size is taken as an index of the inferred damage (Achard et al., 2006; Albert and Barabási, 2002a; Joyce et al., 2013b; Menardi et al., 2021; Santarnecchi et al., 2015). Based on this approach, we were able to demonstrate significant changes in brain topology, and consequently resilience, following exposure to a single pulse TMS protocol. In particular, for both networks tested, we observed a significant and transient decrease in the whole brain modularity after the pulse, followed by a return to baseline levels, as the system would tend to homeostatically reacquire its physiological properties. After stimulation of the DMN, changes in modularity were also accompanied by a significant increase in the measures of clustering coefficient and local efficiency, with the latter showing a sustained

increase even at the later time window. It is known that baseline brain topology distinguishes responders from non-responders to 1Hz stimulation (Downar et al., 2014; Fitzsimmons et al., 2020); moreover, recent literature evidence has reported that low-frequency stimulation can induce changes in brain topology. Indeed, 15 minutes of 1Hz TMS applied to healthy participants resulted in significant changes in core topological measures, such as the clustering coefficient, in the electrodes surrounding the stimulation site that lasted up to 60min after protocol cessation (Qiu et al., 2020). Similarly, 1Hz stimulation applied in patients suffering from major depression and bipolar disorder showed significant changes in topographical measures of degree and edge strength differently in responders who showed clinical improvements and non-responders to stimulation, as well as between the two groups of patients, proving sensitivity in respect of those variables (Zuchowicz et al., 2019). Our results contribute to such findings, proving meaningful changes in brain topology immediately after the pulse delivery. In particular, the observed decrease in modularity following stimulation of both the DAN and the DMN suggests an overall strengthening of connectivity across the network's nodes, resulting in a momentary increase between-modules connections concerning those within. This appears in line with recent evidence highlighting the tendency of the induced TMS effect to spread across several different networks rather than remaining limited to the stimulated area (Beynel et al., 2020). This could also be reflected by the increase in clustering coefficient and local efficiency measures, which we observed after stimulation of the DMN, suggesting augmented connectivity between neighboring nodes, that do not necessarily belong to the same module. In line with such an increase in the processing capacities between the network's nodes, we also observed a transient increase in the resilience of the brain network to the targeted removal of its edges. Indeed, more resilient systems benefit from distributed processing (Santarnecchi et al., 2015), as it allows the information transfer to be more equally distributed instead of relying on a few strong connections, which would cause a significant disruption in the system's capacity if lesioned. In this regard, if a system is highly modular, it implies that different nodes will tend to share a greater number of connections (aka, intra-modular edges). On the other hand, different modules will connect with fewer connections via connector hubs. If lesioned, those inter-modular edges will cause significant damage, as the system will lose an entire set of nodes altogether, hence making a highly modular system more prone to failure following damage. In line with this interpretation, we observe a significant negative correlation between modularity and resilience to the targeted removal of edges. Although this pattern was observed for both the stimulated networks, it occurred at two different frequencies: in the gamma band for the stimulation of the DAN and the theta band following stimulation of the DMN instead. This distinction is of interest, as those frequency bands are specific to some of the cognitive roles sustained by the two networks: attention and memory respectively. In more detail, sustained gamma activity in the DAN has been reported to correlate with attention abilities in healthy young adults (Ossandón et al., 2012), even proving discrimination in inter-individual differences in cognitive efficacy during healthy aging (Akimoto et al., 2014). On the other hand, a reduction in the expression of gamma-band activity has been reported to characterize important attentional deficits, as in individuals suffering from attention deficit hyperactivity disorder (Tombor et al., 2019).

Regarding the DMN, frontal theta activity has been reported as an index of DMN activation during simultaneous EEG-fMRI acquisition (Scheeringa et al., 2008) and to predict memory encoding as a function of DMN deactivation (White et al., 2013). The fact that topological and resiliency changes occurring after single pulse delivery are maximally expressed at EEG frequencies differently for each network and cognitive function might further validate the existence of a tight link between topology, resilience, and cognition. Interestingly, both the DAN and the DMN showed alteration in response to perturbation, at least in terms of the induced topological and resilience changes. Indeed, as reported in the Introduction, we were interested in assessing possible differences in their response to stimulation considering that the DAN and the DMN present opposite functional profiles, as well as different degrees of inter-individual variability (Doucet et al., 2019; Gordon et al., 2017; Yeo et al., 2014). The present findings suggest that stimulation of the brain results in network-specific changes, as outlined above, but also suggest the possibility of doing so in an equally successful way.

To our knowledge, this is the first study that tries to apply *in silico* network lesioning for the study of resilience changes to a TMS protocol, and hence the interpretation of these findings should be handled with caution. First of all, future independent studies should replicate our results in a larger sample size. Secondly, there is a need to better characterize the size and the duration time of the induced changes, possibly through longer and repeated stimulation sessions as those of therapeutic rTMS (Lefaucheur et al. 2020). Finally, the biological validity of this model in respect of real lesioning scenarios will need to be addressed. Yet, the possibility of directly acting on the neural underpinnings of cognition makes brain shielding interventions a possible and desirable aim in future research lines.

SIGNIFICANCE.

The brain network, as an example of a complex network, benefits from an articulate topological architecture that ensures efficient information transfer. Furthermore, being a plastic system, the brain network can undergo substantial rearrangements as a function of its exposure to a variety of environmental stimuli. In this study, we questioned if similar changes in topology could occur after a targeted, personalized exposure to a noninvasive brain stimulation protocol. Although exploratory, our results prove that TMS pulses can transiently alter the degree of modularity of the brain. Furthermore, depending on the site of stimulation, additional changes in the clustering coefficient and local efficiency of the network can occur. Interestingly, such changes in topology appear to mirror changes in the network resilience to the targeted attack on its edges. We argue that such an increase in resilience might be imputable to a more distributed processing of the information through the strengthening of inter-modular connections occurring after pulse delivery. Results have implications for the modeling of neurodegenerative diseases as well as for the definition of protocols aimed at increasing brain resilience to an external perturbation.

7. CONCLUSION

The aim of my dissertation was to investigate the applications of noninvasive brain stimulation techniques to counteract harmful consequences following pathological aging and space exploration. To optimize the stimulation and increase NIBS success in these domains, I explored a new personalized approach able to adapt the stimulation to brain modifications induced by pathological aging and space missions. Even though every chapter could be considered as an independent project aimed at clarifying specific aspects of NIBS applications, they all shared the same main goal: to improve NIBS efficacy in research and clinical domains.

Finally, I would like to conclude my Ph.D., and my thesis, by explaining the reason why I decided to pursue it in the first place. While I was working as a clinical psychologist, I had the incredible opportunity to meet and work with different psychiatric and neurologic patients. During the second week of my internship at the hospital, I met one of the most severe psychiatric cases I would ever have the chance to work with: a young catatonic man in his twenties. That first day, and ever since, I greeted him with a smile, saying my name and trying to meet his gaze. Standing tall, his eyes would look past me. One day, his mother showed me the severity of his disease by raising her son's arm. No reaction. The arm stayed still and stopped in the air. After my supervisor entered the room, we started talking about the medications and potential art courses, cognitive tasks, and another pack of 10 sessions of electroconvulsive therapy. They informed me that after the first cycle, he was able to drink with a straw when it was pushed against his lips. One action he had never done alone since he was seven years old. Before the end, when my supervisor was leaving, I took one of his hands and shook it, saying goodbye. He did not even blink, the other arm still raised.

During the following four years, I graduated and was hired as a consultant at the same hospital. I met him multiple times, over numerous sessions that we had together, following him during the other two cycles of electroconvulsive therapy. I greeted him at the door of the same room, endless times. I would say my name, smiling. No response. He once was hospitalized for not being able to eat. I talked to him for the entire hour of our session while he was looking at the ceiling. Stuck in his world, unable to escape it. Just another afternoon, I saw him walking out of the door, gently pushed by his mom. I smiled at him from the other side of the parking lot.

"CIAO…SARA! CIAO!"

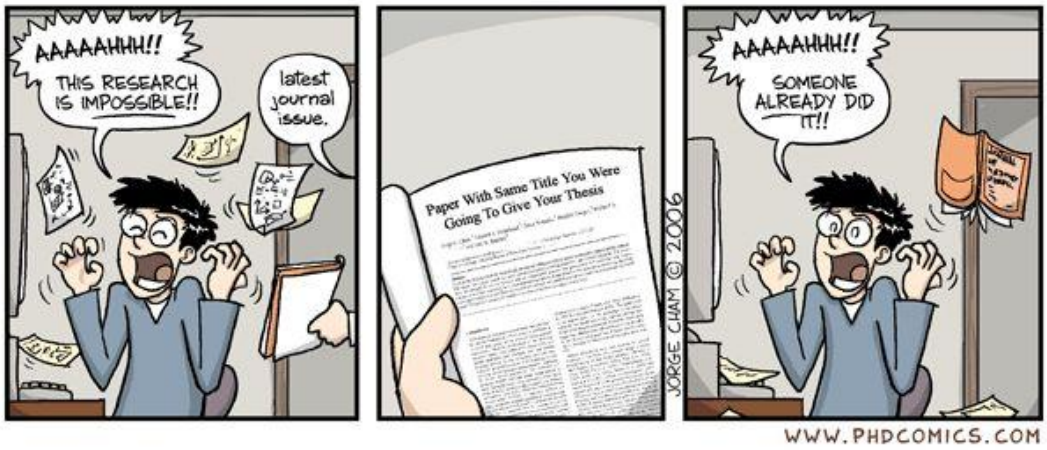
His voice that I never heard before echoed in the yard. I immediately turned to him, noticing a brief glimpse of consciousness in his gaze. He recognized me. He called me. His eyes SAW me for a second. At that moment, his mom shouted his name. My colleagues ran out of the building, alarmed by the yelling, which is rarely a good thing in a psychiatric yard. Then we lost him again to his world of stillness.

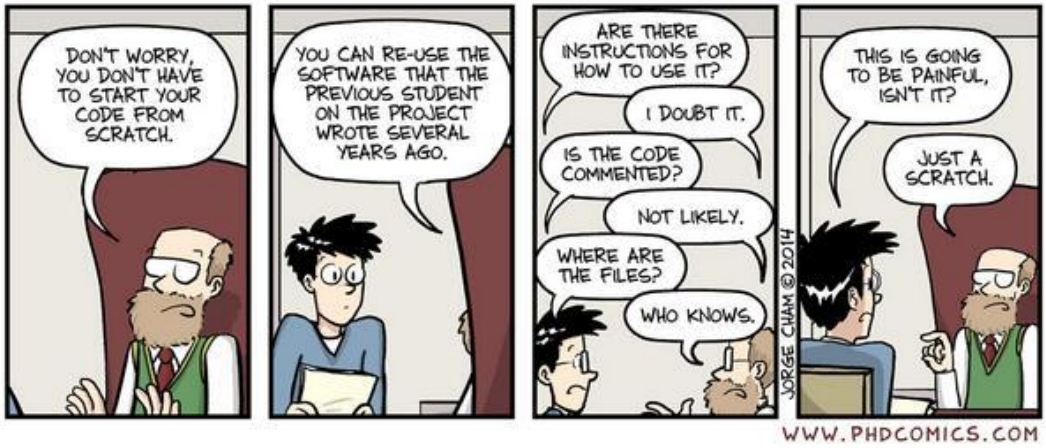
Over the next day, I learned that he was enrolled in a clinical trial employing repetitive magnetic transcranial stimulation. He is the reason why I started studying noninvasive brain stimulation.

I dedicate this thesis to him and that single moment.

SUPPLEMENTARY (FUN) MATERIAL

…that made me laugh in days where all my p-values were over 0.05.





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