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Review

Non-invasive brain stimulation of the aging brain: State of the art and future perspectives

Elisa Tatti[a,*], Simone Rossi[a,b], Iglis Innocenti[a], Alessandro Rossi[a], Emiliano Santarnecchi[a,c,d,*]

[a] *Department of Medicine, Surgery and Neuroscience, Neurology and Clinical Neurophysiology Section, Brain Investigation & Neuromodulation Lab. (SiBIN Lab), University of Siena, Italy*
[b] *Department of Medicine, Surgery and Neuroscience, Human Physiology Section, University of Siena, Italy*
[c] *Siena Robotic and Systems Lab (SirsLab), Department of Information Engineering and Mathematics, University of Siena, Italy*
[d] *Berenson-Allen Center for Non-Invasive Brain Stimulation, Beth Israel Medical Center, Harvard Medical School, Boston, MA, USA*

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ABSTRACT

Favored by increased life expectancy and reduced birth rate, worldwide demography is rapidly shifting to older ages. The golden age of aging is not only an achievement but also a big challenge because of the load of the elderly on social and medical health care systems. Moreover, the impact of age-related decline of attention, memory, reasoning and executive functions on self-sufficiency emphasizes the need of interventions to maintain cognitive abilities at a useful degree in old age. Recently, neuroscientific research explored the chance to apply Non-Invasive Brain Stimulation (NiBS) techniques (as transcranial electrical and magnetic stimulation) to healthy aging population to preserve or enhance physiologically-declining cognitive functions. The present review will update and address the current state of the art on NiBS in healthy aging. Feasibility of NiBS techniques will be discussed in light of recent neuroimaging (either structural or functional) and neurophysiological models proposed to explain neural substrates of the physiologically aging brain. Further, the chance to design multidisciplinary interventions to maximize the efficacy of NiBS techniques will be introduced as a necessary future direction.

Contents

Abbreviations: APOE, apolipoprotein E; BOLD, blood oxygenation level dependent; CACT, computer-assisted cognitive training; cTBS, continuous theta burst stimulation; COMT, catechol-O-methyltransferase; CRUNCH, compensation-related utilization of neural circuits hypothesis; DA, dopamine; DLPFC, dorso-lateral pre-frontal cortex; DMN, default mode network; DMO, dextromethorphan; ECT, electroconvulsive therapy; EEG, electroencephalography; ERP, event related potential; fMRI, functional magnetic resonance imaging; FTT, finger-tapping task; HAROLD, hemispheric asymmetry reduction in older adults; HERA, hemispheric encoding/retrieval asymmetry; HF-rTMS, high-frequency rTMS; ICA, independent component analysis; IFG, inferior frontal gyrus; iTBS, intermittent theta-burst stimulation; JTT, Jebsen–Taylor hand function test; LTD, long term depression; LTP, long term potentiation; MTL, medial temporal lobe; NiBS, non-invasive brain stimulation; NREM, non-rapid eye movement sleep; PARC, parietal cortices; PASA, posterior–anterior shift in aging; PFC, prefrontal cortex; RSFC, resting-state functional connectivity; rs-fMRI, resting-state functional magnetic imaging; rTMS, repetitive transcranial magnetic stimulation; STAC, Scaffolding theory of aging and cognition; tACS, transcranial alternating current stimulation; TBS, theta burst stimulation; tDCS, transcranial direct current stimulation; tES, transcranial electrical stimulation; tRNS, transcranial random noise stimulation; vRT, verbal reaction times; WM, working memory.

* Corresponding authors at: Department of Medicine, Surgery and Neuroscience, Neurology and Clinical Neurophysiology Section, Brain Investigation & Neuromodulation Lab. (SiBIN Lab), University of Siena, Italy

E-mail addresses: elisatatti@msn.com (E. Tatti), esantarn@bidmc.harvard.edu (E. Santarnecchi).

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1. Introduction

1.1. What does “aging” mean to the brain?

Favored by reduced birth rate and increased life expectancy, worldwide demography is rapidly shifting to older ages. According to a recent report by the U.S. Census Bureau, the share of people 65 and older is projected to increase more than 150% in 35 years (He et al., 2016). In line with this projection, from 562 millions of people that were 65 years old or older in 2012, by 2050 the “golden age” will include a population of 1.6 billion of elders. The “golden age” is itself aging rapidly; increase in life expectancy will raise the number of the oldest old from 126.5 million by 2015 to 446.6 million by 2050. This snapshot underlines that the golden age is not only an achievement, but also a big challenge that our society must face promptly, in order to shield self-sufficiency and well-being of this growing proportion of population (Ballard, 2010). As the 2015 United States of Aging survey reported (National Council of Aging, 2016), “keeping the mind sharp” is the main concern of 32% of older Americans. Cognition, a broad term encompassing abilities such as memory, attention, decision-making and problem solving, is indeed a critical component in daily functioning (Li et al., 2001; Seidler et al., 2010) and its age-related decline is cause of concern not only for the elderly but also for their families, the community and the public services. Indeed, aging to senescence encompasses variable impairment in cognitive abilities, especially for some aspects of memory and language, visuo-spatial and executive abilities, and several intervention modalities have been developed to stem it (Bamidis et al., 2014). Recently, neuroscientific research explored the chance to apply Non-Invasive Brain Stimulation (NiBS) techniques (as transcranial electrical and magnetic stimulation) to the aging population.

The present review will overview current scientific evidences on age-related cognitive and neurobiological changes to discuss the feasibility of enhancing cognitive maintenance by means of electrical current stimulation protocols.

1.2. Structural and functional signatures of brain wrinkles

1.2.1. Structural changes

Physiological brain structural and functional adapting brain changes follow human development from birth to death and characterize cognitive differences during lifespan. Neurobiological changes particularly evident in the old age include: reductions in neurotransmitter binding potential and synaptic receptor density and efficacy (Morrison and Baxter, 2012), change in cortical and cerebellar metabolism (Dukart et al., 2013), grey matter atrophy, white matter loss and ventricular enlargement (Bennett and Madden, 2013; Bolandzadeh et al., 2012; Scahill et al., 2003). As Hedman et al. (2012) reported in their review of 56 longitudinal MRI studies, a volume loss of more than 0.5% yearly occurs after age 60, a change that goes along with signs of demyelination, axonal damage, decline in callosal volume (Abe et al., 2002; Nusbaum et al., 2001; Pfefferbaum and Sullivan, 2003; Sullivan et al., 2010; Vernooij et al., 2008), and ventricular enlargement, especially in the frontal horns (Apostolova et al., 2012). Interestingly, ventricular enlargement, white matter and grey matter structural changes, which seem to follow an “anterior-posterior gradient” with an earlier and stronger involvement of frontal regions, correlate with decline in cognitive performance (Chou et al., 2009; Josephs et al., 2008; Persson et al., 2006). In particular, prefrontal white matter hyperintensities and grey matter shrinkage have been linked to poorer executive functions, working memory abilities and speed of information processing and have been independently correlated to perseverative behavior (Gunning-Dixon and Raz, 2003). Also temporal lobes are prone to moderate age-related changes; decrease in the hippocampus volume has been largely reported in healthy aging whereas the entorhinal cortex, whose volume decrease characterizes Alzheimer’s disease, seems to be unaffected by healthy aging (Raz et al., 1998).

1.2.2. Task-related functional activity

As shown by several neuroimaging studies of task-related brain activity, brain structural changes are accompanied by modifications of functional neural activation patterns in the elderly; these evidences gave rise to a flurry of theories among which reduction of task-related hemispheric lateralization (HAROLD model) is one among the soundest, at least for the memory domain (for a review on this topic see Cabeza et al., 2002). However, many cognitive domains, such as attention and memory, executive functions, perception and visuospatial abilities, are usually disrupted with aging and these behavioral changes are also reflected by changes detectable using functional imaging techniques such as functional Magnetic Resonance Imaging (fMRI).

Table 1

Summary of studies using rTMS neuro-enhancement protocols in healthy aging.

Studies	N	Age	Education	Stimulated area	Sham	Localization of the site	Type of coil (mm)	Type and frequency of stimulation	Intensity	Train duration	Treatment duration (d)	Online/ offline	Task	Cognitive domain	Effect	Result
Vidal-Piñeiro et al. (2014)	24	71.75 ± 6.81	/	left IFG	sham device	Neuronavigated stimulation with stereotactic registration	Double-70	iTBS 50 Hz	80% AMT	3 pulse trains repeated every 200 ms during 2”	/	Offline	Encoding and retrieval of words	Episodic memory	iTBS did not produce changes in performance in the memory task. Functional brain TMS-induced changes were found specifically when subjects were performing a deep encoding task in local (left IFG) and distal areas (OC and cerebellum)	No behavioral effects
Kim et al. (2012)	16	63.13 ± 4.90	12.33 ± 3.67 rTMS group 11.50 ±3.46 sham group	left DLPFC (F3)	Coil held perpendicularly to the scalp surface	International EEG 10–20 system	Double-70	HF-rTMS 10 Hz	30% of the maximal stimulator output (0.6T)	13 pulse trains of 2” repeated every 15” (780 pulses daily)	5 days	Offline	Stroop-task	Inhibitory control	Daily HF-rTMS treatment over the left dorsolateral prefrontal region improved reaction times for Stroop task trials with conflicting information. No effect on accuracy rates	↓ RT with conflicting information
Cotelli et al. (2010)	13	70.2 range 65–78	13.8	l/r DLPFC	3-cm-thick piece of plywood applied to the coil on Cz	SofTaxic Evolution Navigator system (V. 2.0)	Double-70	HF-rTMS 20 Hz	90% MT	500 msec	/	Online	Action-naming task	Language	vRTs for actions were consistently faster during left and right dorsolateral prefrontal cortex than during sham stimulation. No significant differences were observed for object naming.	↓ RT for action naming

For what concern episodic memory, Cabeza et al. (Cabeza et al., 1997) showed that, differently from young adults which displayed typically prevailing left prefrontal cortex (PFC) activity during encoding and right PFC activity during recall (HERA model: Cabeza et al., 1997; Nyberg et al., 1998; Rossi et al., 2002; Silveri et al., 2014; Tulving et al., 1994), performance of the elderly was characterized by a bilateral pattern of PFC activity during retrieval, namely a reduction in hemispheric lateralization. Similar data were obtained for other memory components, such as recognition (Grady et al., 2002; Madden et al., 1999), incidental and intentional learning (Stebbins et al., 2002; Logan and Buckner, 2001), and other domains such as executive functions (Nielson et al., 2002; Reuter-Lorenz et al., 2000) and perception (Grady and Craik, 2000; Grady et al., 1994). Reduced hemispheric lateralization is actually one of the most discussed evidence in cognitive aging research field as it raised many conflicting hypotheses, some suggesting a failure to allocate functional resource in a selective manner as it happens in younger subjects and others interpreting it as a compensatory attempt (Grady, 2008).

Another occurring neurophysiological modification encompasses the increased recruitment of frontal areas to the detriment of occipital activity, a phenomenon theorized in the posterior–anterior shift in aging (PASA) model (Davis et al., 2008). Far from being a task-difficulty related phenomenon (Davis et al., 2008), neuroimaging studies widely reported PASA pattern across different cognitive domains, including attention and working memory (Madden, 2002; Cabeza et al., 2004; Grossman et al., 2002; Rypma and D'Esposito, 2000), visual perception and visuospatial processing (Grady and Craik, 2000; Grady et al., 1994; Huettel et al., 2001; Iidaka et al., 2002; Levine et al., 2000; Meulenbroek et al., 2004) as well as episodic memory (Cabeza et al., 2004, 1997; Daselaar et al., 2003; Dennis et al., 2007; Grady et al., 2002; Gutchess et al., 2005). Considering that structural brain changes seem to follow the opposite direction – namely affecting prefrontal areas first – evidences of increased task-related prefrontal activation need more in-depth analysis. As reported by Davis et al. (2008), prefrontal activity could be interpreted as a functional reorganization mechanism to overcome decreased sensory processing abilities (Gazzaley et al., 2005; Park et al., 2004), a compensatory role that has been observed also for parietal areas (Cabeza et al., 2004; Huang et al., 2012). Some recent studies combining structural and functional information found significant correlation between increased activity in some regions and structural preservation of other areas, especially for what concerns prefrontal activity (Braskie et al., 2009; Rosen et al., 2005). Therefore, although increased prefrontal local functional activity could be the result of reduced structural integrity, grey matter integrity of other areas (e.g. medial temporal lobes), as well as preservation of white matter long-range connections, could mediate these effects and give them different significance in terms of behavioral performance (Madden et al., 2009; Maillet and Rajah, 2013).

In addition to the complex relationship between functional overactivations, structural integrity and cognitive abilities in the aging brain, some recent evidences suggested that task-related compensatory attempts could be a response to altered resting-state functional connectivity networks.

1.2.3. Resting-state functional connectivity

Beside task-based fMRI approach to cognitive aging, which often faces practical constrains, a sharp interest in brain resting-state functional connectivity (RSFC) sprang unprecedentedly (for an extensive review on this topic, see Ferreira and Busatto, 2013). As indicator of synchronization of low frequency oscillations (<0.1 Hz) between different brain areas while not engaged in any particular activity (Biswal et al., 1995) RSFC is a feasible and reliable methodology to study cognitive changes in aging, allowing also large-scale data sharing thanks to its great comparability across different research samples (Ferreira and Busatto, 2013).

Among the multiple brain networks retrieved during rest (e.g. primary sensorimotor network, primary visual and extrastriate visual networks, fronto-parietal attentional networks and default-mode network), literature highlighted preferential age-related decrements in the default-mode network (DMN) and dorsal attentional network connectivity, which have been tightly linked to attention, memory and executive functions (van den Heuvel and Hulshoff Pol, 2010; Mevel et al., 2013). For what concerns the DMN, a network that comprises resting activity of medial prefrontal cortex, inferior parietal lobule, hippocampus and posteromedial cortex, evidences report decreased connectivity within this functional organization in old people when compared to young adults (Esposito et al., 2008; Hafkemeijer et al., 2012; Mevel et al., 2011; Prvulovic et al., 2011). More specifically, Independent Component Analysis (ICA) and seed-based studies revealed a specific vulnerability of medial prefrontal cortex, posterior cingulate cortex (Batouli et al., 2009; Koch et al., 2010; Wu et al., 2011) and anterior cingulate cortex connectivity (Esposito et al., 2008; Koch et al., 2010) in aging population, a decrement that probably begins already during the middle age (Evers et al., 2012). Interestingly, evidences of increased DMN task-based connectivity suggest that, although overall resting connectivity within this network is decreased in older people, failure in suppressing DMN during cognitive engagement could potentially explain cognitive impairment, as well as trigger compensatory activations of other networks during cognitive tasks. Moreover, the link between DMN disruption and cognitive impairment is further supported by studies showing that amyloid deposits in the brain are linked to reduced resting DMN connectivity (Sheline et al., 2010).

For what concerns fronto-parietal connectivity, studies show a significant increase in homotopic RSFC – a sign of reduced hemispheric asymmetry (Grieve et al., 2005) – and a consistent anterior-posterior cortical disconnection (Andrews-Hanna et al., 2007; Bollinger et al., 2011; Campbell et al., 2012; Grady, 2012; Grady et al., 2010; Kalkstein et al., 2011). Overall, these evidences highlight that long-range connections seem to be more vulnerable to aging than short-range connections (Tomasi and Volkow, 2012) and support the "last-in-first-out" hypothesis, namely a greater vulnerability of late-maturing regions of the brain to aging effects (Grieve et al., 2005; Kalpouzos et al., 2009; Terribilli et al., 2011). Intriguingly, evidences of increased dorsal fronto-parietal network and decreased ventral connectivity during executive tasks posit some food for thought on the balance between resting and task-related networks; given the reported anticorrelations between DMN and task-positive networks, it may be that resting disruption of DMN could turn into a failure to downregulate it during cognitive tasks, thereby overactivating task-positive fronto-parietal attentional networks to gain greater cognitive control (Reuter-Lorenz et al., 2010).

1.2.4. Electrophysiological changes

A necessary step toward a greater understanding of the functional role of resting and task-related functional activity in the aging brain encompasses the study of the relationship between BOLD signal fluctuations and the real language of neurons, namely brain electrical activity in the form of oscillatory patterns and evoked potentials.

Quantitative analysis of electroencephalography (EEG) is indeed a useful approach to assess neurophysiological changes occurring in aging; this is especially true if we consider the role of oscillatory brain activity in the transfer of information across the brain, in neuroplastic processes and in overall cognitive functioning (Kahana, 2006). One of the most reported EEG correlate of physiological aging is a prominent background EEG slowing (Vlahou et al., 2014) but, as we will discuss, the direction of the changes in specific brain oscillatory patterns and their overlap with pathological aging is still mixed up.

Overall, resting alpha power (8–13 Hz) decrease has been consistently reported and associated to an increased spectral power in slower delta (1–3 Hz) and theta (4–7 Hz) frequency bands (Finnigan and Robertson, 2011). A recent cross-sectional study added specific topographic locations to these changes, reporting linear and non linear changes in parietal, temporal and occipital alpha and in occipital delta amplitude (Babiloni et al., 2006). Modulated by thalamo–cortical and cortico–cortical interactions, resting alpha rhythm is the dominant resting oscillation in the adult awake brain and plays different key roles in the coordination of brain networks; lower alpha frequency band (8–10.5 Hz) seems to be related to the global level of attentional readiness and to long-range connectivity, whereas upper alpha waves seem implicated in the transmission of sensorimotor information as well as to semantic memory retrieval (Lizio et al., 2011). Furthermore, alpha power has been negatively associated to global gray matter and hippocampal atrophy in MCI and AD patients, thereby suggesting the existence of a continuum from healthy aging to Alzheimer's disease and that the characterization of alpha amplitude and coherence could be further investigated to improve differential diagnosis (Bian et al., 2014).

For what concerns increased delta (1–3 Hz) and theta (4–7 Hz) power, reports are quite inconsistent, at times reporting a power increase (Dujardin, 1994; Dujardin et al., 1995; Klass and Brenner, 1995) at others a decrease (Klimesch, 1999; Stomrud et al., 2010). As Finnigan and Robertson (2011) suggested, theta frequency increase could be a consequence of the slowing of the resting alpha peak and could be considered as a candidate biomarker of the aging brain. However, as Vlahou et al. (2014) commented in his work, higher theta power not associated with alpha slowing could be interpreted as a marker of healthy aging per se. This latter suggestion seems to be confirmed by a study by Grunwald et al. (2001), which found a negative linear correlation between theta power and hippocampal volume reduction. Moreover, behavioral significance of these changes are still controversial (Finnigan and Robertson, 2011; Prichep et al., 2006). In a recent study, Vlahou et al. (2014) tried to address this issue by investigating associations between changes in oscillatory activity and cognitive performance. Results showed that healthy aging was associated with a widespread linear decrease of slow wave power (<7 Hz) and that the maintenance of a higher resting delta and theta power was positively correlated with cognitive performances across different domains.

Taken together, these patterns of changes in slower oscillatory activity could be considered as a compensatory attempt to control information processing in order to accomplish task demands. Nevertheless, a clearer characterization of the relationship between cognitive performance and resting EEG activity on the continuum from healthy aging to dementia is needed.

1.3. *Beyond a "wear-and-tear" conception of the aging brain*

Given the correlational, rather than causal, nature of the neuroimaging and neurophysiological studies above mentioned, one still burning question about age-related cognitive and neurophysiological modifications is related to the actual meaning of these functional changes, namely, whether they reflect signatures of brain inefficiency, an adaptive compensatory attempt (Grady, 2008), or both. Far from being a definite effective countermove to aging processes, specific patterns of activation in the elderly aging brain could be non influential or even detrimental to cognitive performances (Fabiani et al., 1998; Stevens et al., 2008). In a classic study by Schacter et al. (1996), for instance, increased posterior PFC activity in elderly during memory retrieval was not associated with better performances. This result, interpreted as an effect of an inefficient phonology-based strategy to retrieve items, tap into the hypothesis that some compensatory attempts reflect nonspecific or less efficient recruitment of neural resources during task performance (Baltes and Lindenberger, 1997; Grady, 2008). Known as the "Dedifferentiation theory of neural processing" (Li et al., 2010), this concept is rooted in the idea that brain functional differentiation during human development is reversed in the elderly, an interpretation supported by evidences of stronger correlations both among cognitive measures and between cognitive and sensory functioning measures (Reuter-Lorenz et al., 1999). Irrespective of the considered model of brain aging, a fruitful avenue to demonstrate whether the different "activations" of the aging brain are necessary to keep on a satisfactory performance is to target these regions with repetitive transcranial magnetic stimulation (rTMS), which transiently disrupts neural activity (Rossini et al., 2015). Using this approach, Rossi et al. (2004) showed that both PFCs contributed equally to retrieval processes in the elderly, according with the HAROLD model, while encoding processes remained left-lateralized for the whole life span.

On the basis of recent literature, therefore, a wear-and-tear conception of the aging brain sounds too hasty: far from being a bare reverse developmental process, aging encompasses dynamic and plastic modifications aimed at preserving cognitive functioning despite the impairment of usual neural resources. Hence, an overloaded neural system attempts an active compensation through the recruitment of reserve neural resources. As the "Scaffolding Theory of Aging and Cognition" expresses (STAC – Park and Reuter-Lorenz, 2009), compensation activity in the aging brain subsumes some neuroplasticity mechanism that sustains cognitive functioning by boosting activity in task-related brain regions and/or engaging alternative brain regions through functional connectivity. Attempted compensation seems to have a complex asymptotic or even inverted-U relationship (Cabeza and Dennis, 2012) both with brain decline and task demands, such that it will be greater with higher levels of brain impairments and task demands but will relentlessly show no change, or even a decrease, once neural resources reach their plateau. This effect is well described by applying the "Compensation-related utilization of neural circuits hypothesis" (CRUNCH – Reuter-Lorenz et al., 2008) to the elderly. As many studies reported, older adults tend to recruit additional areas at lowers levels of task demands, wearing out compensatory resources to meet higher levels of task difficulty and, consequently, impairing their performances (Reuter-Lorenz et al., 2008). Literature reports solid evidences of the compensative nature of age-related brain activations: HAROLD and PASA patterns described before, for example, were found positively correlated with task performances (Cabeza et al., 2002; Davis et al., 2008). Moreover, also large functional networks are involved in age-related compensatory activity: by applying a split-field matching paradigm (Banich and Belger, 1990) to a semantic memory task, Davis et al. (2012) found a stronger functional connectivity between left and right PFC in elderly and a positive relationship between increased cross-hemispheric connectivity and behavioral performance in bilateral presentation condition. Despite evidences of the existence of non-beneficial large scale functional connectivity changes (Andrews-Hanna et al., 2007; Rajah and McIntosh, 2008), this study is in line with findings indicating that cognitive performances of the elderly could be sustained not only by increased local activity but also by large scale networks changes, such as prefrontal-medial temporal lobe (MTL) connectivity during memory tasks (Daselaar et al., 2006; Gong et al., 2009; Li et al., 2010; Meunier et al., 2009; St Jacques et al., 2009; Wang et al., 2010) and frontal and occipital-parietal phase locking in high beta band (21–30 Hz), which seems to compensate reduced alpha power during selective attention tasks (Geerligs et al., 2012).

In light of these evidences, the large behavioral variability observed in the elderly could be explained in terms of the ratio between attempted and successful recruitment of cognitive-related or unrelated brain areas and networks to keep up cognitive performances, raising the possibility of efficiently addressing these efforts through the identification of predictors and the relative creation of proper interventions. Recently, in the wake of the positive results on healthy young and neuropsychiatric patients (Miniussi et al., 2008; Nitsche et al., 2008), rising efforts have been made to test the chance of enhancing cognitive physiologically-declining functions in the aging brain through non invasive brain stimulation (NiBS). The term NiBS encompasses different methods aimed at inducing transient changes in brain activity and, in turn, altering behavioral performance, by means of electrical currents or magnetic pulses applied on the scalp; as we will describe in greater detail in the following paragraphs, different types of stimulation (transcranial magnetic stimulation, TMS; transcranial alternating current stimulation, tACS; transcranial direct current stimulation, tDCS; transcranial random noise stimulation, tRNS), each one affecting neuronal activity with different mechanisms, are used in cognitive neuroscience. An emerging body of research mostly based on two non invasive brain stimulation techniques, tDCS and rTMS, is offering promising evidences on the feasibility of applying these methods to aging population. Therefore, the present review updates and discusses present state of art on NiBS in healthy aging to enhance cognitive functioning.

2. Search strategy and inclusion criteria of the review

Potentially relevant papers have been retrieved by performing a PubMed database search without temporal restrictions. In the attempt of focusing the search on healthy elderly population, the terms “aging”, “ageing” or “elderly” were combined with terms such as “healthy”. To specify the object of the present review, these terms were combined with terms such as “repetitive transcranial magnetic stimulation”, “transcranial direct current stimulation”, “transcranial alternating current stimulation” (a transcranial electrical stimulation based on the application of oscillatory potentials aimed at modulating intrinsic brain oscillatory activity) (Groppa et al., 2010), “transcranial random noise stimulation” (a technique based on an increase of cortical excitability levels through the injection of pseudo-random electrical patterns which alter the signal-to-noise ratio of targeted brain region) (Terney et al., 2008) and related acronyms (respectively rTMS, tDCS, tACS, tRNS). The searches for study population and research topic were combined with AND, resulting in the final search. Results on Google Scholar and Science Direct databases and references of retrieved researches were examined for relevant publications too. We intentionally excluded studies that only focused on elderly patients with a psychiatric, neurological or neurodegenerative disease, in which NiBS was used as a neuromodulatory treatment option, as well as those studies applying NiBS techniques to investigate neurophysiological mechanisms of the aging brain. The final selection comprised 3 studies related to rTMS, 17 studies related to tDCS and 1 study related to tRNS. No studies related to tACS and healthy aging were retrieved on online databases.

For each transcranial Electrical Stimulation (tES) study, we retrieved: (i) number of subjects, (ii) mean age, (iii) mean education, (iv) experimental design (i.e. type of design-within/between subjects, single/double blind, sham controlled, follow up), (v) NiBS specifics (i.e. electrode size, target electrode, reference electrode, intensity, duration, online/offline stimulation), (vi) cognitive task specifics, (v) main results. For rTMS literature, we extracted: (i) number of subjects, (ii) mean age, (iii) mean education, (iv) experimental design (i.e. type of design-within/between subjects, single/double blind, sham controlled, follow up), (v) NiBS protocol specifics (i.e. Sham method, stimulation site localization method, coil type, type of stimulation and related intensity, stimulation duration), (vi) task specifics, (v) main results. A schematic overview of the results of the reviewed studies is shown in Tables 1 and 2.

3. NiBS techniques and neuroenhancement of the healthy aging brain

3.1. Repetitive transcranial magnetic stimulation (rTMS)

First introduced by Barker et al. in 1985 (Barker et al., 1985), TMS is a non-invasive technique to stimulate the brain. Based on Faraday’s principle of electromagnetic induction, TMS discharges brief (200–300 μs) and powerful (0.2–4.0 T) magnetic pulses tangentially to the skull, creating a secondary electrical current that abruptly changes the excitability of the underlying neurons, thus inducing neuronal firing. Trains of single TMS pulses (up to a 100-Hz repetition rate) with a constant frequency and intensity characterize repetitive transcranial magnetic stimulation (rTMS). According to the frequency of stimulation, rTMS induces after effects on cortical excitability, mainly impacting on synaptic efficiency, that may result in a net inhibitory effect when delivered at low frequency (1 Hz or less) or an excitatory one, when delivered at high frequency stimulation (≥ 5 Hz) (Rossi et al., 2009). Long Term Depression (LTD) or Long Term Potentiation (LTP) are the synaptic mechanisms invoked to explain such lasting effects (Cooke and Bliss, 2006). The characteristics of the rTMS/TMS induced magnetic field can be shaped by different types of coils, making it more focal (as in the case of a figure-eight coil) or reaching greater depths (as in the case of deep TMS coils, e.g. the double cone or the H-coils). Despite the use of deep TMS coils could reach potentially harming depths up to 6 cm (Deng et al., 2013), TMS is usually restricted to superficial cortical targets, at a depth of 2–3 cm beneath the scalp. Noticeably, stimulation-induced effects of TMS and rTMS largely depend not only by “technical” features such as device characteristics (e.g. type of coil), parameters set (e.g. intensity and frequency) and experimental procedure (e.g. coil orientation, on-line/off-line pulses discharge, respectively during or before a task) (Thut and Pascual-Leone, 2010); subject-related variables, including state-dependency (level of neural activity during stimulation), age and eventual pharmacological treatments (Miniussi et al., 2010; Rossini et al., 2010; Silvanto et al., 2008) also affect the efficacy of rTMS stimulation. Nonetheless, some major issues make sometimes difficult to disentangle between real and placebo-mediated effects of rTMS protocols; clicking sounds produced by the current flow in the TMS coil, sensory stimulation of the skin and muscular twitches of the face due to direct stimulation of trigeminal and facial nervous fibers could indeed influence task performances and lead to confounding results. One approach to deal with these effects is to hold the coil in a perpendicular orientation: this resembles similar sensory side effects of the active TMS stimulation but do not ward off any possible residual brain stimulation and, of course, limits the blinding of participant and researcher. Conversely, sham TMS coils, which implement a magnetic shield to prevent neural stimulation, strongly attenuate skin and muscles stimulation and require additional surface electrodes to proper control for sensory effects (Duecker and Sack, 2015; Rossi et al., 2007). Alongside issues related to TMS control conditions, the need of MRI scans and neuronavigation systems to precisely target brain areas makes the implementation of TMS protocols less handy than other NiBS techniques.

Despite these potential limitations, a large body of placebo-controlled evidence reports cognitive improvement after high frequency rTMS in healthy young adults and in patients with psy-

Table 2
Summary of studies using tES neuro-enhancement protocols in healthy aging.

Studies	N	Age (mean ± SD years)	Education	Experimental design	Conditions	Electrode size	Target electrode	Reference electrode	Intensity/ duration	Task	Cognitive domain	Online/ Offline	Effects	Follow up	Result
Ross et al. (2011)	14	65	/	Single-blind crossover sham controlled	a-tDCS s-tDCS	7 × 5 cm	ATL (T3/T4)	Contralateral cheek	1.5 mA 15 min	Naming of 130 photographs of famous people and 99 photographs of famous landmarks	Language	Online	Left tdcs increases naming performance for famous people. Only in cases in which the names were not immediately available. Right a-tdcs improves the ability to recall names of places	No	↑ accuracy left a-tDCS for people naming ↑ accuracy right a-tDCS for places naming
Meinzer et al. (2013)	20	68.0 ± 5.7 range 60–76	/	Crossover sham-controlled	a-tDCS s-tDCS	5 × 7 10 × 10 cm (reference)	Left ventral IFG (F5)	Right supraorbital region	1 mA 20 min	Semantic word-retrieval task	Language	Online (fMRI)	Older participants produced significantly fewer errors during a-tDCS compared with sham participants. No effect on RT	No	↑ Accuracy l-IFG
Meinzer et al. (2014)	18	68.38 ± 5.15	15.88 ± 4.74	Within-subject triple cross-over sham controlled	a-tDCS c-tDCS s-tDCS	7 × 5 cm	Primary motor cortex (C3)	Right supraorbital region right motor cortex(c4)	1 mA 30 min	Semantic word-retrieval task	Language	Online	Both active tdcs conditions significantly improved word-retrieval compared to sham-tDCS.	No	↑ Accuracy l-a-tDCS
Fertonani et al. (2014)	20	66.5± 5.5	10.5	Crossover single-blind sham controlled	a-tDCS s-tDCS	7 × 5 cm	Left dlPFC (F3)	Right shoulder	2 mA 4–5 min for online a-tDCS 10 min offline a-tDCS 6–7 min s-tDCS	Picture-naming task	Language	Offline/online	tDCS improved naming performance, decreasing the verbal reaction times only if it was applied online.	No	↓ Verbal RT online a-tDCS
Hummel et al. (2010)	10	69 ± 9.24 range 56–87	/	Counterbalanced double-blind design sham controlled	a-tDCS s-tDCS	5 × 5 cm	Hand knob area of the left M1	Contralateral supraorbital region	1 mA 20 min	Jebsen–Taylor Task (JTT)	Motor	Offline	Significant improvement in JTT function with tDCS relative to sham that outlasted the stimulation period by at least 30 min	No	↓ JTT time a-tDCS
Zimerman et al. (2013)	10 a-tdcs 5 c-tdcs	68.5 ± 3.2 a-tdcs 71.2 ± 1.9 c-tdcs	/	Double-blind, sham-controlled, cross-over	a-tDCS s-tDCS	5 × 5 cm	C3	Contralateral supraorbital region	1 mA 20 min	Finger-Tapping Task	Motor	Online	Improvements when training was applied concurrent with a-tDCS, with effects lasting for at least 24 h	90 min 24 h after	↑ Accuracy online a-tDCS
Lindenberg et al. (2013)	20	68.2 ± 5.0 range 61–77	/	Crossover sham controlled	dual/anodal/ sham tDCS	7 × 5 cm 10 × 10 cm (c-tDCS)	C3	C4 (dual tDCS) contralateral supraorbital region	1 mA 30 min	Choice Reaction Time Task	Motor	Online (during fMRI)	No effect of stimulation condition on the number of errors or reaction times; Task-related fMRI revealed dual but not anodal tDCS enhanced connectivity of the left dorsal posterior cingulate cortex. Furthermore, dual tDCS yielded stronger activations in bilateral M1 compared with anodal tDCS when participants used either their left or right hand during the motor task.	No	No behavioral effects

Parikh and cole (2014)	8	75 ± 8 range 63–84	/	Single-blind crossover sham controlled	a-tDCS, s-tDCS + motor practice (MP) on the Pegboard test	5 × 5 cm	M1 (found with TMS)	Right supraorbital region	1 mA 20 min	Key-slot task tactile sensibility test isometric task grooved pegboard	Motor	Online/Offline	Practice improved performance on the pegboard test, and a-l tDCS + MP improved retention of this performance gain when tested 35 min later, whereas similar performance gains degraded in the sham group after 35 min.	No	Grooved pegboard and key slot task ↓ time a/s-tDCS + MP isometric precision grip task ↑ grip force variability with a-tDCS (negative)
Flöel et al. (2012)	20	62.1 ± 9.2 range 50–80	13.2 ± 2.3	Double-blind design sham controlled	a-tDCS s-tDCS	7 × 5 cm 10 × 10 cm (reference)	Right temporoparietal area (T6/P4)	Contralateral supraorbital region	1 mA 20 min	Object-location learning task	Memory/learning	Online	atDCS did not alter the learning rates on an object-location task in elderly subjects. However, delayed free recall was significantly improved after atDCS.	1 week	↑ Accuracy delayed free recall
Manenti et al. (2013)	32	67.91 ± 4.72	10.75 ± 4.63	Between subjects single-blind sham controlled	a-tDCS s-tDCS	7 × 5 cm	F3/F4 PARC (P7/P3, P8/P4)	Contralateral supraorbital area	1.5 mA 6 min	COLFIS encoding and recognition of abstract and concrete words	Episodic memory	Online	Only tDCS applied over the left regions (dlPFC and PARC) increased retrieval in older subjects	No	↑ Accuracy a-tDCS on left dlPFC and PARC
Sandrini et al. (2014)	36	67.17 ± 3.68	12.05 ± 4.40	Between subjects single-blind	a-tDCS s-tDCS	7 × 5 cm	F3	Right supraorbital area	1.5 mA 15 min	COLFIS encoding and retrival of abstract and concrete words	Episodic memory	Offline	A-tDCS over the left dlPFC (i.e., with or without the reminder) strengthened existing verbal episodic memories and reduced forgetting compared to sham stimulation	48 h 1 month	↑ Accuracy a-tDCS
Berryhill and Jones (2012)	25	63.7 range 56–80	High = 16.9 Low = 13.5	Crossover sham controlled	a-tDCS s-tDCS	7 × 5 cm	F4/F3	Contralateral cheek	1.5 mA 10 min	Visual and verbal 2-back WM tasks	WM	Offline	Improvement in WM performance selectively in participants with higher education. In the low education group, tDCS, especially to the right PFC, impaired visual WM performance but had no effect on verbal WM	No	↑ Accuracy in higher education group ↓ Accuracy on visual WM performance in low education group
Boggio et al. (2010)	28	69.4 ± 8.9 r tDCS 68.9 ± 12.6 l-tDCS 67.0 ± 9.0 s-tDCS	9.2 ± 5.2 r-tDCS 7.0 ± 5.2 l-tDCS 5.2 ± 4.5 s-tDCS	Double-blinded between-subjects sham-controlled	l a/r c-tDCS (N = 9) r a/l c-tDCS (N = 10) s-tDCS (N = 9)	7 × 5 cm	F3/F4	F4/F3	2 mA 10 min	Risk task	Decision making	Online	Left anodal/right cathodal stimulation increased risky choices as compared with sham stimulation and right anodal/left cathodal stimulation.	No	↑ Risky decision-making with left a-tDCS

Table 2 (*Continued*)

Studies	N	Age (mean ± SD years)	Education	Experimental design	Conditions	Electrode size	Target electrode	Reference electrode	Intensity/ duration	Task	Cognitive domain	Online/ Offline	Effects	Follow up	Result
Harty et al., 2014	106	72.13 (6.0) a-r tDCS 69.41 (4.3) a-l tDCS 69.71 (4.2) c-r tDCS 72.08 (5.7) a-r tDCS range: 65–86	14.92 (3.6) a-r tDCS 13.04 (3.5) a-l tDCS 14.58 (3.5) c-r tDCS 14.17 (3.6) a-r tDCS	Single-blind crossover	a-tDCS c-tDCS	7 × 5 cm	F4/F3	Cz	1 mA 5 × 7,5 min	EAT Go/No-go response inhibition task	Cognitive control	Online	Anodal tDCS over right dlPFC was associated with a significant increase in the proportion of performance errors that were consciously detected. No such improvements were observed with l a-tDCS	No	↑ Accuracy in error detection
Manor et al., 2016	37	61 ± 5	/	Double-blinded Crossover design	a-tDCS s-tDCS	7 × 5 cm	F3	Right supraorbital area	Individual current intensity 1.4 ± 0.4 mA 20 min	Single tasks: –Walking –Standing –Counting backward while seated Dual tasks: –walking while counting backward –standing while counting backward	Cognitive control	Offline	tDCS improved performance in dual task conditions. No effect on single task conditions.	No	↓ dual task costs
tDCS multisession + ct	N	Age (mean ±sd years)	Education	Experimental condition	Conditions	Electrode size (cm)	Stimulated areas	Reference electrode	Intensity/ duration	Task	Cognitive domain	Online/ offline	Effects	Follow up	Result
Park et al. (2013)	40	69.7 tDCS group 70.1 ± 3.4 sham group 69.4 ± 3.1	tDCS group 10.9± 4.6 sham group 10.9 ± 4.2	Between subject design sham controlled	a-tDCS s-tDCS 10 sessions a-tDCS/s-tDCS combined with CACT cognitive training	5 × 5 cm	F3/F4 (bilateral anodal stimulation)	Non-dominant arm	2 mA 30 min	Verbal 2-back WM Digit Span Test Verbal Learning Test Visual Span Test Visual Learning Test Auditory Continuous Performance Test (CPT), Auditory Controlled CPT Visual CPT Visual Controlled CPT Word–Color Test Trail Making Test	WM, STM	Offline	The accuracy of the verbal working memory task and digit span forward test were significantly improved with a-tDCS as compared with s-tDCS. The effect lasted for 4 weeks in the verbal WM task.	7 and 28 days after	↑ accuracy verbal WM and digit span ↓ RT in WM
Jones et al. (2015)	72	64.38 ± 5.08 Range: 55–73	/	Between subject design Sham controlled	a-tdcs sham no-training group 4 groups10 consecutive weekday sessions + WM training	5 × 7 cm	a-tdcs F4 a-tdcs P4 alternating a-tdcs F4-P4	Contralateral cheek	1.5 mA 10 min	Trained: Visuospatial WM Automated Operation Span Transfer: Digit Span Stroop Task Spatial 2-back	WM	Offline	All the groups showed improvements ontrained and transfer No difference between F4 and P4 a-tDCS At follow up only participants in the a-tDCS group maintened the results	1 month	↑ accuracy
tRNS multisession + ct	N	Age	Education	Experimental condition	Conditions	Electrode size (cm)	Stimulated areas	Reference electrode	Intensity/ duration	Task	Cognitive domain	Online/ offline	Effects	Follow up	Result
Cappelletti et al., 2015	30	65.5 range: 60 –73	/	Single-blind between subject design sham controlled	t-RNS	7 × 5 cm	P3/P4 C3/C4	/	1 mA 20 min	Numerosity discrimination task	Number acuity	Online	Numerosity discrimination improved after training and was maintained long term (16 weeks). Effects were prominent in P3/P4 tRNS condition. Transfer effects to untrained tasks probing inhibitory ability were found.	7 days and 16 weeks after	↑ Accuracy in number discrimination

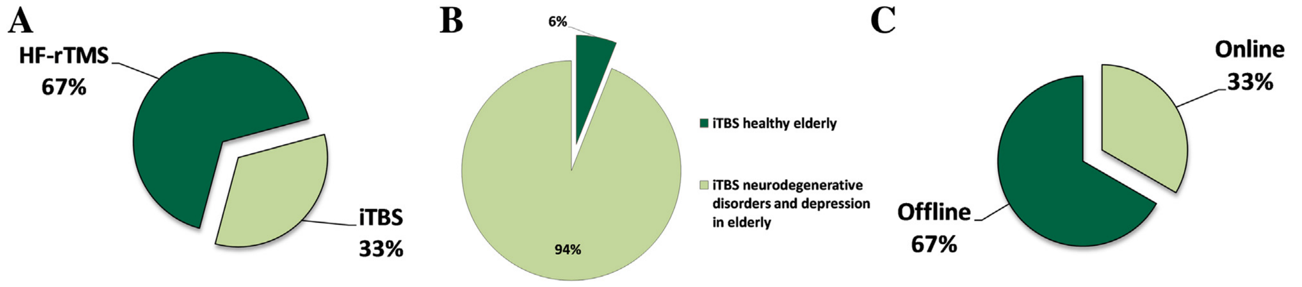

Fig. 1. Brief overview showing the status of the literature about rTMS-based protocols for cognitive neuroenhancement in aging population. Panel (A) type of rTMS protocol adopted; Panel (B) Comparison between number of NiBS studies published on elderly with neurological/neuropsychiatric diseases and those on healthy aging; Panel (C) % of studies employing an Online or an Offline design.

chiatric/neurological diseases (Guse et al., 2010; Lefaucheur et al., 2014; Miniussi et al., 2008). Regarding aging population, greater efforts have been spent in the investigation of rTMS potential in the treatment of cognitive symptoms of neurodegenerative diseases and in the treatment of late-life depression (see Fig. 1, Panel B for a comparison between rTMS applications in aging population). Despite proofs of its feasibility in cognitive neurorehabilitation, TMS literature on healthy aging population is mainly based on “virtual lesion” approach (Pascual-Leone et al., 2000; Walsh and Cowey, 2000; Walsh and Rushworth, 1998; Rossini et al., 2007), namely attempting to find causal nexus between functional activity and a particular cognitive function, and on the impact of TMS on cortical excitability of the aging brain.

As we found in online databases, three studies investigated the potential of rTMS in enhancing cognitive functioning of the healthy elderly (Table 1); one elegant study by Cotelli et al. (2010) extended their previous study on the neuroenhancement of naming ability in Alzheimer’s disease (AD) (Cotelli et al., 2008, 2006) in a group of 13 healthy elderly subjects. They applied 20 Hz rTMS during an action-naming task and found reduced verbal reaction times (vRT) for action naming during both left and right dorsolateral prefrontal cortex (DLPFC) stimulation. Differently from previous results with AD patients, in which also an improvement in accuracy was found, the only vRTs improvement in healthy aging shown in this study was explained in terms of “ceiling” performances”, an effect that could hide beneficial rTMS-effects on accuracy in healthy aging population. A similar result was obtained in another high-frequency rTMS (HF-rTMS) study on inhibitory control (Kim et al., 2012). A five days 10 Hz HF-rTMS treatment over the left DLPFC was conducted in 16 healthy elderly females. A significant positive improvement in reaction times in Stroop task trials with conflicting information was found, a result in line with earlier findings on elderly clinical population (Boggio et al., 2011; Moser et al., 2002; Rektorova et al., 2005). Most notably, given that the cognitive task was performed the day after stimulation, this result stands for the possibility of eliciting long-lasting effect in the aging brain. Recently, the idea that multiple HF-rTMS sessions could elicit longer lasting cognitive effects (Eisenegger et al., 2008) has been systematically reviewed, providing sound evidence that multiple sessions (10–15) of HF-rTMS (10–20 Hz) applied over the left DLPFC is most likely to cause significant neuroenhancement (Guse et al., 2010). Despite the work by Kim et al. designed only five stimulating sessions with no follow up, this study confirmed that multiple HF-rTMS trains applied to DLPFC are able to induce an effect that lasts longer than single session stimulation in the healthy aging brain.

3.2. Theta-burst stimulation

Recently, a new promising paradigm of rTMS has been introduced to produce long lasting effects in neuronal activity in a shorter time of intervention (i.e., few minutes): theta burst stimulation (TBS) uses bursts of high frequency stimulation (3 pulses at 50 Hz repeated at 200 ms intervals) that could be applied intermittently (iTBS) or continuously (cTBS) to induce, respectively, LTP and LTD effects of synaptic activity (Di Lazzaro et al., 2008; Huang et al., 2005). According to the model proposed by Huang et al. (2011), both patterns of stimulation trigger mixed excitatory and inhibitory effects whose sum produce different changes in cortical excitability by the modification of synaptic strength. iTBS seems to elicit LTP-like effects by keeping short-latency facilitation effects dominant on the inhibitory ones; conversely, cTBS enhances longer-latency inhibitory effects resulting in LTD-like effects (Suppa et al., 2016). However, the mechanisms underlying cortical excitability changes induced by TBS protocols are still controversial as some authors refer to the modulation of NMDA receptors (Di Lazzaro et al., 2008; Huang et al., 2005), others to GABAergic receptors (Harrington and Hammond-Tooke, 2015; Thickbroom, 2007) and still others hypothesize a modulation of the expression of transcription factors, such as nerve-growth-factor-induced protein A (NGFI-A) (Aydin-Abidin et al., 2008).

Evidences of the efficacy of TBS in the modulation of cognitive functioning are in their infancy: based on the finding that inhibitory cTBS is able to impair accuracy in working memory (Morgan et al., 2013) and emotional control (Volman et al., 2011), neuroenhancement of cognitive functions could be theoretically possible by using excitatory iTBS paradigms. However, iTBS approaches aimed at enhancing cognitive functions gave rise to still inconsistent results: Restle et al. found speech repetition facilitation after iTBS (Restle et al., 2012), but Läppchen et al. (2015) found surprisingly significantly poorer motor performances in healthy young subjects after daily applications of intermittent theta burst stimulation during a four-day training program. The only study retrieved on the application of iTBS on aging population (Vidal-Piñeiro et al., 2014), assessed the effect of 600 iTBS pulses (3 pulses of 50 Hz at an intensity of 80% AMT, repeated every 200 ms) over left inferior frontal gyrus (IFG) on episodic memory. iTBS did not affect memory performance but it influenced functional activity in a task-dependent manner: when subjects were performing deep semantic encoding, increased blood oxygenation level dependent (BOLD) signal in local (left IFG) and distant related areas (occipital cortex and cerebellum) was found. This result, discussed more in depth in Section 4.3, highlights that iTBS can modulate brain networks (Halko et al., 2014). Lack in behavioral changes could be attributed to unilateral IFG stimulation, instead. Based on theoretical models discussed in the introductive part of the present review, the bilaterality of task-dependent activity observed in healthy aging suggests that bi-hemispheric stimulations could be more effective to induce cognitive neuroenhancement in older subjects. This suggestion is further motivated by some studies arguing on the possibility of inducing bihemispheric plasticity by means of unilateral iTBS (Di Lazzaro et al., 2008; Dickins et al., 2015). Indeed, the great individual variability on the plasticity effects triggered by iTBS makes the understanding of the effects of iTBS more difficult (Lopez-Alonso et al., 2014). Therefore, further studies aimed at identifying the role of intervenient variables-such as the interaction between attention and age (Dickins et al., 2015) are needed.

3.3. *Transcranial electrical stimulation (tES)*

tES encompasses a series of techniques in which weak currents are applied on the scalp to target cortical brain regions (Paulus et al., 2013). Typical dose parameters of tES methods are: the number of the electrodes, their shape, size and position, current waveform, its density and stimulation duration. tES is typically applied on the subject's head by means of at least two surface electrodes soaked with saline water or an electroconductive gel and linked to a current waveform generator. Given the reduced electric conductivity of the skull, which requires high voltages in order to depolarize neurons (a painful procedure usually performed under anesthesia, mostly known as electroconvulsive therapy-ECT), non-invasive tES uses subthreshold electrical currents and ground their potential on the capability of shifting intrinsic neuronal excitability rather than eliciting neuronal firing (Radman et al., 2009; Paulus, 2011). Indeed, excitatory tES has a bimodal polarization effect, that is cell membrane depolarization limited to 2 mV (Fröhlich and Schmidt, 2013) and the hyperpolarization of apical dendrites (Bikson et al., 2004). On the basis of the waveform of the electrical current and its polarity, different non-invasive tES protocols can be implemented, namely: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) (Nitsche et al., 2008; Paulus, 2011) (Fig. 2).

Compared to rTMS/TBS, low-intensity tES protocols have the advantage of being handier and portable. Indeed, low costs associated with the creation of tES protocols, make this technique more feasible both at home or in clinical settings. TES produces only mild transient adverse effects, such as itching, tingling, or reddening of the scalp (Poreisz et al., 2007), and it allows a more reliable sham condition than rTMS/TBS, thereby guaranteeing more robust double-blind designs. However, data are still too few to discern whether cost-effectiveness is in favor of rTMS or tES.

Despite these pros, it must be noted that tES methodic is less accepted than rTMS in the clinical settings due to its lack in spatial specificity (mostly related to the use of bipolar montages and big-sized pad electrodes). In light of this major limit, some technological advancement, such as the use of ring and concentric electrodes (Datta et al., 2008; Nitsche et al., 2007) have been recently made; moreover, computational forward models developed to predict the electrical field induced by specific neuromodulation designs (Bikson et al., 2012) are providing useful information to customize electrode montages in order to reach higher spatial focality and to gain insight on the neurophysiological effects of brain stimulation. However, it must be mentioned that anatomical differences across subjects could still account for differences in the induced electrical field and, lastly, to different behavioral outcomes. For the purposes of our review, this issue is particularly relevant; in line with the observations made on tES in patients with stroke (Liew et al., 2014; Wagner et al., 2007) and with the previously reviewed structural changes in the aging brain (e.g. ventricular enlargement), the distribution of the current applied could be significantly different in the aging brains, a fact that should be taken into account in the design of the electrode montage on aging population. Currently, more realistic models accounting of anatomical differences have been created and, probably, future studies on the effects of tES in healthy aging should resort to individual MRIs in order to reach more controlled neuromodulatory effects on the aging brain (Wagner et al., 2007).

Despite these limits, current evidences strongly support the utility of tES interventions to enhance cognitive functions. In the following paragraphs, specific tES methodic will be individually reviewed in order to discuss their feasibility to enhance cognitive abilities of the aging brain.

3.3.1. *Transcranial direct current stimulation (tDCS)*

tDCS is undoubtedly the most known and studied technique of the tES realm. Based on the application of direct continuous electric currents on the scalp, tDCS elicits both neuronal membrane depolarisation or hyperpolarisation on the base of its polarity, respectively anodal and cathodal (Liebetanz et al., 2002; Nitsche et al., 2003, 2004, 2005; Priori et al., 1998) and in line the concept of homeostatic metaplasticity (Siebner et al., 2004). So, in contrast to TMS, which could elicit action potentials, tDCS can be considered a pure neuromodulatory technique altering spontaneous firing rate of neurons and synaptic responses to afferent inputs (Miniussi and Ruzzoli, 2013). These neuronal changes are attributed both to short-term modification of resting membrane potentials and, in the case of long-term effect, to NMDA-dependent mechanisms related to an increase in intracellular Ca^{2+} levels (Liebetanz et al., 2002). In support to the role of NMDA-receptors in tDCS after-effects, Liebetanz et al. (2002) showed that both anodal and cathodal tDCS after-effects could be prevented by the intake of the NMDA-receptor antagonist dextromethorphan (DMO), while carbamazepine (a sodium-channel blocker) has similar suppressing effects limited to anodal stimulation. Other pharmacological approaches have also demonstrated that tDCS effects involve glutamatergic, serotoninergic, GABAergic and dopaminergic system modifications (see Mederos et al., 2012 for a review on neurobiological mechanisms of tDCS).

According to these premises, tDCS could be an excellent protocol to heal cognitive functioning of the elderly, promoting plastic effects that could increase beneficial compensatory activity or reduce inefficient neural activity. Broad attractively proofs were still provided by research on healthy young adults and on pathological conditions, where tDCS-based cognitive neuroenhancement yielded to promising results in several cognitive domains (Brunoni et al., 2012; Miniussi et al., 2008). In recent years, research on tDCS effects on cognition of the elderly impressively increased. Our online research on tDCS-based cognitive neuroenhancement of healthy aging population resulted in 17 studies (Table 2).

3.3.2. *Motor functioning*

Based on a qualitative analysis, modulation of motor control is currently the most studied aspect with tDCS in the aging brain. This is not surprising, given the impact of motor function on daily self-sufficiency of the elderly, and due to the fact that motor cortex excitability has been the "historical" target to measure tDCS effects (Bastani and Jaberzadeh, 2012). Although evidences on the neurophysiological effects of tDCS are pivotal in the understanding of the behavioral outcomes of tDCS-based interventions, the present section will only focus on the possibility of enhancing motor abilities in the elderly but we refer to the recent meta-analysis by Horvath et al. (2015) for an extensive overview on this topic.

The first non-invasive neuromodulatory attempt on motor functioning of healthy elderly is by Hummel et al. (2010). They examined the effect of a single session of anodal tDCS (a-tDCS) over the left primary motor cortex on a task that mimics activities of daily living (Jebsen–Taylor hand function test-JTT; Jebsen et al., 1969). They found that, compared to sham, the application of a-tDCS (1 mA for 20 min) improved significantly JTT function, an effect that outlived by approximately 30 min and that was most prominent for fine manipulative motor tasks. An intriguingly evidence of this study was that improvement was increasingly more evident the older the subjects were, although this effect probably just indicates that the oldest-old have greater leeway to improvement because they are not able to reach ceiling performances. Moving toward more complex forms of motor control, Zimerman

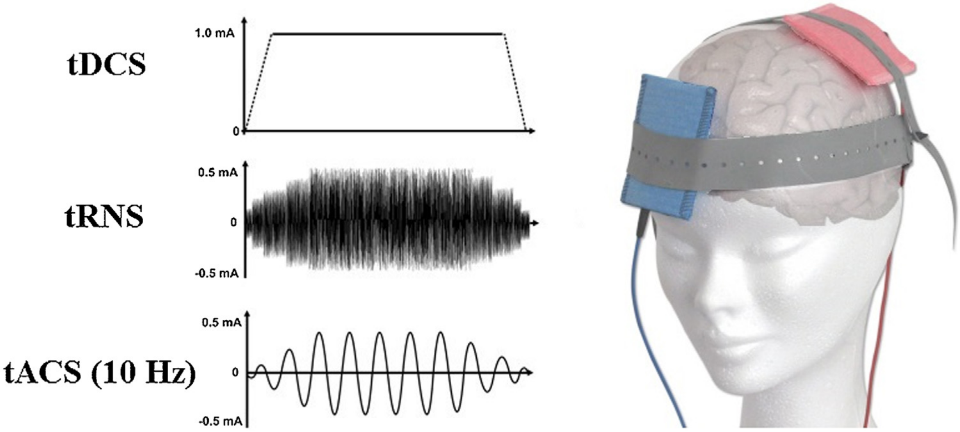

Fig. 2. Non-invasive tES paradigms. By means of the application of subthreshold direct currents, tDCS modulates spontaneous neuronal firing frequency eliciting both neuronal membrane depolarisation or hyperpolarisation on the basis of its polarity (anodal stimulation of the left primary motor cortex is shown in the figure), tRNS encompasses the application of random noise electrical patterns which alter the signal-to-noise ratio of targeted brain region and, supposedly, increase cortical excitability. Finally, tACS is based on the application of oscillatory electrical potentials aimed at modulating intrinsic brain oscillatory activity.

et al. (2013) examined whether a-tDCS resulted in long-lasting improvement of skilled motor performance on a finger-tapping task (FTT), with 20 min of online stimulation during a motor skill acquisition training being able to induce approximately 24 h-lasting effect on accuracy. Noticeably, the neuroenhancement produced by this protocol did not literally improved motor ability per se, but rather the retention of motor sequences. This evidence supports the role of primary motor cortex in the encoding of motor skills, thus the possibility of combining a-tDCS in primary motor cortex with training to enhance motor functioning. Similarly, a sham-controlled crossover study by Parikh and Cole (2014) further tested the possibility of improving fine motor abilities through the combination of a-tDCS of primary motor cortex and motor practice. Results showed that, although a-tDCS did not immediately affect performance on the Grooved Pegboard task, it produced a longer retention of the improvement (at least 35 min) than motor practice alone. Taken together, results by Zimerman et al. (2013) and Parikh and Cole (2014) support the idea that, when combined with motor training, short-term single session neuroenhancement is able to produce lasting-effects in motor functioning of the elderly. For what concern motor adaption, another ability usually declining with aging (King et al., 2013), Hardwick and Celnik, (2014) tested the possibility of stimulating the cerebellum to enhance motor functioning in the elderly. Delivered via 5 × 5 cm electrodes with an intensity of 2 mA, a-tDCS was applied for 15 min during a “center out” reaching task. Compared to subjects who received sham stimulation, participants who received the active condition adapted faster to the introduction of a sudden 30° cursor rotation. This evidence demonstrates that cerebellum may be a suitable target to improve spatial readjustment during movements in aging subjects. As studies currently reviewed performed, tDCS protocols have been usually applied to a single hemisphere, using a “neutral” reference electrode for cathodal stimulation (even though the effect of scalp “return” electrodes should not be considered negligible in tDCS protocols in general). Given complex bi-hemispheric compensatory activity occurring with aging, an intriguingly possibility is to test cognitive effects of dual stimulation in both hemispheres. Lindenberg et al. (2013), made this attempt comparing the effect of unilateral and bilateral primary motor cortex stimulation on functional brain activity and motor behavioral performance. For unilateral a-tDCS, the anodal electrode was placed on left M1 and the cathodal on the contralateral supraorbital area. For dual tDCS, the cathodal electrode was placed over right M1. Although no behavioral improvement on finger tapping task was detected both for dual and uni-hemispheric a-tDCS, task-related activity resulted modified after bilateral stimulation; in particular, dual tDCS on motor cortex enhanced activity in bilateral M1, demonstrating its efficiency in the modulation of interhemispheric activity. This evidence is particularly important because highlights that the mechanism underlying tDCS effects encompasses not only local polarity-related modifications of cortex excitability but also complex interhemispheric connections. The fascinating possibility of modulating brain networks indeed needs more in-depth analysis and will be discussed as a future direction in Section 4.3.

3.3.3. *Language*

One of the most frequently and disabling complains of elders is the difficulty in the retrieval of proper names and a certain slowing of verbal fluency. Therefore, neuromodulation of language especially focuses on the enhancement of naming ability. Despite the presence of substantial literature on healthy adults and aphasic patients (for a review on the topic see Monti et al., 2013), currently, only four studies attempted to improve naming and verbal fluency in healthy aging.

In 2011, Ross et al. tested the possibility of replicating tDCS based facilitation on name recall for famous faces (Ross et al., 2010) in the elderly. 15 min of a-tDCS with an intensity of 1.5 mA was delivered over the right or left anterior temporal lobe (ATL) in a group of 65 healthy elderlies; the cathode electrode was positioned on the contralateral cheek. Stimulation was applied online, during a naming task encompassing the presentation of photographs of famous people or landmarks. Results reported different effects on the base of the availability of the names, with tDCS facilitation being more evident for names that were not immediately accessible. Moreover, the target of the stimulation produced different effects according to the type of the presented stimuli: left a-tDCS tended to increase naming performance for famous people, while right a-tDCS improved the ability to recall names of places. Selectivity of the effects across stimulation site and stimulus type demonstrated that tDCS-induced neuroenhancement was probably not dependent by a general increase in cortical excitability, in line with the notion that tDCS effects take place after the cessation of stimulation rather than during it, at least for the motor cortex (Santarnecchi et al., 2014). Meinzer et al. (2013) employed a sham-tDCS controlled, crossover design to investigate word-retrieval performance during a-tDCS and related brain activity. In line with previous studies showing improved word retrieval after inferior frontal gyrus (IFG) stimulation in younger adults and old patients with stroke (Cattaneo et al., 2011; Holland and Crinion, 2012; Iyer et al., 2005; Meinzer et al., 2012), 1 mA direct current was delivered for 20 min on the left ventral IFG, using right supraorbital region as reference region. Moreover, fMRI was performed both in resting and task related conditions to assess changes at network level. Analysis revealed that 20 min of 1 mA direct current delivered on the left ventral inferior frontal gyrus (IFG) was capable of improving performance almost up to those of young control group. Moreover, the combination between resting and functional MRI and tDCS provided evidence of a negative correlation between enhanced resting bilateral prefrontal connectivity and behavioral performance; this connectivity pattern, evident also during task-fMRI and supporting the dedifferentiation hypothesis of the aging brain, was significantly reduced after a-tDCS. In light of these results, a successive study by the group of Meinzer et al. (2014) investigated the same ability comparing unilateral a-tDCS and dual hemisphere tDCS while subjects were performing semantic word-retrieval and motor speech tasks. In the attempt of elucidating the elusive relationship between motor and language systems (namely, whether motor cortex stimulation could result in an improvement of speech production) anodal electrode was placed over the left M1, using right M1 as cathodal reference in dual stimulation condition. Results indicated that both a-tDCS and dual tDCS alike reduced the number of errors made during the semantic word-retrieval task, thus corroborating the opportunity of targeting primary motor cortices to enhance semantic verbal production well beyond their known impact on action words (Liuzzi et al., 2010, 2008). However, given that the size of the used electrodes limited the spatial focality of the stimulation, the possibility that the highlighted effects were elicited by excitability changes in neighbors' areas (e.g. parietal) should be taken into account. For what concerns task-related activity following a-tDCS, this study found no modification of brain activity in world-retrieval trials but showed a significant decrease in bilateral prefrontal connectivity in motor speech trials. Together, these evidences (further discussed in Section 4.3) stress out the need of a proper assessment of the nature of the increased bilateral connectivity in the aging brain to guide stimulation designs.

Currently reviewed studies on language assessed cognitive performance during the application of tDCS without follow up, an approach that does not allow capturing possible long-term maintenance of behavioral improvements. To uncover this possibility, Fertonani et al. (2014) designed two stimulating conditions; in the online paradigm, 2 mA t-DCS was applied on DLPFC during the task, resulting in 4–5 min of stimulation, while in the offline condition tDCS was applied for 10 min to assure an after-effect. As hypothesized by the authors, in the aged group, only online a-tDCS induced a significant improvement on picture-naming task in terms of reduced reaction times, an effect that resulted inconsistent in the healthy young control group. This effect is in line with previous findings (Kuo et al., 2008; Stagg and Nitsche, 2011) and could suggest that LTP-like neuronal plasticity mechanisms probably induced by offline tDCS may be disrupted in the aging brain. In conclusion, this study strengthens the importance of timing in the neuroenhancement of the aging brain and the need of further studies comparing online and offline stimulation in the same protocol.

3.3.4. *Jogging elderly's memory*

Forgetfulness could be considered a frequent but not inevitable part of aging processes. Variably defined as "Benign senescent forgetfulness" (Kral, 1962) or "Age Associated Memory Impairment" (Crook et al., 1986) by definition, physiological memory lapses have little impact on daily living. Despite its "benign" nature, there may exist a possible continuum between "senior moments" and objective memory impairment (Reisberg and Gauthier, 2008). On this basis, the possibility of preventing harming memory loss in healthy aging population through early brain stimulation interventions have been explored in 6 studies.

Lapse of memory for object-locations, such as forgetting where an object was previously placed, is undoubtedly one of the mostly reported and crippling issues in everyday life of elderly. Given the relevance of this type of memory in daily living, Flöel et al. (2012) attempted to neuroenhance object-location memory through the delivery of a-tDCS over right temporo-parietal cortex. Anodal direct current was administered with an intensity of 1 mA during object-location learning paradigm, for an overall stimulation time of 20 min in 20 healthy aged people. After five learning blocks, where subjects were asked to memorize buildings positions on a street map, learning success was tested immediately and one week later with a free recall task. Results indicated that the learning curve over the blocks of the task did not differ between active and sham stimulation conditions and that immediate free recall was not affected by electrical stimulation. Despite this, compared to sham stimulation, a-tDCS condition resulted in an impressive improvement in accuracy one week later. These results may indicate that a-tDCS could induce strong delayed effects through long-term consolidation mechanisms (Reis et al., 2009). Anyway, the lack of control sites in the experimental design could not disentangle whether only the temporo-parietal site stimulation is critical in determining such effects.

Moving toward broad episodic memory functioning, Manenti et al. (2013) tested the possibility of improving retrieval of abstract and concrete words in a group of 32 elderly individuals. Given evidences of bilateral recruitment of PFC and the activation of parietal cortices (PARC) during episodic memory tasks (Binder et al., 2005; Klostermann et al., 2008), three types of stimulation (right anodal, left anodal and sham) over two target sites (DLPFC and PARC) were applied during retrieval phase (an old/new judgment task). Results indicated that only a-tDCS applied over left targets (both DLPFC and PARC) improved retrieval for abstract and concrete words in the aged group. Intriguingly suggestions come from comparing performances of the elderly with those of a control group of young adults in which facilitation effects were seen with both right and left a-tDCS. While right target stimulation improvement observed in the control group fits with HERA model, sole asymmetric left facilitation observed in the elderly could not be interpreted straightforwardly. Although the authors commented it from the perspective of a dedifferentiation process, probably meaning a reduction in right hemisphere functioning, this result runs counter to the idea that loss of specificity occurring with aging often encompasses the decline of regional specialization and the recruitment of unrelated areas.

In another study by Sandrini et al. (2014), a-tDCS was applied over left and right DLPFC to induce an improvement in the retrieval of previously learned concrete words. The experiment was conducted over four separate sessions, namely a first learning and immediate recall phase, a 24 h delayed reconsolidation session with 15 min of tDCS, as well as a 48 h and a 30 days delayed retrieval. Control condition encompassed the application of a-tDCS during reconsolidation session without a direct reminder of what was done the day before. No sham stimulation without reminder condition was tested. Results indicated that, independently from giving or not a reminder, a-tDCS over left DLPFC was capable of strengthening accuracy in memory retrieval, reducing forgetting up to 30 days. This finding is in line with long lasting effects observed in Flöel et al. (2012), supporting the hypothesis that tDCS mainly acts through long-term consolidation mechanisms of the memory trace. Moreover, this result points out the possibility of strengthen existing memories by means of tDCS. This chance was further addressed by Eggert et al. (2013) exploring whether slow oscillating tDCS (a particular type of stimulation that combines alternating current with DC offset) (Bergmann et al., 2009) could impact sleep-dependent memory consolidation in a group of 26 elderly subjects. Based on evidences proving the role of slow oscillations in memory consolidation in healthy young people during sleep (Marshall et al., 2006), bi-frontal anodal stimulation was applied during early non-rapid eye movement (NREM) sleep with a frequency of 0.75 Hz. Word-pair association and sequential finger tapping (SFTT) tasks were administered in the evening before sleeping to assess both declarative and procedural memory. Morning recall performances were then compared with those of the evening. Results showed that tDCS not only failed to show sleep-dependent performance enhancement both in the declarative and the procedural memory tasks but rather overall non significant performance impairment was observed. This evidence complies with studies reporting reduced sleep-dependent consolidation in aging (Pace-Schott and Spencer, 2011; Spencer et al., 2007), an effect probably depending on changes in sleep structure (Hornung et al., 2005). Given that effectiveness of oscillating tDCS is thoroughly related to the ongoing brain activity, it may be possible that the patterns of brain activity recorded with EEG after a-tDCS, that is an increase of the awake phase as well as reduced NREM stage 3 sleep, prevented tDCS resonance effects. Further studies should therefore assess whether and how slow wave sleep could be a feasible phase to enhance consolidation of memories in the elderly.

Last but not least, we conclude this section discussing available evidences on one of the most affected abilities in the aging brain: working memory (WM). Despite WM loss occurring with aging accounts significantly for impairment in several cognitive tasks (Glisky, 2007), currently only three studies attempted to improve WM abilities in the elderly (Berryhill and Jones, 2012; Park et al., 2013; Jones et al., 2015). The first attempt was designed by Berryhill and Jones (2012), which tested the possibility of improving visual and verbal WM in 25 healthy adults divided on the base of their level of education. Built on the evidence that older adults tend to rely more heavily on bilateral frontal regions to perform WM tasks (Eyler et al., 2011), tDCS was applied across three experimental sessions: a-tDCS to the right (F4) and left (F3) DLPFC and sham stimulation over F3 or F4. Four pseudorandomized blocks each of the visual and verbal 2-back WM tasks were performed after 10 min of 1.5 mV current stimulation. Despite the easiness of the 2-back task, results reported a surprisingly clear dissociation in performance between subjects with higher and lower education. Regardless of stimulation site and WM task, only older adults with more education showed an improvement on WM. Instead, low education group was unexpectedly hurt by a-tDCS (an effect especially evident in visual WM task after stimulation over the right hemisphere). These results raise important questions and mechanistic hypotheses: selective tDCS benefit in subjects with higher education may be related to the fact that they employed a different, more efficient, WM strategy than the low education group and that, in turn, this allows recruiting PFC structures more promptly whether coupled with tDCS. The interpretation of the impressive impairment in visual WM is almost a wild-goose chase, instead. In line with the right hemi-aging model which sustains that right hemisphere cognitive functions are prominently more affected by aging (Dolcos et al., 2002) it may be that bilateral stimulation is needed to recruit additional resources in a worn-out system. A further analysis of differential pattern of activity according to this key variable could indeed be fundamental to address this issue and to design proper neuroenhancement studies.

Finally, a further step towards the creation of proper cognitive interventions encompasses the application of tDCS during cognitive trainings. Despite the large number of positive evidences in healthy subjects (Elmasry et al., 2015), only two studies combined tDCS and cognitive training in healthy aging (Park et al., 2013; Jones et al., 2015). Park et al. (2013) coupled computer-assisted cognitive training (CACT) to multisession a-tDCS on bilateral PFC to evaluate their long-term effects. In this study, a-tDCS and CACT were concomitantly administered for 10 sessions in 40 healthy elderly aged over 65 years. The accuracy of the verbal WM task and digit span forward test was significantly improved with a-tDCS as compared with sole CACT program. Moreover, in the verbal WM task the effect lasted 4 weeks with a significant boosting also in WM reaction times. This result provides evidence that bilateral simultaneous stimulation with external reference electrodes is able to enhance memory accuracy and reaction times in healthy elderly. Most importantly, it suggests that the combination of computerized cognitive training and tDCS can lead to a long-lasting improvement of memory functioning. Jones et al. (2015) further explored the possibility of inducing long-lasting enhancement in WM abilities, as well as to transfer these ameliorations to other cognitive domains. Seventy-two old participants carried out 10 training sessions coupled with a-tDCS or sham stimulation. For what concern active stimulation, three stimulation designs were created: right frontal a-tDCS (F4), right parietal posterior cortex (P4) a-tDCS and P3-P4 alternating a-tDCS. To assess single effects of multi-session tDCS stimulation, a control group without cognitive training was added. Results showed an enhancement of WM abilities in all the groups who carried out the cognitive training. Therefore, after the 10th session, no apparent boosting effect induced by active tDCS was evident. Surprisingly, after 1 month, subjects in the active-tDCS group had a better performance both to trained and un-trained tasks, thereby demonstrating that active stimulation enhanced longer-lasting improvements and solid near transfer effects. This elegant studies provides several sparks: first, the lack of a significant behavioral difference across the different stimulation sites suggests that tDCS could enhance WM by targeting the fronto-parietal network; given the role of both prefrontal and parietal areas to WM ability, future studies should replicate this design adding an unrelated area or/and combing functional imaging. Secondly, it is notably that cognitive enhancements and transfer effects were stronger in the more challenging and adaptive tasks, where a rapid update of information is needed (e.g. 2 n-back task). This effect is in line with some previous studies (Jaeggi et al., 2008; Schmiedek et al., 2010) and is indeed a good starting point in the design of future training studies aimed at enhancing transfer effects.

3.3.5. *Other cognitive domains*

Moving towards other aspects of human cognition, Boggio et al. (2010) attempted to neuromodulate decision making in the elderly. A previous tDCS study on young adults (Fecteau et al., 2007) observed reduced risk-taking after anodal stimulation over the right PFC. In the reviewed study, the same electrode montage (F3/F4) was utilized to assess the effect of a single session of online a-tDCS on decision-making performance of a group of 28 healthy elderlies. Results indicated a different tendency compared to young adults: left anodal/right cathodal PFC stimulation increased risky choices as compared with sham and right anodal/left cathodal PFC stimulation. These results are probably not as paradoxical as authors believed, for the following reasons; a first consideration arises from the fact that the study on young subjects was based on the investigation of the subtle interhemispheric balance between left and right PFC. In particular, the selected montage was chosen to explore the effects of the upregulation of the right DLPFC (commonly linked with conservative decisions) coupled with the downregulation of the left DLPFC activity. The lack of improvement after right a-tDCS observed in the replication by Boggio could be therefore interpreted as a reduction of prefrontal right hemisphere functionality in healthy aging. On the base of recent research on decision making (Fecteau et al., 2007) both right and left DLPFC are needed to obtain a significant effect on decision making. It could therefore be possible that increased risky behavior retrieved after left a-tDCS stimulation is the outcome of an imbalance across PFCs activities. Another possibility is that differences between young and old adults are due to different levels of education, a variable that, as we described in the study of Berryhill and Jones (2012), could mediate the effects of tDCS-based neuroenhancement in aging population.

In order to stick to the issue at hand, namely right DLPFC stimulation to enhance high order cognition in the elderly, we review a recent paper by Harty et al. (2014). The cognitive function under scrutiny in this case is the ability to detect errors: 106 healthy old adults were recruited for four separate experiments with different electrode montages, aiming at studying the role of right DLPFC in error detection and the possibility of recovering awareness deficits in aging population. Under real stimulation condition, 1 mA tDCS was applied for the duration of each of the five blocks of a Go/No-go response inhibition task (Error Awareness Task-EAT) alternating anodal and cathodal active stimulation over right and left DLPFC. The reference electrode was placed over the vertex (Cz) in all the conditions. Results indicated that a-tDCS over right DLPFC increased the number of errors pointed out by the elderly in the Repeat no-go part of the task ("do not press the button whether the same word is repeated"). No significant effect was observed in Stroop no-go subtest. This effect may be due to the fact that repeat no-go error awareness may be facilitated as a result of improved memory capacity and that Stroop No-go performance was close to ceiling (average of 91% across all experiments) and could not be improved further.

Finally, moving toward recent investigations, a brand-new research by Manor et al. (2016) moved beyond the single cognitive domain and approached a "more ecologic" issue. Starting from evidences showing a "dual-tasking" cost in healthy aging (namely a performance decline in one or both task when performed together) (Verhaeghen et al., 2003), these authors tried to improve a basic but fundamental ability: standing and walking while performing cognitive tasks. In this study, 37 older adults underwent 2 sessions encompassing five single and dual tasking blocks; they were asked to stand, walking (with and without counting backwards) or to simply counting backwards while staying seated. Previous neuroimaging evidences showed that performing more than one task together requires a stronger recruitment of prefrontal areas and, as we discussed in the introductive section, the performance of elderly people drops with high cognitive load. On this basis, left frontal a-tDCS (F3) was applied offline for 20 min at an intensity of 2 mA. Results showed no effects on single tasks performances but a significant amelioration of the cost of standing and walking while performing serial subtraction. However, as the authors themselves highlight, the study does not provide any insight on the mechanisms underlying this improvement. This shortage is partially related to a lack of consensus on the neurophysiological mechanisms of dual tasking; when hypothesizing that the two tasks are processed serially (thereby penalizing the one who is processed later), a-tDCS effects could be explained in terms of an improvement in processing speed in healthy aging. Conversely, if we posit that both tasks are processed concurrently, a-tDCS may lead to an enhancement of the ability to allocate cognitive resources or to recruit additional ones. Given the relevance of dual-tasking in everyday life, further research aimed to uncovering the neurophysiological underpinnings of dual-tasking costs and its amelioration after PFC a-tDCS is certainly needed.

3.4. Further nibs-techniques

During the last decades a clear relationship between brain oscillatory activity and the dynamics of cognitive processes has been uncovered. The functional meaning of brain oscillatory activity has been first spotted analyzing changes in oscillatory activity phase or time-locked to specific cognitive and sensorial events. Indeed, synchronization of neural assemblies in specific frequency bands could be considered the language of the brain, allowing the segregation and the integration of a multitude of distributed information-processing activities following external or internal stimulus. Notwithstanding, electrophysiological evidences of the correlation between brain dynamics and cognitive performances could not disentangle whether brain rhythms are just an epiphenomenon or a fundamental mechanism for cognitive functioning. The recent introduction of novel NiBS methods, e.g. tACS and tRNS, could help addressing this issue. Differently from polarity-specific effects of tDCS, tACS and tRNS represent a different approach to cognitive neuroenhancement (Santarnecchi et al., 2015a, 2016). tACS holds the unique capability to directly influence cortical rhythms, namely to induce an "entrainment", that is an alignment between endogeneous and exogeneous (tACS induced) oscillatory potentials (Ali et al., 2013). tACS is effectively suitable to interact with ongoing brain oscillatory activity and modulate them in a frequency-specific fashion (Thut and Miniussi, 2009), a capacity that could contribute to a better understanding of the functional meaning of cortical rhythms. Moreover, tACS is able to influence cortical excitability (Antal et al., 2008; Chaieb et al., 2011; Feurra et al., 2013, 2011; Kanai et al., 2010; Wach et al., 2013) and a series of studies in healthy subjects have recently showed the potential for using tACS to improve basic higher-cognitive functions like working memory (Polania et al., 2012) and fluid intelligence (Santarnecchi et al., 2013, 2016). Typically, tACS is delivered without DC offset at a specific frequency within the canonical spectrum captured by EEG recordings (1–80 Hz) and in the so called "ripple" range (140 Hz) (Moliadze et al., 2010). As long as it lacks superimposed polarity, frequency, phase and intensity are the major parameters defining the effects of stimulation. Despites accumulating evidences in support of the feasibility of this tool, at present no articles have been retrieved using tACS without DC offset in the aging population.

Therefore, this section will only focus on a specific type of oscillating stimulation: tRNS. First experimentally employed in 2008 (Terney et al., 2008) tRNS is the newcomer in the tES family. Based on normally distributed random currents with a frequency spectrum between 0.1 and 640 Hz (Fig. 2), tRNS leads to a long-lasting increase of cortical excitability by a mechanism possibly entailing "stochastic resonance" phenomena (Terney et al., 2008). As research demonstrated, repeated subthreshold stimulations with tRNS could act preventing the homeostasis of the system, enhancing the reaching of firing thresholds and, ultimately, eliciting plasticity (Fertonani et al., 2014). Given that the output from both electrodes is (from a practical standpoint) polarity unspecific, this type of stimulation is appropriate for stimulating two regions at the same time and may also provide longer lasting effects than tDCS, at least as suggested for tinnitus suppression (Vanneste et al., 2013). Such a long-lasting effect could be particularly influential in the design of neuromodulatory interventions on healthy aging population. Currently, only one study assessed the effects of tRNS on healthy elderly's cognition. Cappelletti et al. (2015) designed an elegant investigation aimed at disentangling whether learning effects elicited by cognitive training are due to an enhanced ability to integrate information or to improved inhibitory abilities. To address this complex issue, they trained for five consecutive days 30 young and 30 aged subjects on a numerosity discrimination task with concomitant tRNS. According to literature supporting the role of parietal cortex in numerosity discrimination, electrodes were positioned on parietal regions (P3 and P4) or motor (C3 and C4) regions (control condition). Random noise current was delivered for 20 min with an intensity of 1 mA during one-hour training session. Results revealed that, regardless to age, numerosity discrimination accuracy was improved after training (~19%), an effect shown to be significantly larger (32%) and long lasting (up to 16 weeks) when training was coupled with parietal tRNS. Despite similar improvement in young and aged groups, data revealed crucial age-dependent differences in the content of learning: aging participants improved more in inhibitory abilities, whereas younger subjects improved in cue-integration abilities. Moreover, elderly showed cognitive transfer to other untrained tasks, especially those probing inhibitory abilities and a negative transfer to space processing, a related but untrained ability. Despite these results deserve further in-depth consideration, they unequivocally provide an amazing evidence of the fact that NiBS long-lasting effects are grounded on different mechanisms of learning across lifespan and highlights the high-potential of coupling cognitive training with NiBS in aging population to induce cognitive improvement with remarkably transfer effects to untrained cognitive abilities.

3.5. Summary of the use of NiBS neuro-enhancement protocols in the elderly

NiBS techniques could be considered a promising effective tool in the attempt of counteracting cognitive outcomes of aging, showing preliminary positive effects on several cognitive abilities, and initial evidence that these changes may last in time, which is crucial for improving everyday activities. Specifically, these improvements were observed for motor functioning (75% of 4 available studies), language (100% of 5 available studies), memory (85.7% of 7 available studies), inhibitory control (1 available study), number acuity (1 available study), dual tasking (1 available study) and metacognition capacities (error awareness: 1 available study). Stimulation with tES mainly resulted in improved accuracy (77.8%) rather than reaction times (16.67%) (see Fig. 3, for a more detailed overview on tDCS studies), whereas a major effect on reaction times was observed in all the reviewed rTMS studies (3 studies). Despite growing validation to this method, some issues regarding the use of NIBS to modulate functions should be addressed in upcoming studies in order to customize interventions in aging population. These issues are discussed in the following paragraphs.

4. Future directions

4.1. Giving real-world impact to NiBS

In order to make NiBS techniques really useful even outside laboratory settings, a pivotal goal in the near future is to address their efficacy as long lasting brain enhancers. Although some studies reported long-term enhancement (lasting up to 1 month) after single session (Sandrini et al., 2014), dearth of follow up assessments in the available literature makes difficult to establish unequivocally long-term impact of single session on aging population. Besides this, multi-session NiBS could be a feasible avenue to counteract plasticity reduction in aging population and to elicit late-phase LTP/LTD plasticity. In fact, reviewed studies demonstrated sharper and lasting improvements when tES was applied during multiple sessions, especially when it was coupled with training (Park et al., 2013; Zimerman et al., 2013; Jones et al., 2015). A recent meta-analysis by Hsu et al. (2015) confirmed this hypothesis, showing a larger effect size for multiple sessions of stimulation (mean effect size, 0.89) than for single session studies (mean effect size, 0.44). Noticeably, as we will discuss shortly afterwards, multi-sessions interventions have to be properly designed in order to achieve lasting effects. Moreover, the increasing automatization in the computation of current flow on the base of individual head models could indeed have a positive return in the application of NiBS in clinical settings; in the future, highly customizable interventions on the base of the subjects' specific anatomy could provide higher efficacy and adaptability in multi-sessions protocols.

4.2. The right place at the right time. Best targets and parameters of NiBS in the aging brain

Taking into account the structural and functional changes occurring in the brain of aging population, the selection of areas to be targeted should not be inferred from studies on healthy young adults, but they probably have to be grounded on strong evidences about the cognitive biomarkers of the aging brain. In the matter of this, a first necessary step could be the proper characterization of the functional or dysfunctional role of an area in the targeted cognitive domain. Basic assumptions about NiBS-based enhancement or inhibition interventions should therefore be guided by proven neuroimaging and electrophysiological models of the aging brain. Similarly, the choice of reference electrodes in tDCS experiments should be taken into account carefully. Indeed, different effects depending on electrode's reference location have been described (Vandermeeren et al., 2010); this mainly applies for polarity-specific tDCS, rather than for tRNS or tACS. Moreover, given evidences of task-related bilateral activation in elderly, selection of contralateral areas as reference (a choice adopted by 17.6% of the reviewed papers) should be thought wisely.

A notable criticism against tES methodic is that the outcome of the intervention is largely confounded by electrodes size. Indeed, as modeling of current flow and neuroimaging studies recently claimed, standard pad electrodes size (usually 5 × 5 cm or 5 × 7 cm) does not provide enough spatial focality to allow a clear explanation of the mechanisms underlying tES nor to guarantee the maximum efficacy of the methodic. Several technical solutions have been proposed to shape the current flow (e.g. increasing return electrode size, using an extracephalic reference) and, recently, the use of ring and concentric electrodes have been proposed to overcome the issue of current spread. On this base, a new growing approach to tDCS has been developed to make tES a more targeted and customized technique: high-density tDCS (HD-tDCS) (Datta et al., 2008). Based on the use of multiple arrays of small anode and cathode electrodes, high-density tDCS uses specific electrodes positioning, such as the 4 × 1 montage, where the anode is surrounded by 4 return electrodes positioned in a circular configuration (Minhas et al., 2010). Noticeably, given that the aging brain is often characterized by task-related activation of differently-apparently unrelated- brain areas, this advancement could be very important to localize target areas without affecting the distal ones.

For what concerns "timing" of stimulation, the majority of the tDCS studies designed an online stimulation (52.9%) while rTMS literature mainly adopted an offline protocol (67%). Despite this tendency, positive results were also obtained with offline tDCS, according to motor cortex reactivity to tDCS which mainly changes after stimulation cessation (Santarnecchi et al., 2014), with the exception of Fertonani et al. (2014). Moreover, the positive results obtained by Sandrini et al. (2014) by means of application of tDCS to reinforce acquired memories (i.e. consolidation), raises the possibility of further testing neuromodulation according to the intrinsic temporal dynamics of cognitive processes under scrutiny. In their recent meta-analysis, Hsu et al. (2015) showed a larger effect size for offline (mean effect size 0.92) than for online stimulation (mean effect size 0.23): they cautiously interpreted this difference as an evidence that healthy aged subjects could benefit more from induced LTP-like mechanisms by means of offline stimulation. However, since their analysis pooled subjects who received either rTMS or tDCS interventions, it is difficult to disentangle which of the two techniques was more effective for this cohort and, in turn, which design suits best for each approach. Indeed, the speed up of naming reaction times in the healthy aging group appeared only when a-tDCS was applied online, whereas both offline and online interventions improved reaction times in healthy young subjects (Fertonani et al., 2014). The fact that Hsu et al.'s meta-

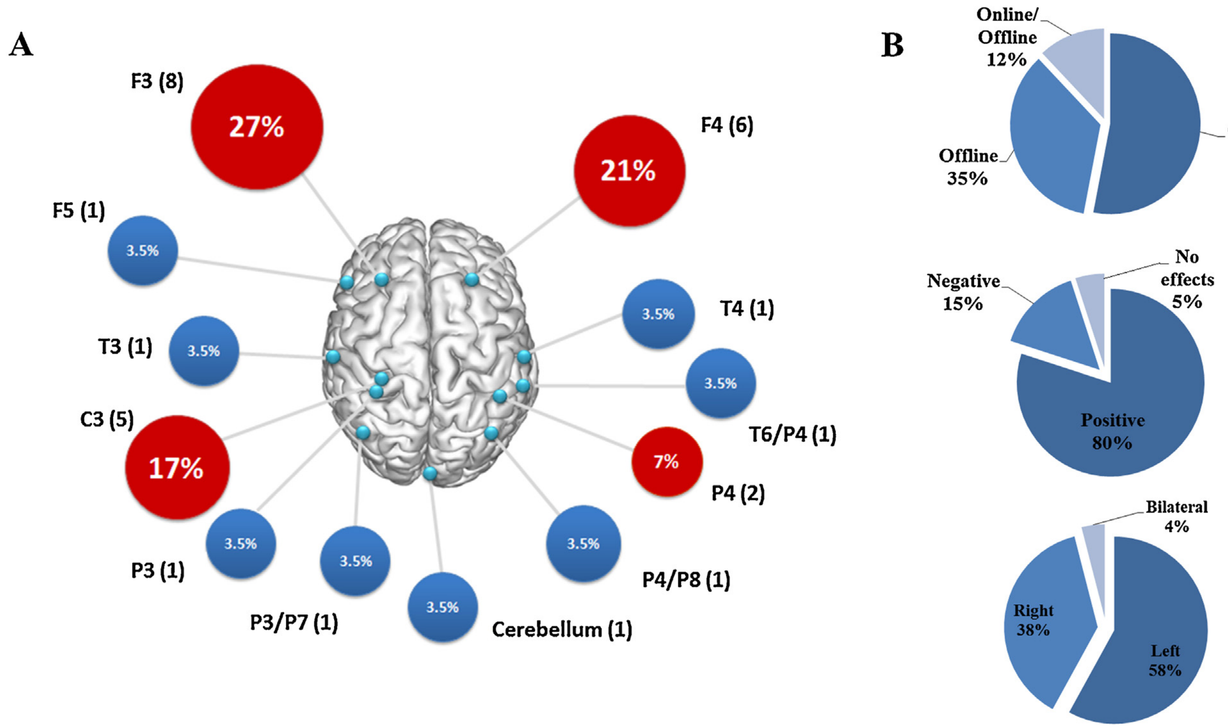

Fig. 3. Brief schematic overview showing main results of tDCS-based protocols for cognitive neuroenhancement in aging population. Panel (A) brain regions stimulated (number of studies are specified in brackets); Panel (B) % of studies employing Online/Offline protocols; behavioral effects of tDCS; hemispheric localization of stimulated area.

analysis further reported a higher effect size for online stimulation (mean effect size, 1.79) than for offline stimulation (mean effect size, 1.04) in AD patients suggests that tES application should be based on strong evidences on the neural changes occurring during the lifespan (e.g. cortical excitability). Therefore, neuromodulatory interventions (either online or offline, with rTMS or tDCS), particularly in the elderly, should be guided by a proper characterization of the different neural mechanisms mediating the expected benefits.

Another issue related to timing encompasses the establishment of the best time-window between multi-sessions tES, in order to stretch induced neuroplasticity. Far off from being a minor variable, the induction of late-phase LTP/LTD plasticity could largely depend on proper spacing interval between sessions. As a recent work by Goldsworthy et al. (2014) remarked, studies on animal models reported longer lasting plasticity effects with closer stimulation sessions (3–30 min), whereas daily treatment schedule is currently the typical gold-standard in human research. This result was confirmed by Monte-Silva et al., 2013; showing that the application of a second a-tDCS stimulation with an inter-stimulation interval of 3 or 20 min (i.e. during the after-effects of the first one) enhanced motor cortex excitability for more than 24 h. Moreover, as a recent review highlights (Prehn and Flöel, 2015), multi-session stimulation with large time intervals (3–24 h) could even prevent neuroplasticity (Monte-Silva et al., 2013). Without exceeding safety and practical constrains, further research should therefore investigate whether “high-density stimulation” could product longer-lasting and reliable improvements than single and widely spaced sessions.

4.3. Connectome-based neuroenhancement

Despite promising evidences emerging from the application of NiBS on aging population, most of the available studies are still grounded on a modular approach, which intrinsically considers complex cognitive functions as an emerging property of segregated brain regions. Although the adoption of this simplistic framework has been, and still is, a necessary step to make proper advancements in this field, an interest is emerging in adapting NiBS protocols to the complex universe of brain connectivity: this because of latest evidence of the interaction between the complexity of individual brain connectivity and cognitive profiles (Santarnecchi et al., 2015b,c; van den Heuvel et al., 2009; Sporns, 2014). An ideal result was obtained by Meinzer et al. (2013) coupling tDCS with concurrent fMRI. They showed that performance improvement was associated to a reduction of the task-related hyperactivity of bilateral prefrontal areas, the anterior cingulate gyrus and the precuneus. Moreover, resting state fMRI analysis revealed that a-tDCS induced a connectivity pattern quite similar to those of younger subjects. More complex pictures could result studying network activity changes after NiBS. As we discussed previously, connectivity analysis performed in the study of Vidal-Piñeiro et al. (2014) revealed that iTBS applied over IFG was associated to broad “Level of Processing-dependent” changes in task-related functional activity. Evidence of IFG-posterior (occipital and cerebellum) coupling under deep encoding condition and iTBS modulation sustains the role of left IFG in semantic processing, and further suggests a possible top-down modulation over posterior areas. Although considerations on temporal dynamics of such coupling could not be made through offline fMRI-TMS, this result could be of special interest in respect to posterior–anterior shift in aging (PASA) model. Neuroimaging-based tES modulation could also help disentangling differential effects of unilateral and bilateral stimulation in aging population. Lindenberg et al. (2013) intriguingly found that dual but not anodal tDCS enhanced connectivity of the left dorsal posterior cingulate cortex. Furthermore, dual tDCS yielded stronger activations in bilateral M1 compared with anodal tDCS when participants used either their left or right hand during the task, thus suggesting that dual stimulation is able to elicit more complex bi-hemispheric modulation than the unilateral one. In closing, food for thought results from the fact that the last two studies failed to find an overt effect in task performances. Given that NiBS demonstrated strong covert neurophysiological changes, efforts should be made to study pattern of neural activity induced by NiBS in order to explain and predict lack of behavioral improvements.

For what concern this possibility, apolipoprotein E (APOE) status has recently been shown to mediate changes in large-scale networks as identified by the analysis of low-frequency fMRI-BOLD fluctuations. In a recent report by (Peña-Gomez et al., 2012), the assessment of the APOE ε4 allele profile, known as one risk factor for the development of AD, was combined with the data of a rTMS study on elders with memory impairment (Solé-Padullés et al., 2006). On the base of the carried genetic profile, two subgroups (APOE-ε4 allele carriers/non-carriers) were created to investigate whether this genetic profile could mediate the response to rTMS. Results indicated that, even if there was not any difference in behavioral performance of the two subgroups, there was a clear dissimilarity between brain connectivity of the APOE-ε4 allele carriers and those of the non-carriers; most noticeably, the statistical analysis revealed that rTMS was able to reorganize brain networks configuration of the APOE-ε4 bearers as those observed in the non-carrier elders prior to stimulation.

Also, different allelic profiles in the Catechol-O-Methyltransferase (COMT) gene, which regulates PFC dopamine (DA) levels, could help the interpretation and design of cognitive interventions in the elderly. Specifically, recent evidences reported that allelic variations in COMT gene accounted for great differences in working memory abilities in the elderly. This is not surprisingly considering the key role of the dopaminergic system in modulating neuronal signal-to-noise ratio, synaptic plasticity and learning processes; prefrontal DA levels show an "inverted-U" relationship with cognitive functioning and accounts for age-related impairment of processing speed, working memory, fluid intelligence and memory (Backman et al., 2010). Moreover, DA seems to modulate brain response to cognitively demanding tasks, as shown by its increase with increasing task difficulty. Moreover, emerging studies reported that DA reduction is related to the under-recruitment of task-specific brain areas and to variable non-selective recruitment of apparently task-unrelated brain regions. Hence, it seems reasonable that age-related decline in DA could largely explain neuronal and cognitive changes occurring with aging. Consequently, a fundamental question that research on NiBS-based cognitive neuroenhancement should address is whether neuromodulation could affect dopaminergic system and how COMT genetic profile could prevent or even reverse these effects. Emerging studies on the interaction between DA and tDCS demonstrate the existence of a delicate balance across genetic profiles, neurotransmitters levels, brain stimulation and response differences (see Medeiros et al., 2012 for a review on neurobiological mechanisms of tDCS). Recent pharmacological studies (Fresnoza et al., 2014a, 2014b; Monte-Silva et al., 2010) highlighted U-shaped dosage-dependent effects of L-DOPA, that is low and high L-DOPA intake abolished the excitatory and inhibitory effects of tDCS on motor cortex plasticity. Therefore, dopamine levels could skew tDCS effects thereby indicating that individual allelic profile could lead to similar different outcomes. Plewnia et al. (2013) showed that the application of a-tDCS on left DLPFC during a Go-NoGo task impaired executive performance only in COMT Met–Met homozyguous young subjects (the ones with the lowest DA levels), whilst c-tDCS showed inhibitory effects only in Val58Val carriers (the ones with lowest DA levels) (Nieratschker et al., 2015). Thus, tDCS is able to modulate prefrontal DA but its behavioral effects are largely dependent on the genetic background of the individual. Given that the effects of COMT genetic profile on cognition are somewhat enhanced in the elderly and new evidences reporting further modulatory effects between BDNF and COMT genotypes (Nagel et al., 2008), future NiBS studies on healthy aging should account on individual genetic profile to design reliable interventions.

In conclusion, the combination of NiBS with other neuroimaging techniques could provide insights in whether and how brain networks are influenced by transcranial stimulation (Santarnecchi et al., 2015a). Thus, in order to target specific connections rather than specific areas, it is necessary to understand in depth both aging-related changes occurring in large scale-networks and whether, how, and when these networks respond during or after tES. Genetic background analysis could indeed become a valuable ally to a better understanding of these issues and to provide useful indications to the future use of NiBS as a tool to help preventing pathological aging; therefore, more studies combining NiBS and genetics are thus yearned in the next years.

5. Conclusions

We have reviewed experimental data supporting the feasibility of NiBS as an effective interventional approach to hinder cognitive decline in healthy aging individuals. Indeed, NiBS can be easily coupled to cognitive trainings to bolster positive effects and could be a feasible and safe tool to partly counteract physiological age-related decline. However, despite some encouraging evidence, most –but not all- of the published studies showed variability and volatility of the induced neuro-enhancement effects. Neuroimaging and genetic measures could indeed be fundamental allies to the refinement of some theoretical and practical issues that limits NiBS feasibility out of the lab's walls. Therefore, a multidisciplinary approach to the study of the best NiBS protocols could represent a key point to offer to the aging population an effective tool to counteract their otherwise unavoidable cognitive decline.

Conflict of interests

Dr. Emiliano Santarnecchi and Prof. Simone Rossi are consultant for EBNeuro Ltd., developing new hardware for non-invasive brain stimulation and electroencephalography. None of the NIBS approaches and/or methods and/or tools cited in the present manuscript are property of EBNeuro, therefore they do not constitute any conflict of interest.

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