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Opinion

Stimulating aged brains with transcranial direct current stimulation: Opportunities and challenges

Annegret Habich[a,b,*], Kristoffer D. Fehér[c], Daria Antonenko[d], Carl-Johan Boraxbekk[e,f,g], Agnes Flöel[d,h], Christoph Nissen[c,i], Hartwig Roman Siebner[e,j,k], Axel Thielscher[e,l], Stefan Klöppel[a]

[a] University Hospital of Old Age Psychiatry and Psychotherpa, University of Bern, Bolligenstrasse 111, 3000 Bern, Switzerland
[b] Faculty of Biology, University of Freiburg, Schänzlestrasse 1, 79104 Freiburg, Germany
[c] University Hospital of Psychiatry and Psychotherapy, University of Bern, Bolligenstrasse 111, 3000 Bern, Switzerland
[d] Department of Neurology, University of Greifswald, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany
[e] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Østvej, 2650 Hvidovre, Denmark
[f] Department of Radiation Sciences, Umeå University, 90187 Umeå, Sweden
[g] Institute of Sports Medicine Copenhagen (ISMC), Copenhagen University Hospital Bispebjerg, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark
[h] German Center for Neurodegenerative Diseases, Ellernholzstraße 1-2, 17489 Greifswald, Germany
[i] Department of Psychiatry and Psychotherapy, Faculty of Medicine, University of Freiburg, Hauptstraße 5, 79104 Freiburg, Germany
[j] Department of Neurology, Copenhagen University Hospital Bispebjerg, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark
[k] Institute for Clinical Medicine, Faculty of Medical and Health Sciences, University of Copenhagen, Nørre Allé 20, 2200 Copenhagen, Denmark
[l] Department of Electrical Engineering, Technical University of Denmark, Ørsteds Pl. 348, 2800 Kgs. Lyngby, Denmark

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ABSTRACT

Ageing involves significant neurophysiological changes that are both systematic while at the same time exhibiting divergent trajectories across individuals. These changes underlie cognitive impairments in elderly while also affecting the response of aged brains to interventions like transcranial direct current stimulation (tDCS). While the cognitive benefits of tDCS are more variable in elderly, older adults also respond differently to stimulation protocols compared to young adults. The age-related neurophysiological changes influencing the responsiveness to tDCS remain to be addressed in-depth. We review and discuss the premise that, in comparison to the better calibrated brain networks present in young adults, aged systems perform further away from a homoeostatic set-point. We argue that this age-related neurophysiological deviation from the homoeostatic optimum extends the leeway for tDCS to modulate the aged brain. This promotes the potency of immediate tDCS effects to induce directional plastic changes towards the homoeostatic equilibrium despite the impaired plasticity induction in elderly. We also consider how age-related neurophysiological changes pose specific challenges for tDCS that necessitate proper adaptations of stimulation protocols. Appreciating the distinctive properties of aged brains and the accompanying adjustment of stimulation parameters can increase the potency and reliability of tDCS as a treatment avenue in older adults.

1. Introduction

In our ageing society, a growing portion of the population is facing the consequences of ageing, with age-related deterioration of cognitive functions having a substantial impact on the quality of life in elderly. Transcranial direct current stimulation (tDCS) provides a means to modulate activity in the human brain in a non-invasive and safe manner, and, apart from its use as a restorative treatment in pathological conditions, a number of studies have attested the value of tDCS in counteracting cognitive decline in healthy elderly (Hummel et al., 2010; Manenti et al., 2013; Meinzer et al., 2013; Sandrini et al., 2014) (however, see (Nilsson et al., 2017, 2015)). A recent comprehensive meta-analysis has further highlighted the potency of tDCS in elderly (Hsu et al., 2015). However, while healthy elderly are a promising target population, the tDCS protocols used are largely adopted from studies in young (mostly student) populations.

Abbreviations: AP, action potential; E/I, excitation/inhibition; GABA, *gamma*-Aminobutyric acid; Glx, glutamatergic metabolites; LTP, long-term potentiation; NMDAR, *N*-methyl-D-aspartate receptor; tDCS, transcranial direct current stimulation

* Corresponding author.
E-mail address: annegret.habich@upd.unibe.ch (A. Habich).

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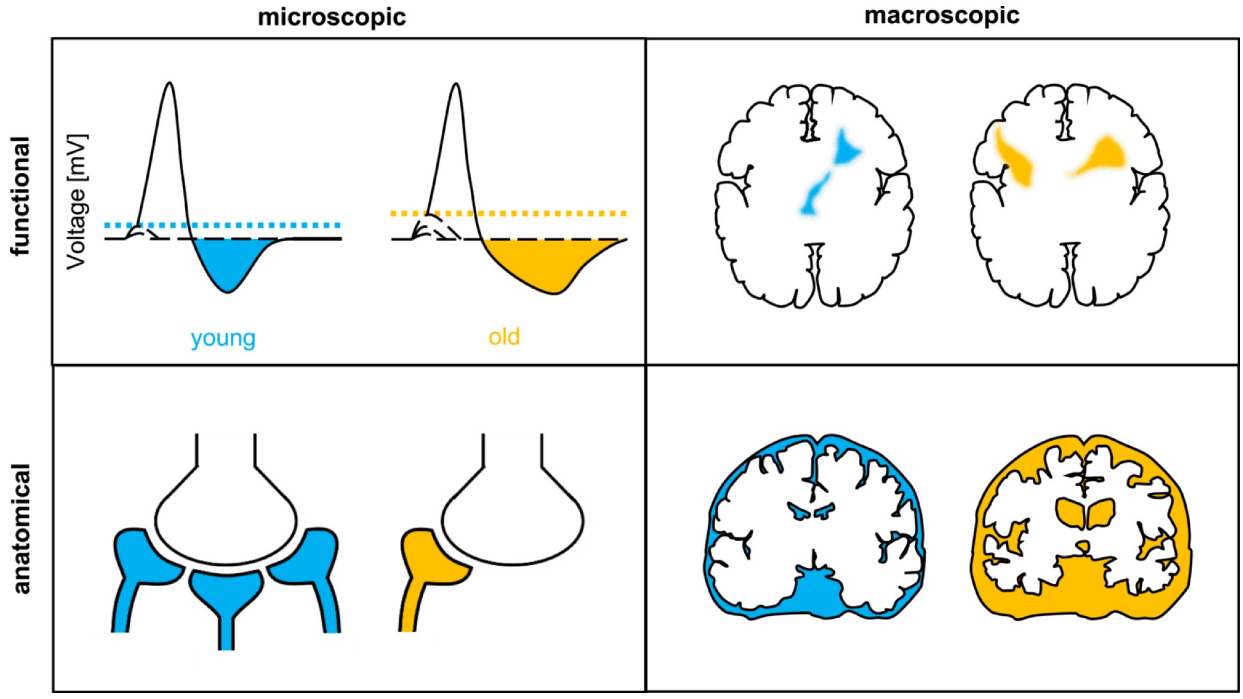

Fig. 1. Overview of general age-related changes. Young and old brains differ in structure and function both on the level of single neurons and synapses (microscopic) as well as on the network level (macroscopic). Microscopic functional changes: depolarisation of the AP threshold and prolonged afterhyperpolarisation phase. Macroscopic functional changes: altered activity patterns. Microscopic anatomical changes: loss of synaptic connections. Macroscopic anatomical changes: brain-wide atrophies, associated e.g. with grey matter loss. Some of these changes may indeed lead to larger tDCS effects, whereas others may impede the benefit from stimulation protocols that are successful in younger populations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The generalizability and above all the transferability of findings between distinct populations (e.g. age groups) has been called into question with regard to many psychology studies (Hanel and Vione, 2016). Until now, there is a paucity of studies that tested the same tDCS protocol in young and older participants with even fewer exploring the interaction between age and stimulation outcome (Antonenko et al., 2017a; Cespón et al., 2017; Fiori et al., 2017; Manenti et al., 2013; Martin et al., 2017, 2013). Nonetheless, they provide evidence that the effectiveness of the applied tDCS protocol heavily depends on age, with the latter serving as an approximation to disturbed brain function commonly associated with ageing.

In the following sections, we will outline how age-related neurophysiological changes affect the influence of tDCS at the network as well as the cellular level, and suggest how systematic age-related changes provide a uniform leverage point for tDCS effects, entailing a potential for greater effect sizes in elderly as compared to young adults. Secondly, age-related neurophysiological changes also necessitate certain vital considerations concerning the stimulation protocol. We address specific anatomical and functional features of brains at advanced age (see conceptual summary in Fig. 1), which need to be taken into account when choosing stimulation protocols. Appreciating the distinctive properties of aged brains and the accompanying adjustment of stimulation parameters can increase the potency and reliability of tDCS as a treatment avenue in older adults.

This review addresses the relationship between the neurophysiology of ageing and the mode of action of tDCS, with special emphasis on the cognitive domain. Of course, the usefulness of tDCS is not limited to counteracting cognitive decline but has also proven effective in many other domains, including geriatric depression (Gálvez et al., 2015), motor (Zandvliet et al., 2018) and language performance (Meinzer et al., 2016) after stroke, and Parkinson's disease (Yotnuengnit et al., 2018). Similarly to acoustic stimulation (Wunderlin et al., 2020 (in this issue)), the potency of tDCS to enhance parameters of sleep (Ladenbauer et al., 2016) as well as to lengthen total sleep time (Frase et al., 2016), which is of particular importance in elderly who exhibit an aberrant sleep pattern, has also been explored. Many of the considerations described below also pertain to the application of tDCS in those clinical populations.

2. Mode of action of tDCS

The non-invasive brain stimulation technique tDCS comprises the application of a weak electrical current (typically 1 to 2 mA for 5 to 20 min) between, typically, two electrodes attached to the scalp. The induced electrical current does not directly elicit action potentials (APs), but its online effects have been attributed to subthreshold shifts in the membrane potential. On a neuronal population level anodal and cathodal stimulation lead to a net depolarisation and net hyperpolarisation respectively of the membrane potential of the stimulated neurons (Nitsche et al., 2008; Purpura and McMurtry, 1965), which brings them closer to or, respectively, farther away from their intrinsic threshold potential for eliciting APs (Jefferys, 1995). In this regard, pharmacological experiments have demonstrated that the sodium-channel blocker carbamazepine and the calcium-channel blocker flunarizine eliminates the excitability enhancement induced by anodal tDCS, corroborating that the applied electrical current modulates the conductance of the respective ion channels and consequently the resting membrane potential (Nitsche et al., 2003). Further evidence for the neuromodulatory impact of tDCS has been provided by magnetic resonance spectroscopy measures insofar as anodal tDCS decreased *gamma*-Aminobutyric acid levels (GABA; (Antonenko et al., 2017b; Bachtiar et al., 2015; Kim et al., 2014b; Stagg et al., 2011)) and increased levels of glutamatergic metabolites (Glx; (Clark et al., 2011; Hone-Blanchet et al., 2015; Hunter et al., 2015); however, see (Bachtiar et al., 2018)). Conversely, cathodal tDCS decreased Glx in the stimulated cortical region (Stagg et al., 2009). Considering that Glx and GABA serve as the principal excitatory and inhibitory neurotransmitters in the brain, shifting their respective concentration has potential

impacts on the cortical balance of excitation and inhibition (E/I balance) in the neural network.

These online effects on excitability are a prerequisite for the prolonged aftereffects following tDCS, which have been linked, in accordance with long-term potentiation (LTP) on the synaptic level, to the involvement of the *N*-methyl-D-aspartate receptor (NMDAR) (Monte-Silva et al., 2013).

3. Amenability to stimulation-induced improvement

Our brain is robust in the face of perturbation, which reflects its active engagement in preserving an optimal level of activity. Local and network activity is precisely calibrated to enable efficient coding and transmission of information in terms of meaningful AP sequences. Since APs are metabolically costly, firing rates are settling around a parsimonious optimum that still suffices to maintain network dynamics and accurately represent inputs (Barral and Reyes, 2016; Koren and Denève, 2017) while higher firing rates are prevented by heightened firing thresholds and greater afterhyperpolarization phases (Shu et al., 2003). As demonstrated in animal studies, a set-point for excitability is established early in life (Colonnese, 2014; Giachello and Baines, 2017). Although it is subject to changes (Mahoney et al., 2014) the regulation of excitability according to this set-point is an integral constituent of homoeostatic plasticity that preserves the excitation-inhibition (E/I) balance of brain networks in the face of perturbations encountered throughout the entire lifespan (Davis and Bezprozvanny, 2001).

This robustness of neural systems to external perturbation has been demonstrated on several scales. In vitro studies have shown that activity deprivation via chronic tetrodotoxin treatment (Kilman et al., 2002; Ramakers et al., 1994, 1990) as well as the administration of a glutamate receptor antagonist (van den Pol et al., 1996) results in rebound hyperexcitability after the disinhibition. Conversely, blocking of GABA-regulated inhibition only initially raises firing rates, which subsequently return to their baseline values, (Turrigiano et al., 1998). On the larger scale, tDCS likewise seems to affect the E/I equilibrium, as attested by its impact on Glx and GABA levels, which serve as indirect measures of cortical excitation and inhibition respectively. Whether this interference moves the neural system closer to its optimum or pushes it away from the latter depends on its proximity to the well-balanced state prior to the stimulation.

In most cases, the brains of healthy young adults can be assumed to function close to their homoeostatic optimum, and therefore, the leeway for modulation through tDCS is relatively small. Thus, we may infer that tDCS-induced alterations beyond the endogenous range of activity of the system will be actively counteracted in an effort of the brain to preserve an activity level within the optimal range (O'Leary and Wyllie, 2011), which is not necessarily equivalent to a high level of activity (compare Schröder and Degen, 2020 (in this issue)). In elderly, an interaction between different environmental influences and the inherent rate of ageing introduces an additional heterogeneity which might be dissociated from chronological age (Penner and Barnes, 2007). However, there is also a common, systematic shift in the E/I balance across individuals. Similar to psychiatric conditions that have been associated with a disrupted E/I balance (Chen et al., 2014; Gonçalves et al., 2017; Salavati et al., 2015), neural homoeostatic dysbalance is also found in elderly. More precisely, hypoexcitability is commonly observed in this population, manifesting as a higher resting motor threshold (Bhandari et al., 2016), a reduced global mean field power of transcranial magnetic stimulation (TMS)-evoked potentials (Ferreri et al., 2017), an enhanced afterhyperpolarization, and subsequently, diminished synaptic transmission due to a reduction of coinciding pre- and postsynaptic activation (Kumar and Foster, 2007). The latter has been attributed to alterations in the Ca^{2+} system. Alterations have been observed in the ion influx through voltage-gated Ca^{2+} channels (Tanabe et al., 1998), the release of Ca^{2+} from intracellular stores (Kumar and Foster, 2004), and the capacity of mitochondrial buffering (Murchison et al., 2004). Furthermore, cognitive decline at advanced age has been related to changes in Na^{+} channel gating, leading to an elevated spike-threshold in aged rats (Randall et al., 2012). Both Ca^{2+} and Na^{+} are involved in the manifestation of online tDCS effects, demonstrated by blocking the respective ion channels with flunarizine and carbamazepine (Nitsche et al., 2003). Apart from changes observed on the level of ion concentration, ageing is also connected to impairments in the GABAergic system that create an E/I imbalance (Rozycka and Liguz-Lecznar, 2017). These systematic shifts, away from a prior optimal state found in a balanced system, may make the aged brain more amenable to the online influence of tDCS. Online effects on excitability are a prerequisite for the prolonged aftereffects following tDCS. However, this is based on the condition that the aged system is still sufficiently flexible and can draw on unexploited resources to respond to tDCS-induced changes.

Ultimately, the successful induction of tDCS effects on the neurophysiological level is mediating higher-order benefits. By way of example, equilibrating the E/I balance may lead to an improvement of the decreased signal-to-noise ratio exhibited by elderly (Cremer and Zeef, 1987; Voytek et al., 2015), thus demasking relevant neural activity and ensuring the transfer of meaningful information. Additionally, tDCS may also support the task-relevant distribution of limited resources. These limitations in processing resources are even more pronounced in elderly (Glisky, 2007). It has been suggested that the problems in task switching performance in older adults reflect a lower flexibility in allocating the fewer available resources to the relevant task at hand (Smith et al., 2001). A failure to flexibly deactivate task-irrelevant brain regions like the default mode network, may also lead to these regions retaining valuable resources (Sambataro et al., 2010; Schlee et al., 2012). By reinforcing task-relevant activity in the appropriate brain regions, tDCS may facilitate the switching between brain states and, accordingly, goal-directed task performance.

4. Age-specific considerations for tDCS protocols

Age-related neurophysiological changes do not only imply differences in the responsiveness of the system to stimulation but also demand that stimulation protocols are adapted accordingly. An omission of using age-adapted protocols may in fact explain previous negative findings (Nilsson et al., 2017, 2015). In some cases, the stimulation of elderly requires an adjustment of parameters used in healthy young populations. Other protocol considerations are unique to the stimulation of brains at advanced age. In the following sections, we specify anatomical and functional characteristics of aged brains that require considerations and appropriate modifications of the stimulation parameters to tap the full potential for stimulation-induced gains in the elderly population (Fig. 2).

4.1. Defining the target

Age-related functional reorganization of the brain makes an individual determination of the target region of interest even more vital than in young individuals. Task-specific brain activation patterns undergo distinct modifications at advanced age, which have been proposed to represent compensational mechanisms (Dockree et al., 2015; Marstaller et al., 2015; Morcom and Johnson, 2015). Despite the discrepancy between cross-sectional and longitudinal studies, which have reported overrecruitment and underrecruitment of frontal regions respectively (Nyberg et al., 2010), there is a consensus that the maintenance of function in the face of age-related decline is achieved by a reorganization of neural activity. While overactivation has also been linked to memory impairments (Haberman et al., 2017), it has been demonstrated that a comparable performance in a working memory task in young and old participants involves a more widespread activation in elderly (Mattay et al., 2006; Reuter-Lorenz and Cappell, 2008).

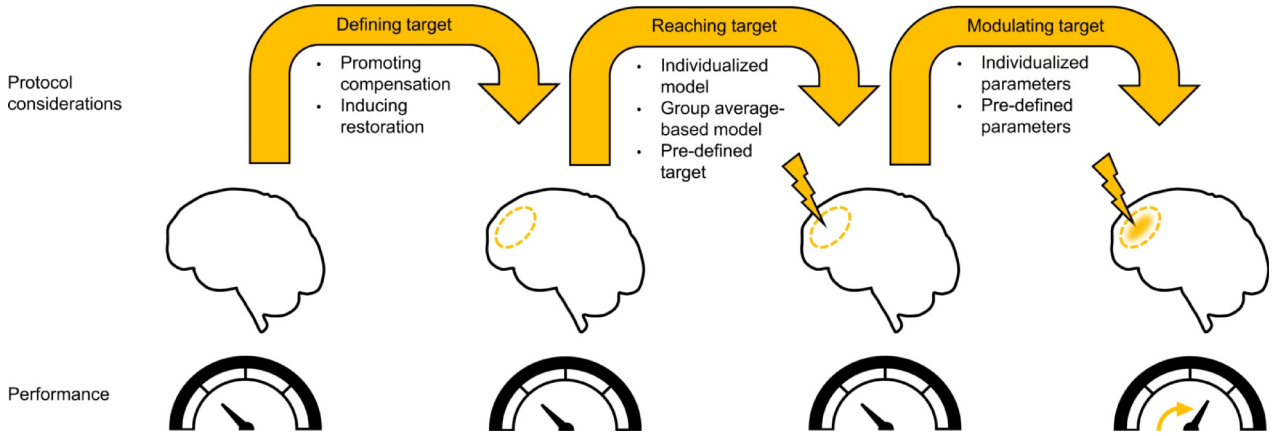

Fig. 2. Overview of protocol considerations to achieve behavioural tDCS effects in elderly: *Defining the target.* Given altered activity patterns in old age, two opposing intervention strategies present itself: promotion of compensational activation or restoration of youth-like activity. *Reaching the target.* The electrode montage can be based on predefined landmarks or on increasingly individualized models of current distribution. Finally, efficiently *modulating the target.* Stimulation intensity, duration and time-window to induce plasticity can be selected according to a standardised protocol or based on individual markers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Imaging studies revealed a shift of activity from occipital to frontal regions (Grady et al., 1994), which has been generalized as the posterior-anterior shift in ageing (PASA; (Davis et al., 2008)). Further, the model of hemispheric asymmetry reduction in older adults (HAROLD; (Cabeza, 2002)) describes the increased bilateral activation pattern in the prefrontal cortex of this population, which is thought to originate from an employment of different strategies to solve a given task. Furthermore, age-dependent changes in functional connectivity, within as well as between brain networks (Betzel et al., 2014; La et al., 2015) may underlie opposite effects of anodal tDCS on large-scale functional coupling in young and older adults (Antonenko et al., 2018b).

This prompts the question whether tDCS should be employed primarily to reverse, or rather to support the age-related functional reorganization of the brain to facilitate task performance at advanced age. So far, results supporting the former intervention rationale remain inconclusive. Two studies (Arciniega et al., 2018; Meinzer et al., 2013) have demonstrated that a tDCS-induced improvement in task performance in elderly is correlated with a larger congruence with brain activity patterns found in young adults, thus favouring restoration over compensation. Restoration to youth-like functional patterns would agree with the brain maintenance view of memory ageing (Nyberg et al., 2012). Accordingly, the preservation of cognitive function in ageing should focus on postponing senescent brain changes, and interventions should aim at maintaining and possibly restoring youthful brain structure and function rather than evoking alternative brain responses. On the other hand, the attenuation of enhanced prefrontal GABAergic tone in elderly to the higher E/I balance of a young cohort by means of continuous theta-burst stimulation (cTBS, a TMS protocol; (Opie et al., 2017)) has not proven advantageous to memory performance (Legon et al., 2016). Moreover, aged networks are more vulnerable to excitotoxic events (Calvo et al., 2015) and thus restored youthful activity may not be supported by a system that has undergone degenerative processes and, at worst, may even accelerate the decline of the neural system. In this regard, future brain stimulation studies should directly test contemporary theories of brain ageing, such as brain maintenance or compensation-related theories (Gleichmann et al., 2011; Gregory et al., 2017).

4.2. Reaching the target

Two conditions have to be fulfilled to effectively target the region and process of interest. First, non-invasively applied current must enter the brain in an effective dose. Intracranial measurements of electric fields (Huang et al., 2017; Opitz et al., 2016), together with in-vivo visualization of the amount and spatial extent of the tDCS-induced current by magnetic resonance imaging methods (Jog et al., 2016; Kasinadhuni et al., 2017), have provided evidence that electrical current is indeed effectively entering the human brain. Second, the current has to arrive at the previously selected target region, involved in the process that is to be modulated with tDCS. In this respect, knowing and efficiently targeting the pertinent brain structures on a macroscopic as well as a microscopic level are indispensable for an effective intervention. Progressively refined models of current flow and current density distribution have been developed based on detailed anatomical parameters (Datta et al., 2012; Kim et al., 2014a; Opitz et al., 2015; Truong et al., 2013). These models have revealed how the distribution of the induced electrical field is influenced by skull thickness, gyration and concomitant thickness of the highly conducive cerebrospinal fluid (CSF), ultimately resulting in non-uniform current densities. While the spatial distribution of electric fields is highly similar between young and older adults, the latter exhibit a higher inter-individual variability (Antonenko et al., 2018b). Preliminary evidence has suggested that decreased grey matter volume and increased CSF may lead to lower magnitudes of the electric field in the cortex (Laakso et al., 2015; Mahdavi and Towhidkhah, 2018; Opitz et al., 2015). Increasing the tDCS amplitude accordingly may alleviate this particular problem, but at the same time skin sensations and/or irritations under the electrode as well as the emergence of phosphenes (especially in case of orbitofrontal stimulation) will increase proportionally, making the stimulation less tolerable and possibly unfeasible.In contrast, by channelling and refocusing the current, lesions can also result in local hotspots of electric field densities (Minjoli et al., 2017). In this context, the use of electrode montages that ensure higher focality of the applied current (Alam et al., 2016; Edwards et al., 2013) may be advantageous to prevent inadvertent stimulation of non-targeted brain regions.

Albeit structural changes related to healthy ageing are less isolated compared to stroke-induced lesions, the pattern of atrophy across the cortex is not equally distributed but mainly affects frontal and parietal areas (Thambisetty et al., 2010) with both reduced and higher cortical field intensities being conceivable (Thomas et al., 2017). For this reason, not only the amount of global atrophy but also the location of the target region and its specific change caused by age-related volume reduction needs to be considered (Fig.3). For example, comparing the field distributions in two elderly subjects with those of a young control (Fig. 3) did not reveal differences in the amount of cortical volume receiving the strongest fields (> 0.1 V/m) for a bilateral frontal electrode montage (electrode positions F3-Fp2). However, distinctly higher intensities in the young control occurred for a left parietal – right

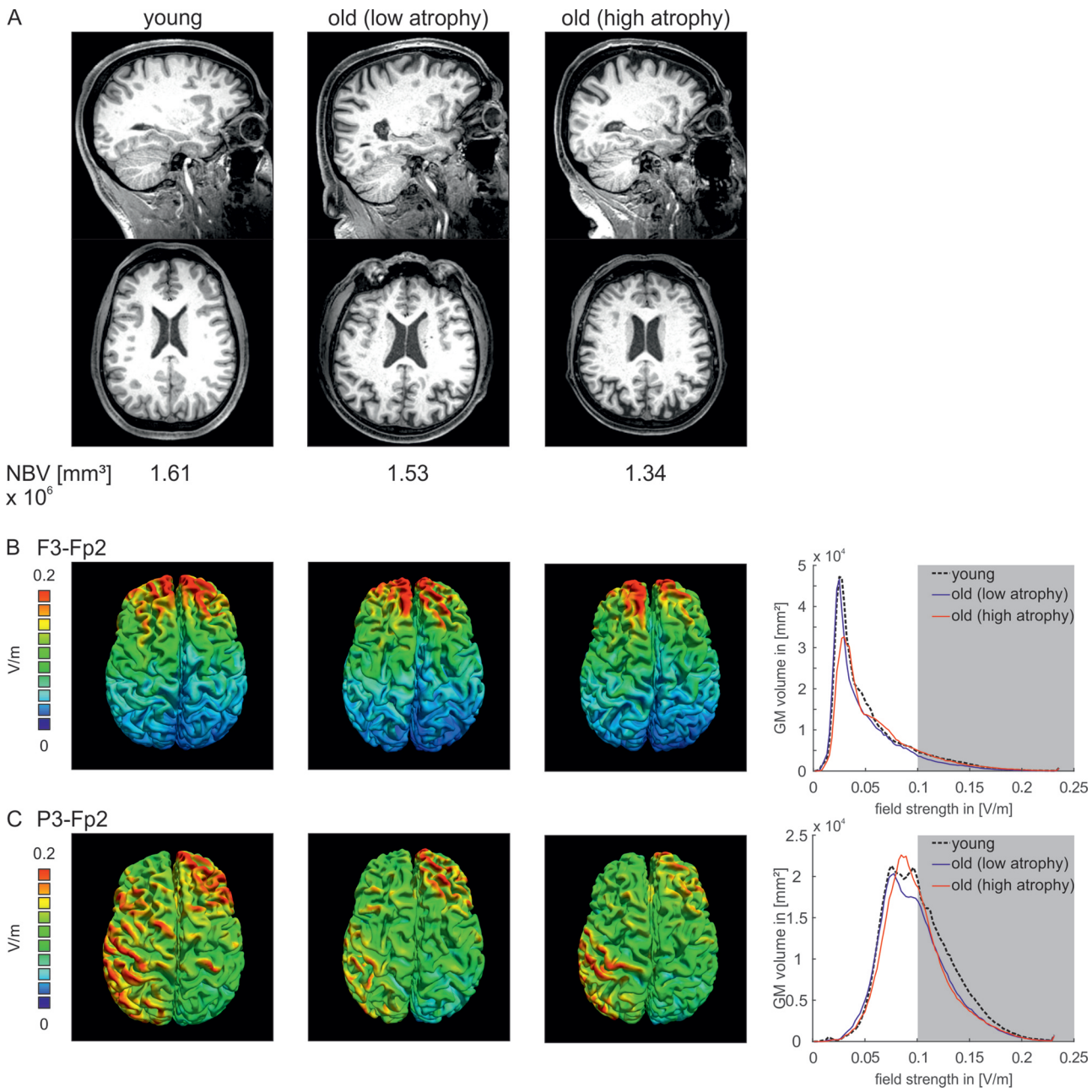

Fig. 3. Modelling of current fields induced by tDCS in three subjects: young adult (male, 21 years), older adult with low atrophy (male, 69 years), older adult with high atrophy (female, 72 years). (A) Sagittal and transversal slices for each subject, including brain tissue volumes, normalized for each subject head size (NBV), estimated with SIENAX (Smith et al., 2002), part of FSL (Smith et al., 2004). (B) Modelled current fields given a frontal stimulation montage with anodal electrode centred over F3 and cathodal electrode centred over Fp2, according to the international 10–20 system for electrode positioning (Jasper, 1958). Probability density function shows the distribution of field strengths over grey matter volume. (C) Modelled current fields given a parietal stimulation montage with anodal electrode centred over P3 and cathodal electrode centred over Fp2. Probability density function shows the distribution of field strengths over grey matter volume. (B) and (C): Grey boxes indicate the grey matter volumes receiving field strength > 0.1 V/m. This volume does not substantially differ between the young adult and the older adults for montage F3-Fp2. However, the young adult receives substantially stronger stimulation for montage P3-Fp2. Current fields were calculated using SimNIBS 2.1 (see Supplements for technical details). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

frontal electrode montage (electrode positions P3-Fp2). Notwithstanding that generalizable estimates for clinically relevant montages based on group level computational modelling studies are desirable, their advantage or even feasibility remains debatable, especially in view of the accumulating heterogeneity at advanced age (Antonenko et al., 2018b). Consequently, the higher validity of individualised models and the clinical practicability of their implementation need to be carefully weighed against each other.

Apart from an altered gyral and sulcal anatomy in advanced age, morphological changes also occur at the level of single neurons. This includes the deterioration of the myelin sheath (Spilt et al., 2005) as well as altered electrotonic parameters in dendrites (Kabaso et al., 2009). These changes to the biophysical properties of neural membranes impact likewise on the neurons' receptiveness to an externally applied electrical current (Paulus and Rothwell, 2016) and may hence call for additional tuning of the stimulation protocol.

4.3. Modulating the target

The clinical value of tDCS rests on its long-term effects, requiring

the targeted system to be sufficiently plastic. Despite the loss of synaptic boutons and diminished postsynaptic densities (Morrison and Baxter, 2012), aged brains retain an ability to undergo plastic changes up to a certain degree (Pascual-Leone et al., 2011). This is supported by the observation of use-dependent changes during motor skill acquisition (Berghuis et al., 2017) as well as the ability for training-induced rehabilitation after stroke (Darkow and Flöel, 2016), even at advanced age. In the latter case, functional recovery after stroke was most substantial when the training occurred in a window of heightened plasticity (Kitago and Krakauer, 2013). Also with regard to tDCS studies, the interval in which plastic changes are most likely to ensue is a pivotal aspect. More precisely, a study demonstrated that whereas the application of tDCS both prior to as well as concurrent to a picture-naming task improved verbal reaction times in young volunteers, positive effects on task performance in older adults were restricted to the condition in which tDCS was applied during but not prior to task execution (Fertonani et al., 2014). The lack of such offline effects of tDCS indicates changes to the mechanism of LTP in elderly. This is in line with the observed impact of ageing on the synapse, which involves the loss of synaptic spines (Morrison and Baxter, 2012; Petralia et al., 2014) as well as a decreased responsiveness of the NMDAR (Magnusson, 2012). Especially the late LTP, which is induced by gene expression and protein biosynthesis, is impaired in older animals, leading to a shortened duration of LTP (Ryan et al., 2015). Similarly, a general age-related decline in inducing plastic effects is also evident in humans, as demonstrated in the motor cortex (Fathi et al., 2010). However, as long as the respective synaptic mechanisms are not entirely inoperative, tDCS aftereffects can also arise in older adults. Particularly, this holds true when tDCS coincides with intrinsic brain activity (e.g. during cognitive training (Antonenko et al., 2018a)).

So-called priming protocols capitalize on the insight that external stimulation does not encounter a quiescent system. The rationale of these protocols rests on the concept of metaplasticity, i.e., the observation that the threshold for synaptic plasticity induction is shifted according to previous activity (Müller-Dahlhaus and Ziemann, 2015). Not all priming protocols are similarly effective in young and older participants. For instance, the effectiveness of priming via cTBS, a TMS protocol, has been shown in young but not in older adults (Opie et al., 2017). In contrast, cathodal tDCS has been shown to facilitate the subsequent effect of anodal tDCS in a motor task in elderly (Fujiyama et al., 2017). Furthermore, even within a specific priming protocol the choice of the exact parameters determines the outcome. Differential age-dependent effects were shown for paired associative stimulation (PAS; (Classen et al., 2004)), a protocol that combines median nerve stimulation with TMS of the motor cortex to induce associative plasticity in the latter. Specifically, an inter-PAS interval of 10 min led to increased plasticity induction in younger but not in older adults (Opie et al., 2017) while another study showed that an inter-PAS interval of 30 min proved to be more effective to increase plasticity induction in older adults as compared to 10 min (Sidhu et al., 2017). This finding demonstrates that metaplasticity is still inducible in old age. Nevertheless, its time course may diverge from the one displayed by younger individuals (compare (Fujiyama et al., 2014)), and may thus necessitate the use of different protocols.

Other than priming the neural system by means of a priorily or concurrently executed task or non-invasive brain stimulation methods, pharmacological approaches are conceivable to facilitate metaplasticity. Prolonging serotonergic (Prehn et al., 2017) as well as catecholaminergic neurotransmission (Nitsche et al., 2004) via respective reuptake blockers enhanced the effect of anodal tDCS. While both of these studies were performed in young participants, such pharmacological priming may have an even larger effect in elderly considering that, amongst other changes in the endocrine system, the concentrations of neuromodulators decline with age (Li and Rieckmann, 2014; Rehman and Masson, 2001).

5. Transfer to clinically relevant memory impairments

Aged populations with pathological incidences of neurodegeneration require further reflections on the objectives of tDCS application and the respective stimulation protocols. As mentioned previously, an association between disrupted E/I balance and behavioural deficits has been observed both for neuropsychiatric (Chen et al., 2014; Gonçalves et al., 2017; Salavati et al., 2015) as well elderly populations. Heightened excitability has been associated with cognitive impairment in rats (Haberman et al., 2017). The same holds true for humans, in whom mild cognitive impairment (MCI) as well as dementia due to Alzheimer's disease (AD) are characterised by aberrant excitability and activity (Meinzer et al., 2015; Pennisi et al., 2011), that can be interpreted as a compensatory mechanism against cortical thinning (Niskanen et al., 2011). However, it should be noted that the relationship between excitability changes and cognitive decline also displays certain non-linearities. Aged mice that were genetically modified for increased excitability and facilitated induction of LTP outperformed control animals in the Morris water maze (Murphy et al., 2004). Other than age-related changes in excitability, it has also been suggested that the interplay between the neural network hyperactivity and coinciding failures of synaptic homoeostasis drives AD at its early stage through a perpetuating deviation from normal brain activity (Styr and Slutsky, 2018). Restoring the activity pattern in prefrontal regions to the one displayed by healthy controls via tDCS already proved successful in reversing the underperformance of MCI patients in a cognitive task (Meinzer et al., 2015). This implies however that the protocol parameters of tDCS might need to be balanced between counteracting detrimental functional alterations and supporting adjuvant compensatory changes. While this poses a considerable challenge, the realisation of such individually fine-tuned protocols may become conceivable with so-called closed-loop protocols to calibrate stimulation parameters to induce a pre-defined target state as recently proposed by Lorenz and colleagues (Lorenz et al., 2016). This approach may provide a means to establish such balanced and necessarily individualized protocols that prevent overshooting the target state, which is particularly important in disequilibrated systems.

6. Conclusion

In the elderly population, tDCS offers a promising opportunity to counteract or compensate for neurophysiological alterations. In order to optimally benefit from this intervention, however, tDCS parameters derived from studies in young adults have to be appropriately adapted to the elderly population. Accordingly, a systematic exploration of tDCS benefits elicited by different stimulation protocols with regard to distinct paradigms in young and elderly adults is expedient. By now, it has become clear that tDCS protocols need to factor in systematic neurophysiological changes that are common across the aged population both by adjusting parameters used in young adults and by integrating additional considerations specific to the aged population. We have shown here how altered activity patterns in elderly may necessitate the choice of different target regions for tDCS, while current flow models based on individual anatomical images can help to choose suitable electrode positions to assure that the applied current reaches the defined target site. Apart from spatial considerations, the application of tDCS should also occur in a time window, in which the system is most receptive for the favourable alterations induced by the stimulation. In all this, the implications of tDCS on a relatively fragile system need to be considered as it is critical to avoid that tDCS aggravates the pre-existing imbalance in the aged neural system. Despite these obstacles, we have also outlined how the system's dissociation from a previous optimal state in healthy as well as pathological ageing renders tDCS-mediated improvements more extensive compared to the better calibrated systems present in young populations. Provided that the potential pitfalls outlined in this review are taken into account, elderly can be a

particularly promising target population for the clinical application of tDCS.

Declaration of Competing Interest

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None of the other author reports any conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2020.111179.

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