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Electrical Brain System Perspective for Alzheimer Disease Prevention and Therapy

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The Alzheimer disease (AD) is one of the most devastating neurodegenerative alteration of the brain in the elderly population. Clinically characterized as a progressive, neurodegenerative disease, including functional and cognitive impairments, AD is also well histopathologically demarcated by the presence of amyloid deposits and tau-related neurofibrillary tangles correlated with loss of synapses and neurons in crucial regions of the brain [1-3]. These pathological elements are well identified with cerebrospinal biomarkers (i.e., amyloid beta (Aβ42) and phospho-tau (p-tau) levels) [4-6].

In spite of intense basic researches, the prevention and therapy remain largely problematic and must be urgently reinforced [6]. From the most optimistic view, a definitive biological solution seems not to be attainable before twenty years.

Following a system perspective the brain is considered as a complex network linking the different regions into privileged connected nodes such as small-world, hubs and rich clubs with hierarchical modularity [7-9]. Alteration of this system can be viewed as a possible final outcome in neurological disorders [9]. In addition, the dynamic of these networks and related brain functions mainly resulted from electrical oscillations [10-15] which can be approached with non-invasive electrophysiological tools.

Among these interventions, the transcranial direct or alternating current stimulation (tDCS/tACS) coupled with other tools issued from the brain computing interface (BCI), mental imagery (MI) and virtual reality stimulation (VRS) is one of the most promising approach [16,17]. Briefly, the tDCS/tACS method consists in the application of small intensity of current (~2 mA during ~20 min) applied by means of sponge electrodes placed on the skin head at privileged sites. The choice of the site for the anodal and cathodal current application is important because current induces excitatory effect on the neuronal network situated just under the anode and conversely induces inhibitory effect at the cathode. The neurophysiological effect consists of an increase or a decrease of the spiking threshold of the neurons [18]. This must conduct research effort to find new technological tools based on artificial manipulation of these neuronal oscillations in order to enhance or restore the failed communication described in AD and individuals with mild cognitive impairment (MCI). The non-invasive electrical stimulation may also represent very promising strategy to improve neural circuits functioning as a complement tool to pharmacotherapy [19].

The tDCS/tACS approach can be seen as rather simple but still must be carefully and systematically controlled, regarding the complexity of the involved neural network and the induced neural plasticity. To do so, tDCS/tACS must be combined with neuroimaging procedures (fMRI, MEG and EEG dynamic combined to transcranial magnetic stimulation (TMS)) to follow the involvement of the excitatory/inhibitory process. It was recently demonstrated that tDCS can improve cognition in AD and MCI patients [20-27] reinforcing the idea that this therapeutic avenue deserves to be urgently developed.

The tACS only differs from tDCS by the fact that sinusoidal currents are given at a specific frequency in place of continuous and constant currents. tACS directly modulates oscillatory brain activity in such a way that the stimulation frequency can be adapted to the frequency of the specific targeted oscillation of the brain. Although there is an exponential use of tDCS in different conditions, the application of tACS on the cerebral cortex and the cerebellum is only recently explored [28]. However, the related perspectives are very promising and may occupy a privilege position in future AD therapies.

The aim is to modulate neuronal oscillations correlated with sensori-motor and cognitive alterations in MCI and AD patients. As an example, alpha oscillation can be seen as representative of internal brain states and as a predictive index of sensory and cognitive performance [29].

In this context, Zaehle et al. (2010) [30] demonstrated that tACS set at the same alpha rhythm as the individual participant significantly enhanced the endogenous alpha power in parieto-central electrodes of the scalp and induced significant plasticity. In accordance to the spike timing dependent plasticity (STDP) rule, this effect was reproduced in artificial neural network. Following a STDP paradigm [31], a specific frequency input can produce long term potentiation (LTP) in the oscillating circuit only if it presents a similar resonance frequency in the circuit. Conversely, if the resonance frequencies between the input and the circuit are different a long-term depression (LTD) is produced. Such type of plasticity has been recently observed after gamma tACS (70 Hz) applied on the left primary motor cortex (anode) and the right cerebellum (cathode) producing a significant improvement of visuo-motor performance [32].

Ultimately, it seems that the increase or decrease of the spiking threshold of the neurons explains the short-term effects of tDCS while the induced synaptic plasticity (LTD and LTP) account for the long-lasting effects. Still, the exact neural mechanisms underlying tDCS and tACS are largely unknown.

Attempts to treat AD with medication have shown controversial effects or minor efficacy [27,33]. Furthermore, ways to improve and stabilize the tDCS and tACS effects should be investigated. Future

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studies should also try to untangle the mechanisms sustaining long-lasting effects of transcranial current stimulation, as it might interplay with pathological mechanisms of dementia neurodegeneration with either beneficial or deleterious side effects [33].

Finally, to move transcranial current stimulation into regular treatment, large-scale randomized and multi-site controlled studies that integrate these techniques into traditional methods such as pharmacological treatment and psycho-cognitive therapy should be conducted. Non-invasive brain stimulation is an awaited complement to the weak therapeutic arsenal of AD. Moreover, future large-scale clinical studies may demonstrate its efficiency in other types of dementia [27,33].

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