The scientific foundation for the PlatoWork neurostimulation headset

Onarheim B[1], Holm SU[1], Friis-Olivarius M[1]

[1] PlatoScience Neurostimulation Aps, Copenhagen, Denmark

An introduction to tDCS neurostimulation

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation method, used to modulate neuronal activity and increase synaptic plasticity by applying a low intensity current to the scalp through two or more electrodes. The method holds the ability to affect the potential for activation in the targeted neurons, while not being strong enough to force neural activity. The history of neurostimulation dates back to before the common era; ancient greek philosophers as Plato used the electric torpedofish for therapeutic purposes, and the Romans were the first to document the use of electric stimulation to treat medical conditions such as migraine (Finger, 2001). Since the beginning of this millenium tDCS has been *rediscovered* (Brunoni et al., 2012); there is increasing evidence of the therapeutic properties of this method and is now almost 4,000 peer reviewed articles establishing the effect of tDCS (https://www.ncbi.nlm.nih.gov/pubmed/?term=tdcs). tDCS is now widely used by clinicians and researchers (Fregni et al., 2015), the military (Nelson & Tepe, 2015) and by private individuals (Wurzman et al., 2016). There is growing evidence that tDCS improves conditions such as tinnitus (Wang et al., 2018), depression (Borrione et al., 2018), mild cognitive impairment (Meinzer et al., 2015) and many others (Kuo et al., 2014). Furthermore, tDCS has proven beneficial in healthy subjects; it seems to aid cognitive properties as learning (Simonsmeier et al., 2018), memory (Arciniega at al., 2018; Fregni et al., 2005; Mancuso et al., 2016) and reduced risk taking (Bell, 2017; Cheng & Lee, 2016): and motor skills as endurance (Angius et al., 2018; Vitor-Costa et al., 2015) strength (Tanaka et al., 2009) and speed (Edwards et al., 2017). While the physiology of tDCS is still not fully understood, it is widely accepted that the current reaching the neurons has the ability to modulate neural activity (Stagg et al., 2018). Furthermore, it is considered a safe neurostimulation method with no known Serious Adverse Events (SAE) but commonly only mild and temporary adverse events (Antal et al., 2017; Bikson et al., 2016).

Practical application of tDCS

tDCS works by applying two or more electrodes to the scalp of the subject, thereafter a weak electrical direct current is sent from one electrode (anode) to the other (cathode). Where the current enters the brain under the anodal electrode, there is an increase in neuronal excitability, and where the current exits the brain under the cathodal electrode there is a decrease in excitability. In normal applications, the electrodes are wet electrodes varying from 16-35cm2, the current varies from 1-2mA and the duration of a session 20-30 minutes.

The PlatoWork tDCS neurostimulation headset

PlatoWork is a neurostimulation headset developed by PlatoScience Neurostimulation ApS, designed and manufactured in Copenhagen, Denmark. The headset was first released as a commercial product in May 2017, and is currently marketed for cognitive training and enhancement. PlatoWork utilizes industry standard tDCS parameters, and the key purpose of the headset is to offer safe and standardized tDCS neurostimulation for home usage, with cloud-based data collection and logging. While there is an increasing number of tDCS devices available, these are either high cost stationary lab devices, or simple and often unsafe and/or imprecise do-it-yourself (DIY) devices. PlatoWork provides high-accuracy tDCS in-context, in a safe and fail-proof manner, through a headset that ensures correct and consistent electrode placements, across users and in repetitive sessions. Furthermore, PlatoWork is the first cloud-based tDCS headset that can also collect usage data real time, allowing for large scale studies of tDCS home usage, and distributed scientific studies.

Application of tDCS in PlatoWork

The application of tDCS in PlatoWork is based on the current body of tDCS studies, defining the functional hypotheses, the technical specifications of the tDCS, and the current output limitations in the headset. The primary aim is to ensure that the tDCS stimulation is accurate, safe, and effective, without challenging the core principles and safety limitations of the method itself. PlatoWork utilizes three 20 cm2 sponge + saline electrodes, with a current operation range from 1.0-1.4mA (0.05-0.07mA/cm2 current density) in 30 minutes sessions. We do not recommend more than 30 minutes stimulation a day, based on standard safety recommendations. The three electrodes are placed on the prefrontal cortex, a) left and b) right, and over the c) precuneus region in the default mode network – corresponding to F3, F4 and Pz in the 10-20 system. By activating two electrodes at the time, one as anode and one as cathode, the headset seeks to modulate neural activity in the underlying regions with the purpose of affecting different types of cognitive states.

The headset is operated using a smartphone app, where the user can choose between four predefined 'modes', each activating a flow of current between two of the three electrodes in the headset. In the current version these four modes are designed to support cognitive states related to the broad topics of creativity and focus, for the user termed 'Create' and 'Focus', as elaborated in the following section.

PlatoWork functionality

The functionality of PlatoWork is based on a novel network-based stimulation approach, in which mental states are induced by differential modulation of large-scale cortical networks in the brain, as well as their balance across hemispheres. In recent years, neuroscience research has shifted from understanding brain regions in isolation, to also understanding the brain as interactions between regions. The ability to think creatively or focused has since been shown to correlate with the synchronization of large-scale associative cortical networks, particularly the executive control network (ECN) in the dorsolateral prefrontal cortex (DLPFC) and the default mode network (DMN), which is centralized in the precuneus (Pz) (Buckner et al., 2008). Changing activity levels in these networks differentially modulates the cognitive states of creative or focused thinking (Gonen et al., 2017; Takeuchi, et al., 2011; Friis-Olivarius et al., 2015; 2017). More concretely, PlatoWork operates by shifting the balance in the interhemispheric rivalry (Sack et al., 2005), or by tilting the synchronization between the ECN and DMN (Takeuchi, et al., 2011). The underlying mechanisms for PlatoWork is based on a large body of functional magnetic resonance imaging (fMRI) and tDCS evidence. For instance, for shifting the balance between hemispheres it has been demonstrated that positive tDCS stimulation of the left DLPFC increases performance on intelligence based complex verbal problem-solving (Cerruti & Schlaug, 2009; Zimrod, et al., 2015), whereas a negative stimulation of the same area increases performance on idea production (Chrysikou et al., 2013). Also, positive stimulation of the right DLPFC has been shown to significantly increase creative performance in less-experienced pianists (Rosen et al., 2016). Because PlatoWork utilizes the natural hemispheric rivalry, both left cathodal and right anodal stimulation, and *vice versa,* have similar net effect on the overall hemispheric balance.

The PlatoWork function of tilting the synchronisation between the ECN and DMN is based on recent fMRI evidence, which has documented an anti-correlation between the ECN and DMN (i.e. Takeuchi, et al., 2011; Friis-Olivarius et al., 2015; 2017), meaning that when we concentrate on a given task and thus have high activity in the ECN, the brain automatically turns down the production of spontaneous thought from the DMN, and *vice versa* when we are in a relaxed or un-focused state of mind. That frontal executive-control regions are connected to the DMN is also supported by a series of recent studies showing that tDCS applied to the prefrontal cortex can modulate the amount of reported mind-wandering in participants (Axelrod, 2015; Kajimura 2015), which is an important indicator of spontaneous activity in the DMN.

PlatoScience research activities

While the functionality of PlatoWork is based on years of tDCS studies, it is crucial for PlatoScience to actively engage in specific studies using the PlatoWork headset. Thus PlatoScience has a research strategy consisting of four core elements, which are all ongoing or initiated:

1. Retention- and usage data from real world users, investigating usage patterns over time as an expression for perceived real life efficiency (ongoing).
2. Systematic data collection from headset users in context, documenting effects and changes to cognitive states through subjective and objective measurements, comparing actual stimuli to sham and/or reverse stimuli (subjective measurements initiated).
3. Traditional tDCS lab-studies using stimulation/sham to measure effects on standardized cognitive tests, both reproducing previous studies and testing new hypotheses (pilot studies performed, application for ethical approval submitted).
4. Traditional tDCS lab studies in combination with electroencephalography (EEG) and standardized cognitive tests, a novel approach to documenting tDCS effects (grant received, collaboration with Technical University of Denmark initiated, application for ethical approval submitted).

Physiology of tDCS

tDCS works by applying a weak electrical direct current to the scalp, with the current running from one electrode (anode) to another (cathode). Laboratory studies have demonstrated that tDCS induces polarity-dependent changes in membrane excitability, with anodal tDCS causing depolarization and cathodal tDCS hyperpolarization of membrane potential in neurons of the stimulated areas (Stagg & Nitsche, 2011, Stagg et al., 2018). Anodal stimulation increases cortical excitability both during and after stimulation, provided the stimulation period is of sufficient duration, and cathodal stimulation leads to a decrease in excitability within the cortex. The effects of anodal tDCS during stimulation appear to be solely dependent on changes in membrane potential. Neurostimulatory agents seems to have no effect on neurostimulation whereas calcium blockers abolish the effect, suggesting the importance of voltage gated calcium channels in the effects of tDCS. Both anodal and cathodal tDCS primarily affect resting membrane potential during stimulation, with no significant effects on synaptic plasticity. However, the aftereffects of anodal tDCS are enhanced by the addition of amphetamine, but only in the absence of DMO (NMDA-R antagonist), suggesting that the lasting effects of tDCS is due to increased synaptic plasticity, more specifically modulation of NMDA-dependent LTP-like plasticity (Nitsche et al., 2004). Also on a molecular level tDCS induces changes that is linked to synaptic plasticity; the neurotrophic factor BDNF is increased after neurostimulation on both protein and gene level (REF). These neuroplastic processes are important foundations for various cognitive functions such as learning and memory formation and are pathologically altered in numerous neurological and psychiatric diseases. This explains the increasing interest to investigate DCS as a therapeutic tool (Stagg et al., 2018).

Safety of tDCS neurostimulation

PlatoWork stimulates with a current density of up to 0.07 mA/cm^2, which is similar to traditional tDCS applications, standard tDCS devices, and the levels that are repeatedly proven to be safe and without Serious Adverse Events (SAE). Meta-analysis on safety found no reports of (SAE) or irreversible injuries across more than 33.200 sessions (Bikson et al., 2016) with stimulation strengths interchangeable to PlatoWork. Repeated stimulation post no increased risk for adverse events (Nikolin et al., 2018). Unlike most pharmacological neuromodulators tDCS is associated with few side-effects. Some individuals report mild, but transient adverse events such as skin irritations beneath the electrodes, cognitive discomfort (e.g. moderate fatigue, headache and in rare cases nausea) and a metallic taste in the mouth (Antal et al., 2017). Conventional neurostimulation with tDCS use has been used within research for decades, and more reports on safety has been done, establishing that tDCS is safe in human. Furthermore, translational studies have established that the stimulation threshold for brain is more than a 100 times higher than the strength+time commonly used in tDCS (Liebetanz et al., 2009, Bikson et al., 2016) and in PlatoWork.

Limitations

Just as fingerprints no two brains are identical (Valizadeh et al., 2018). Therefore, despite of comprehensive research on the anatomical and physiological properties of brain regions of interest, there will be individual differences of the effect of neurostimulation (Kim et al., 2014; Hsu et al., 2016). Therefore, as some groups show effects of tDCS on e.g. cognition and motor skills, others report negative results (Chrysikou et al., 2017). Within the scientific community the effects of tDCS is widely discussed (Buch et al., 2017, Chrysikou et al., 2017) and there is a common understanding that the field needs larger multicentered randomized studies. At PlatoScience we are aware of the limitations of tDCS and investigate how the differences between users (everything from head shape to education level to mood) affect results. In line with the physiological foundation of tDCS, the most effects of tDCS is seen in a learning situation, where the brain is modulated e.g. by synaptic plasticity (Simonsmeier et al., 2018, Buch et al., 2017). Therefore we attempt to guide our users so that they undertake the most sufficient tasks while using neurostimulation.

Current state of regulations for tDCS devices

In most major markets, and EU/US specifically, tDCS products with a limited current output in the range of typical tDCS standards are currently not regulated, unless they are marketed with claims of medical effectiveness. With its current purpose and limited output values PlatoWork is thus only subject to international safety standards governing all electrical consumer devices, and compliant with consumer CE requirements and CE marked.

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