Surface EEG-Transcranial Direct Current Stimulation (tDCS) closed-loop system: a feasibility study

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Abstract

Conventional tDCS protocols rely on applying electrical current at a fixed intensity and duration without using surrogate markers to direct the interventions. This has led to some mixed results; especially because tDCS induced effects may vary depending on the ongoing level of brain activity. Therefore, the objective of this preliminary study was to assess the feasibility of an EEG-triggered transcranial direct current stimulation (tDCS) system based on EEG online analysis of its frequency bands.

Six healthy volunteers were randomized to participate in a double-blind sham-controlled crossover design to receive a single session of 10 min 2mA cathodal and sham tDCS. tDCS trigger controller was based upon an algorithm designed to detect an increase in the relative beta power of more than 200%, accompanied by a decrease of 50% or more in the relative alpha power was used based on baseline EEG recordings.

EEG-tDCS closed-loop-system was able to detect the predefined EEG magnitude deviation and successfully triggered the stimulation in all participants. This preliminary study represents a proof-of-concept for the development of an EEG-tDCS closed-loop system in humans. We discuss and review here different methods of closed loop system that can be considered and potential clinical applications of such system.

Keywords: EEG-tDCS closed-loop system, EEG algorithm

1. Introduction

Closed-loop brain computer interface (BCI) systems, for real-time detection and controlled by electroencephalogram (EEG)-patterns have been developed in order to allow humans to interact with their environment without peripheral nervous system involvement.[1] Most BCI studies focus on improving motor function in people with severe motor disabilities.[2] In this context, BCI system relies on acquiring a brain signal, preprocessing it, extracting and classifying target features, and governing a secondary device via a control interface. Such a control system will then act in a loop, feedforwarding responses at the same time that it is actively monitoring the existent brain activity for the target feature detection. In the recent years, several noninvasive brain stimulation (NIBS) techniques have been extensively studied. One of these techniques suitable for BCI adaptations is transcranial direct current stimulation (tDCS). In tDCS, weak electric currents are applied to the brain via scalp electrodes. This constant electric current induces shifts in neuronal membrane excitability, resulting in secondary changes in cortical activity. TDCS is a safe and noninvasive neuromodulatory technique. Depending on the targeted cortical region and activity state as measured by EEG, tDCS can modulate cognitive performance[3-5] or suppress symptoms in a range of neuropsychiatric diseases such as neuropathic pain, depression, schizophrenia, and addiction among others.[6-8] Although tDCS has most of its neuromodulatory effects on the underlying cortex, tDCS-induced effects are also observed in distant neural networks. Therefore, concomitant EEG monitoring of the effects of tDCS could provide valuable information on the mechanisms of tDCS and identify opportunities for closed-loop tDCS-based systems.

Conventional tDCS protocols rely on applying the electrical current at a fixed intensity and duration, without using surrogate markers to direct the interventions. This has led to mixed results in clinical trials, in part because the extent to which tDCS modulates cortical excitability is dependent on the ongoing level of cortical activity.[9] Therefore, the development of a closed-loop system that can trigger tDCS at specific levels of ongoing cortical activity is appealing because it will allow rapid neuromodulatory intervention after detecting a specifically predefined EEG-oscillatory activity, thus promoting the enhancement of specific EEG patterns associated to cognitive functioning, or in the opposite direction, by inhibiting aberrant EEG oscillations or pathological electrical activity as in the case of ictal states. It can also be helpful to determine adequate tDCS parameters for specific applications by monitoring EEG signals. In such a system, specific changes in the EEG signal would be used for triggering external tDCS devices using specific BCI-derived algorithms. Accordingly, a wearable neurofeedback system involving surface EEG and transcranial electrical stimulation was recently proposed.[10] Nonetheless, the system despite being useful, has not yet been applied to a clinical trial.

EEG signals are sensitive and reliable to detect cognitive changes related to performance of certain tasks [11], which therefore could be monitored with real-time EEG analysis.[12-15] Also, EEG power is a reliable measure to detect specific cognitive and motor features across sessions,[16,17] as well as the effects of tDCS.[18,19] Invasive closed-loop systems incorporating EEG and brain stimulation techniques have been demonstrated in both animal and human studies.[20,21] To our knowledge, the only study testing a non-invasive closed-loop system in humans is a recent feasibility study showing that motor-imagery induced desynchronization detected by surface EEG can trigger transcranial magnetic

stimulation (TMS) leading to increased excitability of the motor cortex.[22] But, so far there are no studies assessing the feasibility of using surface EEG to guide tDCS stimulation in humans. A closed-loop system has some challenges such as (i) accurate triggering of tDCS device; (ii) defining an algorithm based on a neurophysiological signal that would be clinically relevant and (iii) defining a task to modify a neurophysiological signal.[23]

Here we assessed the feasibility of a closed-loop system based on scalp-recorded EEG that is able to detect specific patterns of electroencephalographic oscillations based on a pre-defined algorithm. In our system, the EEG signal is acquired, filtered, sampled, and digital-signal-processed to obtain quantitative data that identify specific profiles of brain oscillations. This EEG system is also connected to a noninvasive brain polarization device, a tDCS apparatus, which would allow the specific EEG changes to automatically trigger the stimulation. For this proof-of-concept study, the triggering algorithm chosen to initiate cathodal tDCS was based on a combined increase of relative power in the beta band and a decrease of relative power of the alpha band. This threshold was arbitrarily selected in order to mimic the cognitive effort involved in task engagement, and simultaneously preventing the system from being triggered by very small changes in EEG power (e.g. 5%).

The primary aim of this study was a proof-of-concept and assessment of the feasibility and safety of an EEG-triggered tDCS closed-loop system in healthy subjects. As a secondary aim, we explored whether EEG-guided active tDCS induced significant changes in EEG power as compared to EEG-guided sham tDCS.

2. Technical aspects of closed-loop systems for brain stimulation

Current monitoring technology allows for portability and miniaturization of circuits intended to record and process signals with the intention to control NIBS devices. Those signals can be obtained from the endogenously generated and functionally-dependent cortical activity or related with oxygen binding for metabolic rate, these signals can be captured using technology suitable for demanding environments such as rehabilitation centers or the ever complex hospital settings, EEG or near-infrared spectroscopy (NIRS) measurements are the prototypical systems due to practicality and safety, especially if the main objective for application is to keep the system as portable and non-invasive as possible. The ideal closed loop system needs to process the signals in real time as to allow for feedback control and trigger response, this closed-loop system must also benefit for brain-state dependent oscillatory activity or cortical hemodynamic changes, so it allows for the modulation of ongoing motor or cognitive training/tasking on line. For the purpose of this manuscript and because a EEG-based closed-loop system is presented, a review of this methodology is reviewed.

The design of a closed-loop system differs significantly between different methods, and because this is an evolving multidisciplinary field the language used to describe the systems can vary among devices. An intelligent EEG-based, NIBS closed-loop, can be also called EEG-based feedback stimulation control, such a device or system must interface with the nervous system via electrographic signals, providing an input which will responds to pre-specified quantitative EEG criteria. A closed-loop first needs to recognize, discriminate and classify the EEG patterns into a language that can be delivered to the system for further action. Briefly, we can separate the operational structure of the system in four major components; 1) data acquisition operation and signal recognition; 2) feature extraction and reduction of data dimension; 3) classifier design; and

4) classification and decision making for output. Altogether, these components serve as a basic structure for the development of an intelligent EEG-based closed-loop device (see figure 1).

[Insert figure 1 about here]

3. Methods

This was a feasibility pilot trial in which we assessed in healthy volunteers a closed-loop tDCS system triggered by specific EEG patterns based on a pre-defined algorithm.

3.1 Participants

Six healthy subjects were recruited (3 females, age: 27 ± 5.87 years old). Subjects were excluded if there were (a) existence of major neurologic or psychiatric condition (i.e. epilepsy, severe depression); (b) history of head injury resulting in more than a momentary loss of consciousness; (c) previous neurosurgery; (d) history of significant alcohol or drug abuse in the prior 6 months; (e) presence of unstable medical conditions, such as uncontrolled diabetes mellitus, cardiac pathology, cancer, kidney insufficiency and acute thrombosis; or (f) general contraindication to tDCS, such as metal implant in the head; implanted electronic medical devices; and pregnancy.

All subjects gave written informed consent prior to their inclusion in this study. This experiment was approved by the Institutional Review Board (IRB) of Spaulding Rehabilitation Hospital (SRH), and was conducted according to the Declaration of Helsinki.

3.2 tDCS stimulation

In this study, participants were randomized in a counterbalanced order using a computerized randomization technique to start with either sham or active tDCS. The second session was performed one week later in order to prevent carryover effects. Cathodal tDCS was delivered by a customized 1X1 tDCS device (Soterix Medical, US) and using two rubber electrodes in 35cm^2 saline soaked sponges. The parameters for cathodal tDCS were 2mA for 10 minutes (30 seconds ramp up/down), with the cathode placed over the left dorsolateral prefrontal cortex (DLPFC, F3) and anode electrode on the contralateral deltoid muscle. By applying 10 minutes of tDCS, it will be possible to measure an effect that can outlast the stimulation period up to one hour.[24-26] Sham stimulation followed the same parameters except that the duration of the stimulation lasted only 30 seconds ramping up/down, as this is a reliable method to ensure the blinding.[27]

3.3 Electroencephalography

The brain electrical activity was registered through Powerlab 26T (ADinstruments, Australia). The EEG electrodes were placed according to the 10-20 International System, over Cz and another one on the right earlobe (A2) in a monopolar montage (see figure 2), whereas the reference was placed at the left mastoid apophysis.

EEG signal was passed through a band pass filter between 0.1 and 35 Hz, before being sampled at 1000Hz. Offline processing of EEG data (for baseline and after tDCS) involved ocular artifact removal following the Gratton and colleagues algorithm [28] and averaging of 4-sec epochs (15 in total). Fast Fourier transformation (FFT) using Labchart

8.1 (AD instruments, Australia) was applied to calculate power in the following frequency bands: delta, theta, alpha and beta.

3.4 *Procedures*

3.4.1 The triggering algorithm

This closed-looped system consisted of triggering the customized 1X1 tDCS device (Soterix Medical, US) after a pre-specified EEG power threshold was reached. For this specific project, the threshold was arbitrarily established at an increase of relative beta power of 200% with a simultaneous decrease of 50% in relative alpha power – this would prevent the system from being triggered by very small changes (e.g. 5%). Once both conditions were met (i.e. decrease in alpha and increase in beta), the Powerlab 26T would automatically send a trigger pulse to the tDCS device, which will then start the stimulation. After the period of stimulation has ended, the closed-looped system would actively search again for the pre-established threshold, and if it was reached, the tDCS would be triggered once again (see figure 2). The goal of this proof of concept was not to determine the threshold. Instead, it was to develop a system where changes on the EEG activity could be detected and that would automatically trigger (or not) the tDCS device based on a pre-established threshold.

[Insert figure 2 about here]

During the first minute of baseline EEG recordings, participants were asked to look at a fixator cross in front of them, and then they were asked to keep their eyes closed for

the remaining 9 minutes of registration. This period was used to calculate pre-specified thresholds using offline EEG analysis. Following the baseline EEG recording, a computerized Stroop task was used in order to induce the EEG changes required to reach a pre-determined threshold. Once it was reached and tDCS was initiated, subjects were asked to close their eyes. After tDCS had ended, another ten minutes of EEG were recorded (figure 2).

The baseline parameters (eyes open) for the closed-looped system were defined based on the relative alpha and beta power. These values were calculated reflecting the percentage of the actual power of the frequency band (i.e. alpha or beta) in the total power (i.e. of all frequency bands).

3.4.2 *Analysis*

In order to assess if the cognitive task triggered successfully tDCS, Fisher´s exact test was used. In order to assess the differences across active and sham tDCS, Mann Whitney tests were used for each brain rhythm. All the statistical analyses were performed using SPSS (version 21.0). Due to the exploratory nature of this study we only analyzed differences between sham and verum tDCS.

4. Results

In all cases, the EEG threshold tDCS triggering was induced during the performance of the Stroop task ($p<.001$). The system detected correctly the pre-determined controller algorithm (increase in the relative power of beta by more than 200%, accompanied by a decrease of 50% or

more in the relative power of alpha) and initiated the stimulation successfully. There were no adverse effects associated with stimulation.

[Insert figure 3 about here]

One participant who dropped out during the trial was excluded from the power analyses. After the EEG threshold induced tDCS triggering, in the period immediately following tDCS, cathodal tDCS did not result in any significant change for any of the EEG power bandwidths (see figure 3).

5. Discussion

We demonstrated the technical feasibility of a closed-loop EEG-tDCS system which detected a task-induced EEG change in all participants and triggered tDCS stimulation in all trials. This is one of the first studies showing the feasibility of a closed-loop system consisting of surface EEG and tDCS, where tDCS was delivered as a result of consistent EEG oscillatory changes derived from a cognitive challenge in multiple healthy subjects. Participants exposed to the interventions did not spontaneously report any adverse effects or on the tDCS adverse effects questionnaire, and had no acute changes on neurological and cognitive examinations.

The closed-loop system acquired EEG signals and sent an output trigger based upon the predetermined algorithm that processed the EEG signals and once threshold was reached, tDCS was activated. The activated tDCS device then delivered the stimulation current and EEG signal was monitored again to form the closed-loop. The algorithm consisted of an online FFT for all the

frequency bands (with an initial delay of 500 msec), followed by an active threshold monitoring. Once the threshold was reached (i.e., alpha power decreased by 50% and beta power increased by 200%), tDCS was triggered. Once tDCS stimulation has ended a new active threshold monitoring was initiated, thus closing the loop.

With regard to the secondary aim, there were no significant effects of cathodal tDCS on EEG frequency band power. This was likely due to reduced lack of statistical power in the current design and also because the parameters of tDCS were not aimed to induce significant EEG changes in healthy subjects.

Historical notes on closed loop system

The idea of combining electrical stimulation and cortical outputs is not new. By using functional electrical stimulation (FES) it is possible to connect cortical outputs directly to muscles, and to thereby induce a movement. For instance, EEG beta rhythm generated by the imagination of foot movements has been already used to induce grasping movements.[29] In fact, in medicine, there is a good number of examples of successful closed loop systems. One of them is the automatic cardiac defibrillator, in which a constant electrocardiogram (ECG) system monitors the heart's electrical activity and can trigger a portable defibrillator that can revert cardiac arrest.[30-33] The combination of tDCS and EEG is, on the other hand, a feasible practice that has not being tested. One of the advantages of tDCS is its small size and portability characteristics.[34]

Closed loop system using tDCS

TDCS is a technique that has had a significant technical and clinical development in the past 15 years;[35] however some of its effects are still moderate.[36-38] One area of development to

optimize the effects of tDCS is through the use of a closed loop system. The closed-loop system using specific signals from the brain involves (i) specific neural patterns found, for instance, in EEG for behavior/cognition and (ii) corresponding tDCS-polarity induced effects to modulate these effects. This closed-loop system will allow more effective modulation of cognitive performance as the effects of tDCS also depends on the ongoing level of brain activity.[24,39,40] For this system to be effective it is necessary to understand: (1) specific EEG signals that translate in specific behaviors or prediction of behaviors and (2) specific tDCS parameters that can lead to a specific EEG signature associated with a specific behavioral change. Although the main goal of this feasibility report is to test the technical requirements and feasibility of the system, there is still a need for intensive research for each clinical application as to define steps 1 and 2.

There are potential applications using tDCS to develop a closed loop system. For instance, there is growing evidence on effects of tDCS on motor learning [25,41,42]. In this context, when tDCS is integrated in a closed-loop system within a BCI, which promotes motor learning, the therapeutic effects of such a system can be substantially enhanced. In fact, such a closed-loop system employing TMS has been suggested as a potential tool to improve post-stroke motor recovery [22]. Moreover, tDCS closed-loop systems were already successfully tested in animal models of epilepsy. In a previous study, Berényi and colleagues [20] showed that seizure-triggered, feedback driven tDCS was able to detect and reduce spike-and-wave in a rodent model of generalized epilepsy. This type of intervention could be a possible alternative to other forms of brain stimulation (such as deep brain stimulation), where the continuous application of electrical current is associated with increased side effects[43]

Another potential application of a closed-loop tDCS system is in chronic neuropathic pain or fibromyalgia. It has been demonstrated that the primary motor cortex is a critical neural

modulator of maladaptive pain related neural circuits [44-46] and that interventions to modulate the primary motor cortex, such as tDCS or mental imagery, can affect motor cortex excitability and reduce pain.[47-49] Therefore, one potential application is to use behavioral interventions such as visual illusion (mirror therapy is an example) to induce changes in motor cortex excitability and combine with TDCS to modulate pain-related circuits.[50] In such study, a detailed recording of motor cortex excitability could be used to trigger (and also stop) tDCS of primary motor cortex to reduce pain. In fact, unnecessary prolonged tDCS could lead to opposite effects.[51]

In this scenario, a closed-loop system that is able to detect specific abnormal EEG activity and is able to trigger a pre-specified stimulation and thus restore brain activity with less exposure to electrical currents could have a better risk/benefit ratio and also more optimal results. Moreover, these systems can be used to monitor neurophysiological indicators of potential side effects such as pre-seizure EEG abnormalities in high risk populations and therefore abort the stimulation preceding the clinical symptoms.

Potential clinical impact of closed loop systems

The development of non-invasive closed-loop systems might have future implications in disorders characterized by transient abnormalities of cortical excitability and connectivity. Since these systems would incorporate dynamic stimulation techniques (i.e. tDCS), which are responsive to online physiological monitoring (EEG), they can be used in combination with other forms of therapies and increase the success rate of such interventions. Moreover, designing specific algorithms able to determine individualized thresholds based on intrinsic abnormalities recorded on EEG will allow optimization of these therapies and stimulation techniques.

For example, in disorders such as epilepsy, designing algorithms to predict, detect and treat an ictal event is of particular importance as these algorithms might be used in closed-looped systems which could trigger preventive or therapeutic interventions. [52] Such systems have been recently investigated using invasive devices [53]; however, there are no studies assessing the feasibility and efficacy of completely non-invasive closed-loop systems in epilepsy. Cathodal DC polarization has already been shown to reduce epileptiform EEG activity in patients with epilepsy [54]; closed-loop systems incorporating these methods should be developed to detect ictal patterns and initiate stimulation. Neurorehabilitation, including cognitive remediation, is another potential application of a tDCS closed-loop system Moreover, the closed-loop system can be adapted to other forms of non-invasive stimulation, such as stimulation of the sensory somatic sensory fields of the trigeminal or vagal nerves, in which sympathetic/parasympathetic modulations can be used for therapeutic purposes.

Recently, transcranial alternating current stimulation (tACS) was integrated into a feedback-controlled interface, for the purpose to boost sleep spindle activity, Lustenberger et al, successfully demonstrated positive modulation of oscillatory sleep spindles, by applying an algorithm for the detection of such distinctive electrographic feature pattern, and triggering tACS in the 12Hz range to enhance a rhythm associated with improvements of motor memory.[55] This works adds evidence for the integration of intelligent monitoring of EEG activity and efficiently applied noninvasive brain stimulation.

Another field that has benefited for advanced research on closed-loop systems is DBS and Parkinson's disease. Recent studies have tested adapted DBS (aDBS) with promising results (for a review see [56]). In this review, they pointed out that not every symptom could benefit from an

adaptive closed-loop system or are even more challenging to deal with. For instance, in Parkinson disease, the effects of DBS on dystonia may appear after several days or more, while for tremor the benefits are more direct.[57]

In this case, aDBS system aiming at treating tremor shows better results than those for dystonia. In the scenario of epilepsy, most of the drugs have a direct effect when a seizure occurs by modulating membrane potentials and seizure threshold, while for NIBS, these techniques seem to have an impact on frequency of seizure occurrence as well as on reducing the interictal epileptiform activity.[58] These preliminary results show that focal epilepsy seems to be a proper target to benefit from a closed-loop approach. In our proof-of-concept study, we can conceptually approach the idea to avoid or prevent seizures by decreasing epileptiform cortical activity, by placing the cathode electrode over a theoretical epileptogenic area. The rationale behind comes from evidence of decreased seizure frequency and interictal discharges, when subjects with focal epilepsy (mesial temporal lobe epilepsy) were exposed to cathodal tDCS[59] The EEG-tDCS model seems to fit the requirement of a realistic and efficient closed-loop system and, therefore, it is essential to pursue investigations on the potential benefits of NIBS in reducing the risk of seizure using this closed-loop approached.

6. Important points to develop a closed loop system

The most single important aspect to consider when developing such closed-loop system is the threshold criteria. In the present study, as a proof of feasibility, our threshold was pre-established on rather arbitrary values that were chosen in order to reduce the probability of tDCS being triggered by very small changes. Thus, the next step will be the implementation of adaptive thresholds based on very specific brain changes related either to task performance or to neurologic condition. Such a system should behave similarly to the already available automatized QRS

detectors in ECG, where it is possible to detect and categorize different peaks which also represent different types of cardiac activity.[60]

Determining the proper trigger in a closed-loop system is a key point if not the most important part of the model. Theoretically, creating a closed-loop system based on a causal relationship between the output (e.g, brain activity) and the stimulus generator is feasible. However, it is well known that a specific behavior or symptom is not driven by a single pattern of brain activity. Therefore, the algorithm that will be used in the model should take into account several well defined parameters to have an appropriate and accurate response. Indeed, it is of a high importance to clearly define the symptoms aimed to be modulated. Regarding seizure prediction, several criteria have been defined by Mormann (2007)[61] to evaluate the efficacy of a seizure prediction algorithm: algorithms should be developed upon long term recordings from patients; the sensitivity and specificity the algorithm should be assessed under the prediction time horizon, but also under the false warning portion of time; the prediction is above change level, as determined by appropriate statistics; and finally, needs to be tested in an out-of-sample data to increased its external validity.[61]

Measurements tools for a closed loop system

It is essential to determine an accurate measure that indicates the occurrence or the demonstration of the target symptom to treat. Many closed-loop systems have used on scalp-recorded EEG or electrocorticography (ECoG). EEG and ECoG recordings have the advantage to be straightforward; however, they are surrogates of the symptom that it is aimed to be modulated or healed. On the other hand, clinical triggers (e.g, muscle contracture or tremor) may induce better results since they represent the final outcome to modulate. Nonetheless, clinical triggers might be

more complicated to record. The most challenging issue would certainly be to distinguish the problematic clinical measure from other normal and desired clinical behaviors.

Other physiological measures, such as heart rate variability or kinematics by using accelerometers, represent an interesting alternative to EEG. They have been proposed to be used to extract salient biomarkers of seizures [62]. An important challenge would be to determine how to measure, record, and remove noise. Nevertheless, this can be challenging since physiological signals are prone to be easily changeable by many factors unrelated to the targeted symptom, leading to a high rate of errors of classification by the algorithm. If this issue can be solved, an interesting approach would be the incorporation of different physiological measures to EEG recording in order to improve the accuracy of the closed-loop system and, as a consequence to improve seizure prediction and intervention.

Cognitive modulation by closed-loop stimulation could be reached not only by monitoring electrical brain activity, but by feeding cognitive task performance into the algorithm as well. This model represents a level of modular efficiency where ongoing EEG signals are analyzed and correlated with behavioral responses. In this scenario, reaction time, omission and commission errors on a continuous performance task, can be used as surrogate markers of network modulation and by accounting online EEG signal analysis. The same can be used for memory or arithmetic tasks, and all of these components will improve the sensitivity and functionality of the controller algorithm, and might promote an adequate delivery of electrical stimulation, since brain oscillations would be coupled with behavioral responses for a more accurate calculation of network performance under the effects of the stimulation itself. In this scenario, the main challenge would be to define a sensitive cognitive outcome that would be related to a meaningful clinical result.

Challenges of closed-loop systems.

Current closed-loop systems have three main caveats: 1. They are based on a causal relationship between the trigger and the outcome, while it is not how the brain or the body works; model encompassing multiple triggers should be design to improve the accuracy and efficacy of the system; 2. The algorithm should be built to be adaptable over time since the treatment (e.g. NIBS) will improve patients' symptoms and the threshold that has been first determined would need to be adapted over time.

To address this issue, future studies would need to incorporate machine learning systems; 3. It is essential to well, if not entirely, understand the (neuro)physiological mechanisms of a disease to actually be able to detect the best input to record and determine how to stimulate or modify it. However, so far, not all conditions meet this criterion and, might not be a good target for successful closed-loop approaches. Moreover, based on the current literature, closed-loop systems have only been tested for short period of times. Thus, it is crucial to investigate the feasibility of this patients' tailored treatment in long-term studies in order to know if these cutting-edge technologies are durable treatment and could be translated clinical setting.

Use of machine learning into closed-loop systems

The main limitation in implementing online EEG analyses is the development of complex algorithms and learning methods in order to overcome within subject variability and provide more precise information with favorable signal-to-noise ratio.[63]

Machine learning is the field of science that can address this important point to implement a closed-loop system in clinical practice as aforementioned. The principle of machine learning is

to learn a mathematic model, or classifier, that can recognize and segregate novel patterns. These systems can either be auto-corrected, while others first have to look at the results to be further corrected and better adapted. For a closed-loop system involving EEG and NIBS, based on previously collected data, several algorithms are developed to correlate the outcome measure (EEG) to the parameters of stimulation and the clinical outcomes. Since continuous EEG data collection is being managed and stored into the system, future algorithm development must start using the EEG data to drive the electrical stimulation, moreover, the representation and the algorithm must account for the identification of neurophysiological patterns which will control the input/output based on these transformations, accordingly, this learning program for pattern recognition must be capable to modify the stimulation parameters based on a continuous recognition on previously classified EEG characteristics under the influence of the stimulation, as well as without it, in order to optimize the delivery of the current and its effects on excitable tissue. Moving forward into the intelligent design of these machine learning units, will be the incorporation of prediction models based on EEG estimates of modulation. This can be achieved by understanding the regular and prototypical responses to the stimulation by accounting the probability for these *regularities* to happen, this will have a profound impact on how the stimulation can facilitate cognitive performance in a standardized task for a healthy volunteer, or in the case of M1 neuromodulation in a post stroke subject undergoing rehabilitation for his/her paretic limb.

From a clinical perspective, a recent DBS trial on Parkinson Disease has used this machine learning concept to optimize patients' treatment.[64] They investigated if the incorporation of patient-specific symptoms and medications into a machine learning algorithm would better predict the treatment outcomes in comparison to stimulation parameter settings alone. They used three

different machine learning methods (i.e., support vector machines, Naïve Bayes, and random forest) and identified that several clinical parameters were significantly correlated with postoperative outcomes. Using these results, the combined machine learning algorithms were able to predict almost 90% of the motor improvement at one year post-DBS surgery. These preliminary results based on a small sample of patients demonstrate that more robust machine learning systems could be adequately trained and programmed using data from larger clinical trial.

7. Summary

In summary, we demonstrated the feasibility of developing a closed-loop system that was able to recognize specific patterns of EEG activity to trigger tDCS stimulation. This study represents a proof-of-concept for the development of a non-invasive EEG-tDCS closed-loop system in humans, which should facilitate future research, on the development of adaptive thresholds and identification for clinical applications. NIB stimulation and NIB recording provide a safe and theoretically efficient closed-loop system. Moreover, the interaction between the two, might also lead to a better understanding of the mechanisms of action of the targeted (neurological) condition. Indeed, if a solid closed-loop system taking into account several triggers and outcomes – inputs and outputs could be created, it may lead to a better understanding of the interaction between the cause/mechanisms of the conditions and its symptoms.

8. Limitations

This study produced valuable evidence for the use and application of an EEG-controlled tDCS stimulation device, however, we should see this work as an initial attempt to test the idea of a physiology based system for NIBS. This trial was designed to probe feasibility and as proof-of-

concept principle, due to the nature of the design some weakness can be accounted for, such are; small sample size, the development of an arbitrary algorithm, and the lack of a control group. We believe the basic principle of the study was reached, but further research is needed to refine the characteristics of the monitoring algorithm and the cognitive-behavioral tasks used to promote changes in the targeted network. Transition to clinical applications is of great interest to the field, long-lasting EEG monitoring and multiple sessions of stimulations are going to be required for the appropriate design of a EEG tDCS closed-loop applied to specific pathologies.

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Figure Legends

Figure 1: Schema of the main components of the present closed-loop system.

Figure 2: Illustration of the setting in this study. The closed loop system includes an amplifier & controller device to filter and amplify EEG signals, a laptop to provide the Stroop task and to process the algorithm for trigger decision, and a tDCS device that can be triggered by the amplifier & controller device. The EEG electrodes are placed on the vertex (Cz) and right earlobe (A2) while tDCS cathode is placed on the left dorsolateral prefrontal cortex (DLPFC, F3) and anode on the right deltoid muscle.

Figure 3: Changes in Delta, Theta, Alpha, and Beta power of cathodal and sham groups after triggered tDCS, wherein the data are expressed as mean ± SD.

Figure 1

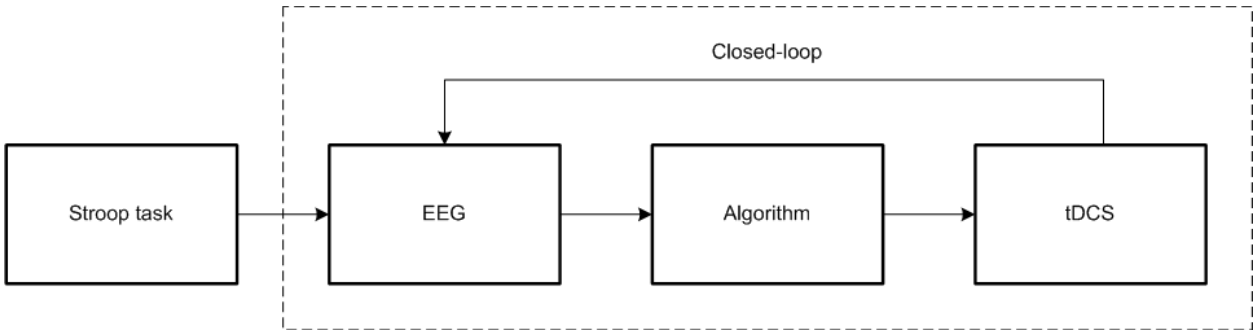


Figure 2

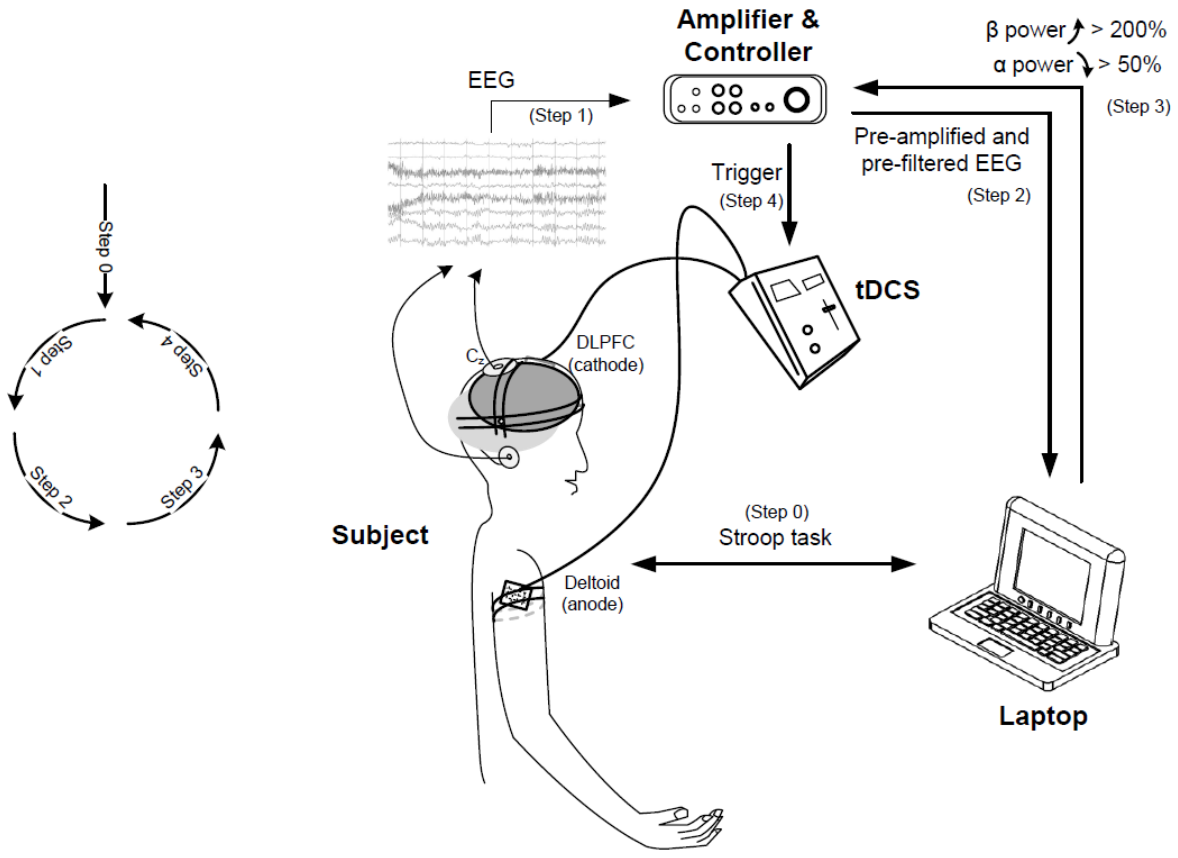
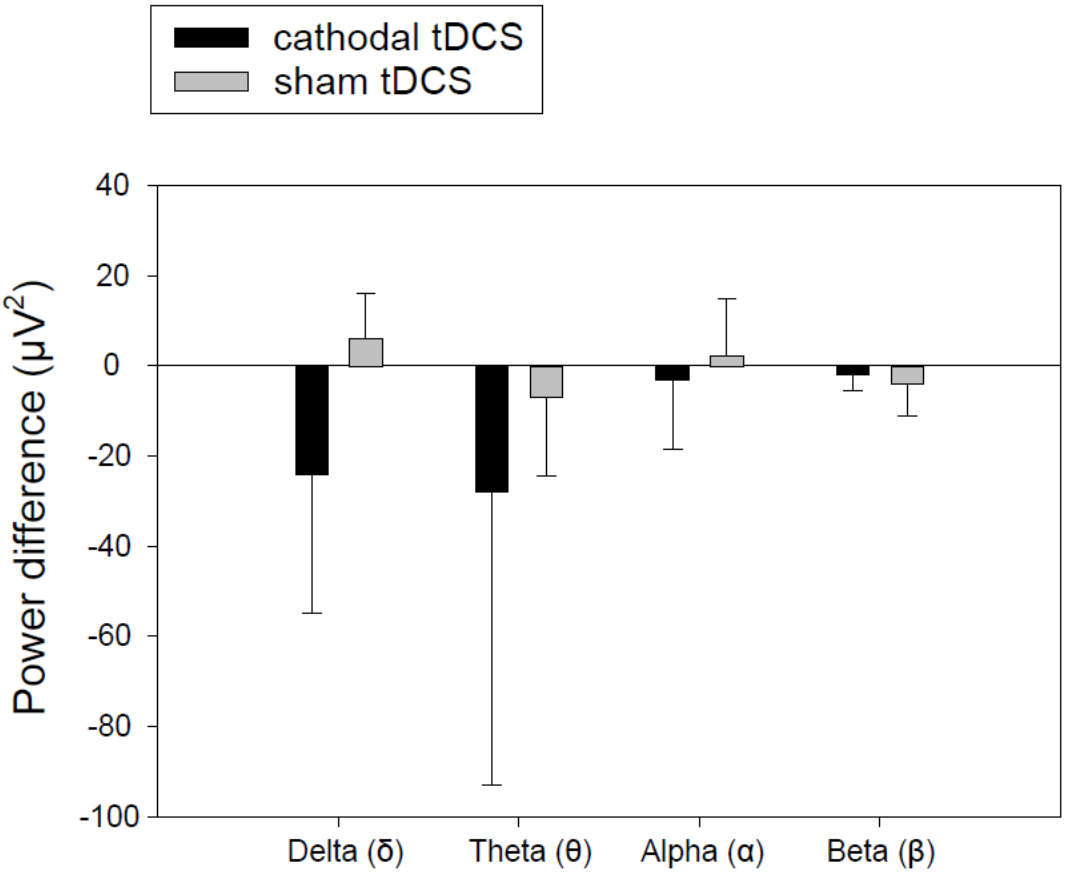


Figure 3


cathodal tDCS
sham tDCS
Power difference (μV²)
40
20
0
-20
-40
-60
-80
-100
Delta (δ)
Theta (θ)
Alpha (α)
Beta (β)