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PERSONALIZED TRANSCRANIAL ALTERNATING CURRENT STIMULATION FOR THE SYMPTOMATIC TREATMENT OF COGNITIVE DEFICITS IN PARKINSON'S DISEASE

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ABSTRACT

Cognitive symptoms, including inhibition disorders (i.e., decreased capacity to refrain from performing specific actions), impair the quality of life of Parkinson's disease (PD) patients, and no efficient drug treatment is available to date. Inhibition is supported by specific neural oscillations in the so-called beta band (12–25 Hz) in the right inferior frontal gyrus (rIFG). Recent studies evidenced that transcranial alternating current stimulation (tACS) can target neural oscillations and improve cognitive performance in healthy participants and patients. Here, we aimed at exploring the therapeutic potential of personalized tACS to enhance inhibition performance in PD. To investigate this, we have designed a randomized, double-blind placebo-controlled protocol that will be conducted in healthy subjects and PD patients. Real and sham rIFG stimulation will be delivered in a personalized frequency for each participant, while they perform an inhibition task. Our pilot data confirm the feasibility of the protocol, especially regarding the identification of participants-specific beta frequency. The confirmation of these tACS benefits could pave the way for personalized, at-home and non-invasive treatments of cognitive symptoms in PD.

INTRODUCTION

Parkinson's disease (PD) is a multisystem neurodegenerative disorder characterized by motor and cognitive symptoms that have a major impact on patient's quality of life [1]. Cognitive alterations affect approximately 30% of patients at diagnosis and up to 50 % of those progress to dementia [2]. To date, there is no available treatment to efficiently relieve cognitive symptoms [3], motivating the exploration of alternative options. Among these cognitive alterations, PD patients display inhibition disorders, *i.e.* a difficulty in stopping an ongoing action [4]. Inhibition is a cognitive process associated with neural oscillatory electrical activity of the right inferior frontal gyrus (rIFG) in the beta frequency band (12–25 Hz) [5]. Interestingly, several studies have shown that rIFG beta-band activity is impacted in PD [6], raising the possibility to envision therapies able to normalize such beta-band activity to improve inhibition.

Non-invasive electrical stimulation techniques, using electrodes placed on the scalp, enable the targeting of neuronal oscillations in predetermined brain regions at specific frequencies. Among those techniques, transcranial alternating current stimulation (tACS) applies a low current (1–2 mA) that can modulate endogenous oscillatory activity in a frequency-dependent manner [7]. Recent studies evidenced that tACS can improve cognitive performance in healthy participants [8]. Although beneficial effects have been reported on some cognitive functions, tACS has not yet been explored to improve the cognitive symptoms of PD patients. To our knowledge, only one recent study has been conducted using the combination of tACS with a physical activity protocol in PD patients [9]. However, the design of this study prevents conclusions regarding the specific effects of tACS alone. Furthermore, recent evidence suggests that tACS can, and should, be tailored to each patient: stimulation frequency can be chosen specifically to match a patient's own task-related frequency, which maximizes the effect of the stimulation [10]. One difficulty in characterizing neural electrophysiological activity is that oscillatory power can be conflated by the presence of aperiodic activity (also called “ $1/f$ component”), which can result in extracting frequency-specific power even in the absence of true neural oscillations [11]. Thus, a prerequisite for proposing patient-specific tACS protocol at a personalized frequency is the identification of “true” beta oscillations. Therefore, here we propose to explore the therapeutic potential of personalized tACS to alleviate cognitive symptoms in PD.

Our hypothesis is that targeting rIFG oscillations at patient-specific beta frequency (after correction for aperiodic activity) with tACS will improve inhibition performance in PD patients. Moreover, tACS may lead to changes in patients' brain networks during the inhibition process, which could mechanistically explain tACS behavioral effects. To investigate this, we have designed a randomized, double-blind placebo-controlled protocol that will be conducted in healthy subjects and PD patients. Participants will receive “real” and “sham” rIFG stimulation while performing an inhibition task. Behavioral analyses and High-Definition-Electroencephalography (HD-EEG) will be used to evaluate tACS impact and potential changes in brain networks during the inhibition process. Confirmation of these hypotheses would support tACS as a relevant therapeutic solution to cognitive impairment in PD. In this paper, we will outline the methods that will be used to perform this study and present some pilot results that support the validity of our approach.

METHODS

Participants and study design

This study is a randomized, double-blind, crossover clinical trial that will test the efficacy of personalized tACS on inhibition performance in PD patients. We will enroll 35 patients with idiopathic PD, as well as 35 healthy controls (HC). Both groups will be matched in sex ratio, age, and level of education. Three different phases will take place (Figure 1A). A *first phase* will consist in a neuropsychological assessment as well as a measure of inhibition performance (see Task section) and associated HD-EEG activity (see EEG recordings and analyses) in HC. HC behavioral results will be used as a baseline to ensure that only PD patients with a lower performance than the median performance of HC will be recruited. PD patients will complete the same assessment which will also enable the definition of patient-specific target frequency for tACS. The *second phase* will consist in the tACS (sham) stimulation session. Participants will perform 3 blocks of task trials, while HD-EEG recordings will be performed, followed by 5 blocks while tACS (sham) is applied, and finally by another 3 blocks of HD-EEG recordings. The *third phase* will be identical, except that the tACS condition will be reversed: participants who had “real” tACS in the second phase will be stimulated in

the “sham” condition, and vice versa. The second or third phase will also include a neurological exam of patients from a trained neurologist to assess disease severity. All participants will provide informed consent for participation in the study, which has been approved by a national ethics committee review board (CPP ID-RCB: 2022-A00767-36; approval number: 22.02017.000135).

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Figure 1: **A.** Randomized, double-blind, crossover experimental design and overall organization of the tACS sessions. **B.** Stop signal reaction time (SSRT) task design. **C.** HD-EEG is recorded during the experimental task.

Task and behavioral analyses

Inhibition will be measured using the classical stop reaction time task (Figure 1B). The task consists in pressing a left or right button as fast and as accurately as possible according to the direction of an arrow displayed at the center of a computer screen. On some trials (25%), a “stop” signal will occur right after the stimulus and will indicate the participant to stop his impending button press. The programming of the task was done following rigorously the standards described in [12]. Briefly, each block consists of 40 trials with 30 Go trials and 10 Stop trials. In each phase of the study, a total of 11 blocks will be performed. The delay between the presentation of the arrow stimulus and the stop signal will be adjusted to ensure a final 50% accuracy (decreased following an accurate response and increased after an error), which is necessary to comply with the assumptions for a robust calculation of the stop signal reaction time (SSRT). The SSRT will be the main variable of interest, and represents the time needed to stop the ongoing action. This measure is not directly available in the data and has to be estimated (see [12]). The effect of tACS will be evaluated on the patients’ SSRT. Calculation of the SSRT will rely on the independent race model between the processings triggered by the Go and Stop signals respectively [13].

EEG recordings and analyses

We will record a HD-EEG in all participants to determine the target frequency for tACS in each participant. HD-EEG quantitative analysis will also be used to evaluate the effect of tACS on the functional networks associated with behavioral task performance. HD-EEG will be recorded using a 256 channels net (Magstim EGI) at a sampling frequency of 1 kHz (Figure 1C). Determining the target frequency for tACS will be achieved using Brainstorm [14] running on Matlab (v.2020; The Mathworks) in several steps: *i*) preprocessing of EEG data by filtering line noise (notch filtering), band-pass-filtering data (0.5–40 Hz), removing bad channels and interpolating them, removing ocular and muscle artifacts using independent component analysis (ICA), applying an average reference montage, epoching the data from –1000 ms to 1500 ms around the stop signal in correct trials, and finally removing remaining noisy epochs following visual inspection; *ii*) cortical source activity will be estimated by solving the inverse problem with the “weighted minimum norm estimate” (wMNE). Cortical source activity will be projected on the Desikan–Kiliany atlas with 68 regions of interest, including the *pars opercularis* part of the rIFG that is the region of interest; *iii*) a trial-averaged spectrogram will be calculated using Welch’s method. Power will then be parameterized using the *spectparam* algorithm [11] to identify oscillatory peaks while correcting for the aperiodic offset and exponent. This step is crucial to ensure the presence of actual (not artifactual in origin) neuronal beta-band oscillations. Finally, we will identify the peak beta frequency in the *pars opercularis* of the right IFG, which will be used as tACS target frequency. Further EEG analyses will be performed to estimate beta-band networks by estimating functional connectivity (*i.e.*, statistical relationships between signals from different cortical regions) between cortical sources using the so-called

“weighted phase lag index” and the “orthogonalized amplitude envelope correlation,” which are phase- and amplitude-based measures of signals correlation, respectively, that remove zero-lag connections associated with volume conduction [15,16].

tACS protocol

We will use the frequency previously defined using HD-EEG for delivering tACS. A stimulation period of 12 to 15 minutes during the inhibition task (depending on the participants’ speed at the task) will be applied over the rIFG at 1mA using a Starstim device (Neuroelectronics, Barcelona). A 10 second fade-in/fade-out period will be included to minimize current perception of the stimulation at onset and offset and optimize blinding of conditions. Impedance of electrodes will be kept under 10 kOhm. Stimulation will be delivered using two round electrodes (1 cm in diameter, filled with a conductive paste – SAC2-10 paste from Spes Medical) located at F8 and Cz standard EEG positions (i.e., according to the 10-10 system). The choice of the appropriate montage was done with SimNIBS [17] based on dosimetry optimization using numerical head models to maximize the electric field at the rIFG level (Figure 2C). Sham stimulation will be performed using the exact same protocol, including the ramp at the onset and offset of the stimulation epoch, except that no stimulation will be delivered in between (i.e., during the entire execution of the task).

Statistical Analyses

The main variable of interest here is the SSRT, which quantifies the time required to inhibit the ongoing action. There will be 3 experimental conditions observed in HC or PD patients: before tACS, after “real” tACS, and after “sham” tACS. The effect of tACS will be estimated using mixed-model linear regressions. Importantly, these models will be built to fit a random intercept for each subject in order to take into account inter-individual variability. These analyses will be performed using R [18] with the *lme4* [19] package. The effect of tACS on beta-band functional networks will be evaluated using the *brain connectivity toolbox* (BCT, [20]). Finally, we will investigate if changes in functional connectivity (raw connectivity and standard graph-theoretic metrics: degree, clustering coefficient, path length) are associated with changes in behavior following tACS by calculating correlations between these two variables. Since these correlations are exploratory, a Bonferroni correction for multiple comparisons will be applied.

RESULTS (pilot data)

Here, we present pilot results regarding the feasibility of behavioral analyses and identification of tACS target frequency for one subject using HD-EEG during the inhibition task.

Figure 2A illustrates clear differences in “Go” and “Stop” reaction times and SSRT estimation ($t = -34.2$, $df = 106.5$, $p < 0.001$; Cohen’s $d = 2.2$). “Stop” signals, when erroneously responded upon, are associated with faster reaction times than “Go” trials. The probability to respond to a “Stop” signal was 0.54, thus complying with the assumptions of the race model [12,13] to calculate the SSRT which was estimated at 309 ms. Therefore, our pilot subject needed on average 309 ms to stop the ongoing action. Reconstruction of cortical sources activity revealed beta oscillations in the rIFG as hypothesized (Figure 2B). A clear peak in beta power was observed in the *pars opercularis* of the rIFG at 24 Hz (Figure 2B), which would be the target tACS frequency for that subject. Importantly, this activity was corrected for aperiodic activity, ensuring that those beta oscillations were not artifactual.

Overall, for our pilot subject, the subject-specific protocol would involve delivering tACS at Cz-F8 using a frequency of 24 Hz to decrease SSRT, and thereby increase the associated inhibition performance.

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Figure 2: **A.** Behavioral results showing “Go” and “Stop” reaction time as well as the estimated SSRT for one pilot subject. **B.** Reconstruction of cortical activity filtered between 18 and 26 Hz. The rIFG is outlined in white. **C.** Power spectrum of the *pars opercularis* of the rIFG corrected for its aperiodic component. A clear peak in power can be observed at 24 Hz. **D.** Electric field dosimetry of the Cz-F8 montage computed using SimNIBS.

DISCUSSION

The major impact of cognitive deficits on the quality of life of PD patients and the lack of current treatment underline the importance of identifying innovative treatments. tACS is a drug-free, safe and promising technique; especially if some methodological constraints are taken into account (e.g., personalized frequency, $1/f$ correction). Therefore, our study has been designed to provide a proof-of-concept of tACS as a suitable therapeutic option. Our pilot data showed that the task design was appropriate in the sense that behavioral results complied with the assumptions needed to calculate our variable of interest: the SSRT. We were also able to isolate and identify the characteristics of rIFG cortical activity and, after careful correction of the aperiodic component in the power spectrum, to identify the subject-specific beta peak in power that makes it possible to deliver subject-specific stimulation.

CONCLUSIONS

Our pilot data confirms the feasibility of the protocol, especially regarding the identification of participants’ source-specific and task-related beta frequency. Confirmation of our hypothesis could pave the way for safe (low-intensity) personalized, at-home and non-invasive brain stimulation treatments for cognitive symptoms in PD.

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