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Research paper

Use of the P300 event-related potential component to index transcranial direct current stimulation effects in drug users

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ABSTRACT

Drug use causes significant social and financial problems and these are exacerbated by difficulties in stopping use and subsequent maintenance of abstinence. There is also difficulty in identifying the beneficial treatment for an individual, made more problematic given the high drop-out rates in treatment programs. Here, the effects of transcranial direct current stimulation (tDCS) on the amplitude of the P300 event-related potential component, previously suggested to be indicative of successful remission, was measured in recently abstinent amphetamine users. This component was collected during a Posner cuing task which was presented to this group and to control (non-user) participants, using task cues of neutral and drug-related images. The abstinent drug users were divided into two groups, one of which received tDCS daily for five days, with the cathode over the left dorsolateral prefrontal cortex (DLPFC) and the anode over the right DLPFC, and one receiving sham stimulation over the same time period. Behavioral performance and P300 amplitudes were measured before and after the period of tDCS delivery. Control participants were tested with the same time-schedule of task presentation but without administration of tDCS. Drug users initially showed a larger cost of invalid cues on task performance compared to control (non-drug user) participants and this was reduced following delivery of tDCS. Additionally, tDCS resulted in increased amplitude of the P300 component, significantly so for neutral cues, with the resulting pattern being more similar to that of the non-users. This provides a good basis for further investigation of both the utility of tDCS in modulation of cognition in addict groups, and to investigate the effects of modulating the P300 component on remission rates, a relationship that seems to be the case for this measure without use of tDCS modulation. Importantly, this study also provides a further addiction group showing P300 amplitude modulation as a result of tDCS administration.

1. Introduction

Drug use is a significant problem, resulting in major health consequences for many individuals. There are also significant difficulties when it comes to treating addiction and helping to maintain abstinence from use, with this being problematic even when affected individuals have clear knowledge of the negative consequences of continued drug use (Hyman and Malenka, 2001). Ameliorating the presumed dysfunctional activity in brain areas associated with drug use would be highly beneficial for reduction of drug dependency and the desire to use drugs. Unfortunately, there are significant problems in terms of remission rates when treating drug use and in terms of the time scale over which the effectiveness of treatments should be considered (see, for example, Fleury et al., 2016). Additionally, while treatments are available for some addictions, there are currently no FDA approved pharmaceutical therapies for use in treating methamphetamine abuse.

It is thought that chronic drug use results in changes in reward-related pathways in the brain, altering both cortical pathways and excitability (Hyman et al., 2006; Kauer and Malenka, 2007). One potential avenue of approach to treatment is therefore the use of neuromodulatory brain stimulation techniques, which have the potential to produce brain activity changes and require no pharmacological or surgical intervention. These techniques can be broadly divided into those using magnetic stimulation (transcranial magnetic stimulation, TMS) and those using electrical stimulation (transcranial electrical stimulation, tES, or transcranial direct current stimulation, tDCS). Both are

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approaches which have good safety records when used appropriately and have been shown to be of use in modulating and characterizing the roles of brain activity in many studies (e.g., Rossi et al., 2021; Bikson et al., 2016). Delivery of tDCS stimulation for several minutes has been shown to result in modulation of excitability of a stimulated brain region for a sustained duration following the end of stimulation (e.g., Nitsche and Paulus, 2000). Whereas single sessions of stimulation with tDCS are employed in many studies investigating motor or cognitive processes, of more relevance here are the effects of multiple sessions of stimulation, with typical examples being stimulation delivered once or twice a day for a period of five days or a week. These are often employed when the aim is to produce a more sustained change in brain activity/behavior beyond the relatively brief period of effect seen following a single instance of stimulation. Consequently, this multiple stimulation approach is common to many clinical studies, where the aim is to provide a therapeutic benefit for the group of interest. An example of this, and relevant to the treatment of addiction, is a study which reported an effect of tDCS stimulation on alcohol craving which used weekly stimulation for five weeks (da Silva et al., 2013). Of particular note is that craving was the measure of interest in this study rather than, for example, a more direct cognitive measure. This is consistent with many studies of addiction. Ekhtiari et al. (2019) reported that craving was the most common primary measure, used in more than three quarters of studies they looked at, and it was stated that this might result in an unavoidable subjectivity in the measure of interest. More objective measures of drug use, such as urine or breath tests, have been relatively infrequently employed (17%, again Ekhtiari et al., 2019), and this was also the case for other, non-subjective indices of behavior.

While brain stimulation seems a promising avenue for neuromodulation to help with drug-treatment, the research field looking at the use of these techniques is relatively nascent (Ekhtiari et al., 2019). Consequently, better characterization of effects that such stimulation may have in drug users, and in particular how this compares to effects in non-user, control groups, is an important step prior to moving on to apply the stimulation with a therapeutic aim. In the current study, cognitive performance and brain electrophysiology were measured, the latter using event-related potentials (ERPs), to assess modulatory effects of transcranial direct current stimulation in drug users. More specifically, the effects of tDCS in recently-abstinent amphetamine addicts were examined on behavior, using a Posner cueing paradigm (Posner, 1980), and the electrophysiological measure of interest was the P300 ERP component (the reasons for choosing these are outlined below). In terms of effects of tDCS stimulation, a previous study has shown effects in addict populations using tDCS delivered over the left and right dorsolateral prefrontal cortex (dlPFC) for a period of five days (Nakamura-Palacios et al., 2016). The stimulation protocol they used is based on the work of Monte-Silva et al. (2013), which applied tDCS for 13 min, had a gap of no stimulation for 20 min and then a second stimulation for 13 min. Their rationale for this schedule was that similar 'period stimulation' has been shown to produce prolonged excitability changes in animal slice and in vivo work and can be related to changes in protein expression and receptor activity, amongst other changes. The timing of 13 min relates to work showing that tDCS delivered for this duration can produce modulation lasting for an hour following stimulation and a 20-minute gap to the next stimulation means it will be delivered during the window of altered activity. Monte-Silva and colleagues (Monte-Silva et al., 2013) found this to be the most effective of conditions they looked at for providing prolonged activity changes in the stimulated area. It could, and could be blocked by a NMDA receptor antagonist, meaning the mechanism of the effect was likely in line with their expectations. Consequently, a similar stimulation protocol was employed in the present study.

The Posner cueing task provides data related to the effects of cue locations on task performance, where the cue frequently validly indicates where a visual target will appear, but, less frequently, can indicate an incorrect location. As such, manual responses by individuals performing such a task are typically faster to validly cued targets than to invalidly cued targets (Posner, 1980). Cue reactivity in addicts has been reported, with, as might be expected, neural activations seen in a range of brain regions in response to cues, but also with activity in these regions predictive of relapse (see Schacht et al., 2013 for a review). Event-related potentials provide one means for indexing such activity and suitable EEG indices have also been suggested as one of several measures for craving, along with a more general recommendation of use of a 'biologic metric' in addiction studies (Ekhtiari et al., 2019). In the Posner cueing task, the behavioral measure in the task is obtained from the differences in response times between the invalidly and validly cued targets and reflects a compound of the cost of disengagement from the cue, time to shift attention, and the time for target engagement. This is therefore a quantitative measure that may be better related to relapse, particularly in conjunction with a suitable ERP measure.

The P300 component is of interest in this context, both in relation to the Posner cuing task and, importantly, when considering addiction. This component can be seen in the EEG responses to invalidly cued targets in the Posner cueing task and is not elicited by the physical attributes of a stimulus but rather the 'status' of the stimulus, being seen in response to 'oddball' stimuli (hence for the invalidly cued targets in this task). A larger P300 amplitude is thought to mean either greater prioritization of information for encoding to working memory or higher 'value' in the updating of stimulus representations (e.g., Yeung and Sanfey, 2004), consistent with a larger amplitude being reported for stimuli that are, essentially, less expected. This can be due to infrequence, less probable appearance or novelty. P300 amplitude has also been linked to inhibitory control and response inhibition (Huster et al., 2013). Importantly, this component is affected in addiction, normalizes with abstinence, and also was frequently predictive of likelihood and time of relapse (see the review by Houston & Schlienz, 2018). Any modulation of P300 amplitude by tDCS may therefore be a useful indicator in assessing the benefit of such stimulation, with an increased amplitude potentially indicative of beneficial modulation.

A further reason for carrying out this investigation comes from some concerns about the variability or reliability of tDCS effects (e.g., Horvath et al., 2015b), meaning that caution in interpretation of results in conjunction with accumulation of information, for both presence and absence of effects, represents a sensible approach when considering potential effects of tDCS stimulation. Overall, tDCS is an appealing technique with factors such as tolerance, side effects, portability, and cost all in its favor (Bikson et al., 2016), but care should be taken when trying to determine whether beneficial effects can realistically be obtained.

The present study investigated the patterns of performance on a Posner cuing task with drug-related and neutral cues, in conjunction with electrophysiological recording to allow measurement of the P300 component typically elicited during performance of this task. This was presented to both recently abstinent amphetamine users and control (non-drug-user) participants. Performance following tDCS delivery in users was measured with the prediction that both task performance and P300 amplitude would become more 'normal' following such stimulation. Such an effect could be an indication of improved inhibitory control in users but, more importantly, could also potentially represent a beneficial reversal of the lower P300 typically seen in addict populations.

2. Materials and methods

2.1. Participants

Thirty participants took part in the experiment, of which nineteen were currently abstinent amphetamine users (hereafter referred to as 'users') and eleven were control participants. For all users, amphetamines were their only drug of abuse. All gave informed consent prior to taking part in the experiment and all procedures were approved by the

local IRB committee (approval number B-BR-105–100). While one group consisted of the control participants, the users were randomly divided into two groups. The first consisted of ten users (8 males, 2 females, mean age = 36.3 years, S.E.M. = 2.79 years) who received tDCS in the experiment (see below for details of the stimulation and experimental design). The second was made up of nine users (9 males, mean age = 32.33 years, S.E.M. = 1.55 years) who received sham-tDCS during the experiment (again, see below). The user participants were not made aware of the type of stimulation they were to receive (whereas the experimenter was aware of all conditions). The control group, comprised of the eleven non-user control participants, was comprised of 8 males and 3 females (mean age = 31.55 years, S.E.M. = 3.32 years). There were no significant differences between groups for age ($F(2,27) = 0.925$, $p = 0.409$) and all participants were right-handed. Abstinence in the user groups during the study was confirmed by urine tests.

2.2. Design

The experiment consisted of an initial day of behavioral testing (Day 1). This was carried out with concurrent EEG data collection (see details below). Data from a range of questionnaires was also collected on this day, with the Brief Substance Craving Scale, Behavioral Inhibition Scale (Carver and White, 1994), Negative Mood Regulation Scale (Catanzaro and Mearns, 1990), Situation-Trait Anxiety Inventory (Spielberger, 1983) and Raven's Graphical Reasoning Test all presented. The first drug-user group (10 participants) received tDCS stimulation daily for the subsequent five days (Days 2–6, for details of the stimulation see Section 2.5., below). The second drug-user group (9 participants) received sham tDCS stimulation over the same time period (Days 2–6). For control participants there was a five-day break (again, this was for Days 2–6). For all groups, after the five-day period, retesting on the behavioral task with concurrent EEG recording was carried out (Day 7). Questionnaire data was collected again on the retest day. While testing/tDCS times varied across participants, it was consistent within an individual such that a participant was tested and received tDCS at similar times throughout the experiment.

2.3. Behavioral task

The task employed was a typical variation of the Posner cuing task (Posner, 1980). For each trial of this task there was a centrally presented fixation cross (shown for 300 ms) followed by a cue (250 ms duration) presented equally frequently to either the right or left of the fixation. This cue was an image (see below for details), size 2 × 2 degrees of visual angle, and centered 2 degrees offset laterally from the fixation. After the offset of the cue image, there was a blank screen for 50 ms, followed by presentation of a target. This was a 0.4 × 0.4 degree 'x' character, and this was also presented to either the left or right of the central fixation and was centered on the cue locations.

For 75% of the presented trials, the cue location validly indicated the following target location. For the remaining 25% of trials, the cue and targets appeared in non-corresponding locations (i.e., a cue to the left of fixation was followed by the target appearing to the right of the fixation and vice versa). Participants were instructed to indicate quickly and accurately the side of the screen on which the target was presented. This was done by means of a keypress, with '1' on a computer keyboard number pad for left and '2' for right, using the first and second fingers of the right hand for the corresponding responses.

Each participant performed 400 trials of the task, with half of the trials using neutral images as cues and half using drug-related cues. All neutral cue images were taken from the International Affective Picture System (IAPS) (see Lang et al., 2008), with a set of 100 such images used. Drug use images were sourced from the National Institute on Drug abuse (https://nida.nih.gov/) and the Substance Abuse and Mental Health Services Administration (https://www.samhsa.gov/) with, again, 100 images used. These were expected to be effective given previous reports of drug-related cues in experimental investigations (e.g., Bedi et al., 2011, for smokers and Ehrman et al., 1992 for cocaine). The orders of the trials, and consequently the orders of both the cue types and the validity of the cues, were randomized for each participant. Trials were presented in blocks of 80 trials, allowing participants to take a rest between blocks if desired. Both response times and response accuracy were collected. For analysis, performance was measured in terms of the difference in mean response times for invalidly cued targets minus response times for validly cued targets and this was also calculated for all trials as well as separately for the neutral cues and for the drug-related cues.

2.4. Electrophysiological recording

Electroencephalography data was acquired using a NeuroScan Synamps system in combination with Scan 4.2 software (Compumedics USA, Charlotte, USA) and was recorded during performance of the behavioral task via a 34-electrode arrangement with placement of electrodes following the International 10–20 system. The ground electrode was placed on the forehead and vertical and horizontal electro-oculograms (EOG) were recorded from electrodes placed above and below the left eye and 1 cm external to the outer canthus of each eye. The impedance of all electrodes was kept below 5 kΩ throughout recordings and the analogue signals were filtered with a 100 Hz low-pass filter and a 60 Hz notch filter before digitization at a frequency of 500 Hz. Prior to ERP analysis, which was all carried out using the EEGLAB software, the recorded signals were filtered with a 12-dB band pass filter with a high-pass cut-off frequency of 0.05 Hz and a low-pass frequency of 30 Hz. Any trials with evidence of eye blinks or with movement artifacts, both using a threshold criterion of a 100 μV component in the recording, were excluded from further analysis. Additionally, at least 16 trials were required for analysis. This led to there being data for 10 tDCS participants, 8 sham participants, and 11 control participants.

The component of interest from the recording was the P300, which is typically measured for, and seen in response to, the target onset for invalidly cued trials. The time interval selected for determining the P300 amplitude was based on those reported in a meta-analysis of the P300 component and latencies associated with it (van Dinteren et al., 2014). For the ages of participants in this study, a range of 300–370 ms encompasses the majority of the data reviewed. Additionally, given that diseases/disorders have been reported to affect P300 latency, the upper limit of this range was increased by around 10%, to give a range of 300–410 ms for the analysis. This is slightly larger than the percentage delay seen in a study looking at early cognitive decline (Braverman and Blum, 2003), but lower than that reported in relation to depression (Tripathi et al., 2015).

The P300 amplitudes of the target-locked ERPs were therefore obtained from the activity in the 300–410 ms time window. This processing was performed for data collected from the Cz electrode, with the P300 recorded from this site typically thought to relate to anterior cingulate cortex activity. For example, it has previously been concluded that the pattern of P300 activity recorded from such a central electrode location reflected deficiencies in anterior cingulate cortex activity in schizophrenic patients (Neuhaus et al., 2007). Average waveforms collected for the different groups and conditions are shown in Fig. 1 and scalp topographies for the P300 time-window for invalidly cued trials are shown in Fig. 2.

2.5. Transcranial direct current stimulation

Transcranial direct current stimulation was delivered using a DC Stimulator (neuroConn, Ilmenau, Germany) via a pair of 5 × 7 cm rectangular electrodes. The electrodes were placed with locations according to the 10–20 system for electrode placement with the cathode placed over the left dorsolateral prefrontal cortex (DLPFC) (location F3) and the anode over the right DLPFC (F4). A 13:20:13 stimulation schedule was used for each day of stimulation, with tDCS delivered for

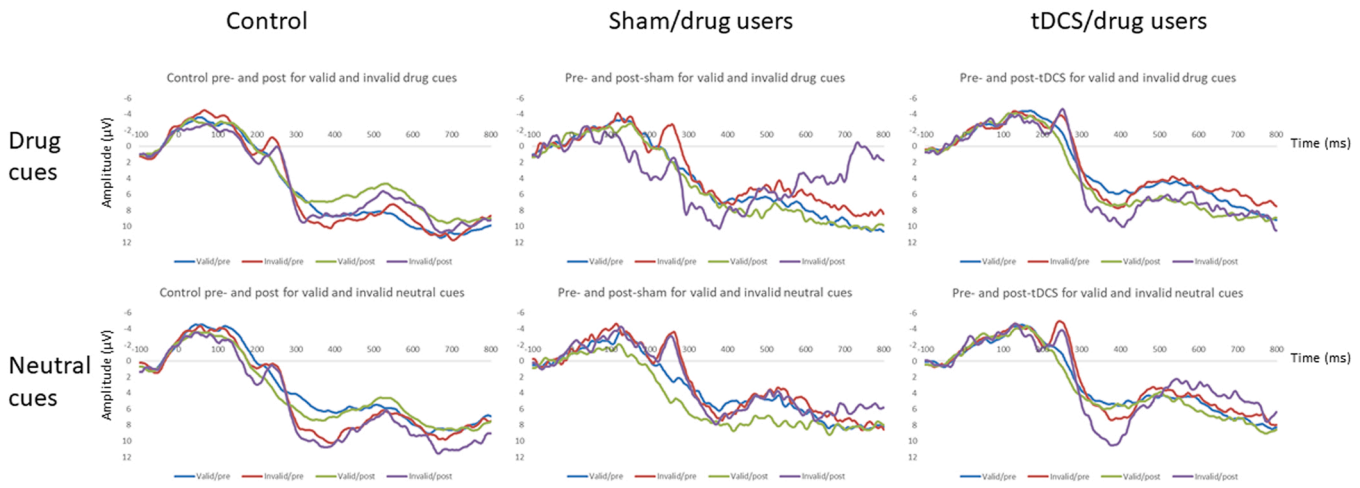

Fig. 1. Electrophysiology for each of the three groups: tDCS/drug users, sham/drug users, and control participants. Plots are shown for the two cue conditions (valid or invalid) as well as whether the data was collected prior to tDCS/sham/control (pre) or after the five-days of tDCS/sham/control (post).

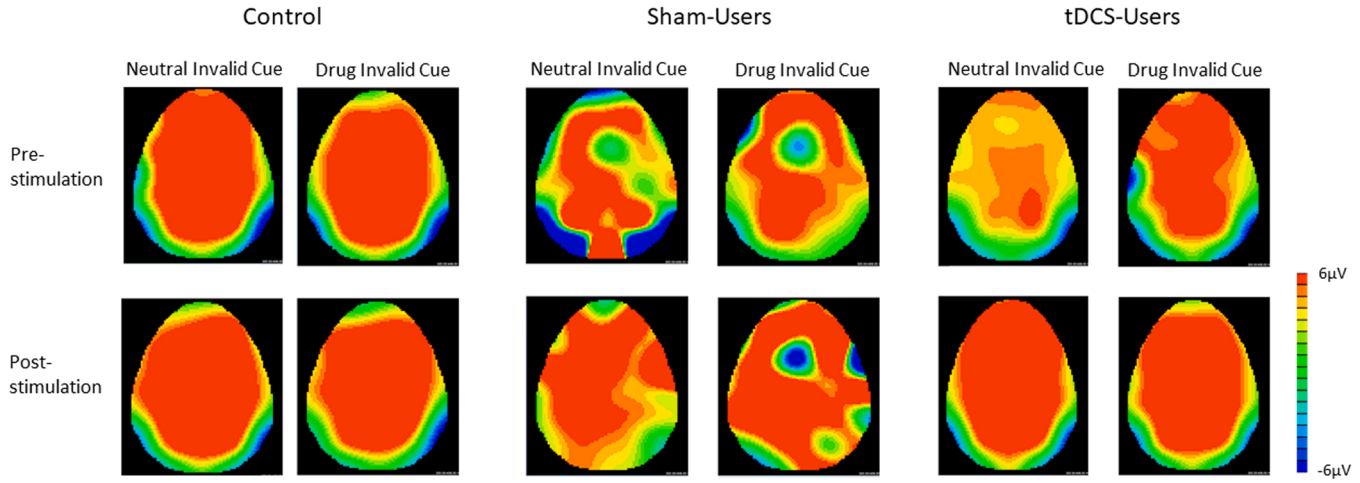

Fig. 2. ERP scalp topographies of the P300 component. The scalp topographies elicited by the neutral and drug invalid cued stimuli were obtained for the time window used for the P300 component (300–410 ms).

13 min, followed by 20 min of no stimulation then a further 13 min of stimulation. At the start of each 13-minute block, the current was increased from 0 to 2 mA (equivalent to 0.0571 mA.cm^{-2}) over a 30 s time-period, and was sustained at this level until 30 s from the end of the stimulation period. Stimulation was then reduced to 0 mA over the final 30 s of stimulation. This is a protocol previously employed in an investigation of tDCS effects in alcoholics and drug-users (Nakamura-Palacios et al., 2016). For sham-tDCS, for the time periods with tDCS were as in the above-described schedule, with the same 30 s ramp-up of current applied but this was immediately followed by a 30 s ramp-down to 0 mA current, although 'stimulation' was delivered to these participants for the same time duration. As mentioned in *2.2. Design*, stimulation was administered daily for 5 days, with the type (real or sham) depending on the group to which participants had been assigned.

3. Results

3.1. Posner task performance

Performance on the Posner task was evaluated in terms of the difference between response times for invalidly and validly cued target locations (this is often termed the 'disengagement score'). This was done by subtraction of the mean response times for validly-cued locations times from the response times for the invalidly-cued locations individually for each participant and for drug and neutral cues. Data were then analyzed with repeated measures analysis of variance (ANOVA) with factors of group (tDCS, sham, control), cue (drug, neutral), and time (a factor with two levels, one for 'pre', relating to pre-stimulation/sham/control, and one for 'post', relating to post-stimulation/sham/control).

There were no main effects seen in this analysis for group, time, or for cue (all $p > 0.05$). There was a significant interaction between time and group ($F(2,27) = 4.724$, $p = 0.017$). This indicates that performance differed over time differently for the groups investigated. *Post-hoc* t-tests to assess this showed no significant effect of time for any of the groups, but an effect approaching significance was seen for the tDCS group ($t = 2.115$, d.f. $= 9$, $p = 0.064$), with a lower invalid-valid cue RT difference following tDCS (58.7 ms before, 44.2 ms after tDCS), whereas other groups showed an increase. Further analysis comparing *changes* in disengagement scores showed that there was a significant reduction for the tDCS group (a 14.5 ms reduction) compared to the control group (a 11.9 ms increase) ($t = 2.61$, $p = 0.017$). No other main effects or interactions approached significance (all $p > 0.22$). See Fig. 3(a) and (b).

3.2. P300 amplitude

P300 amplitude was analyzed with repeated measures ANOVA,

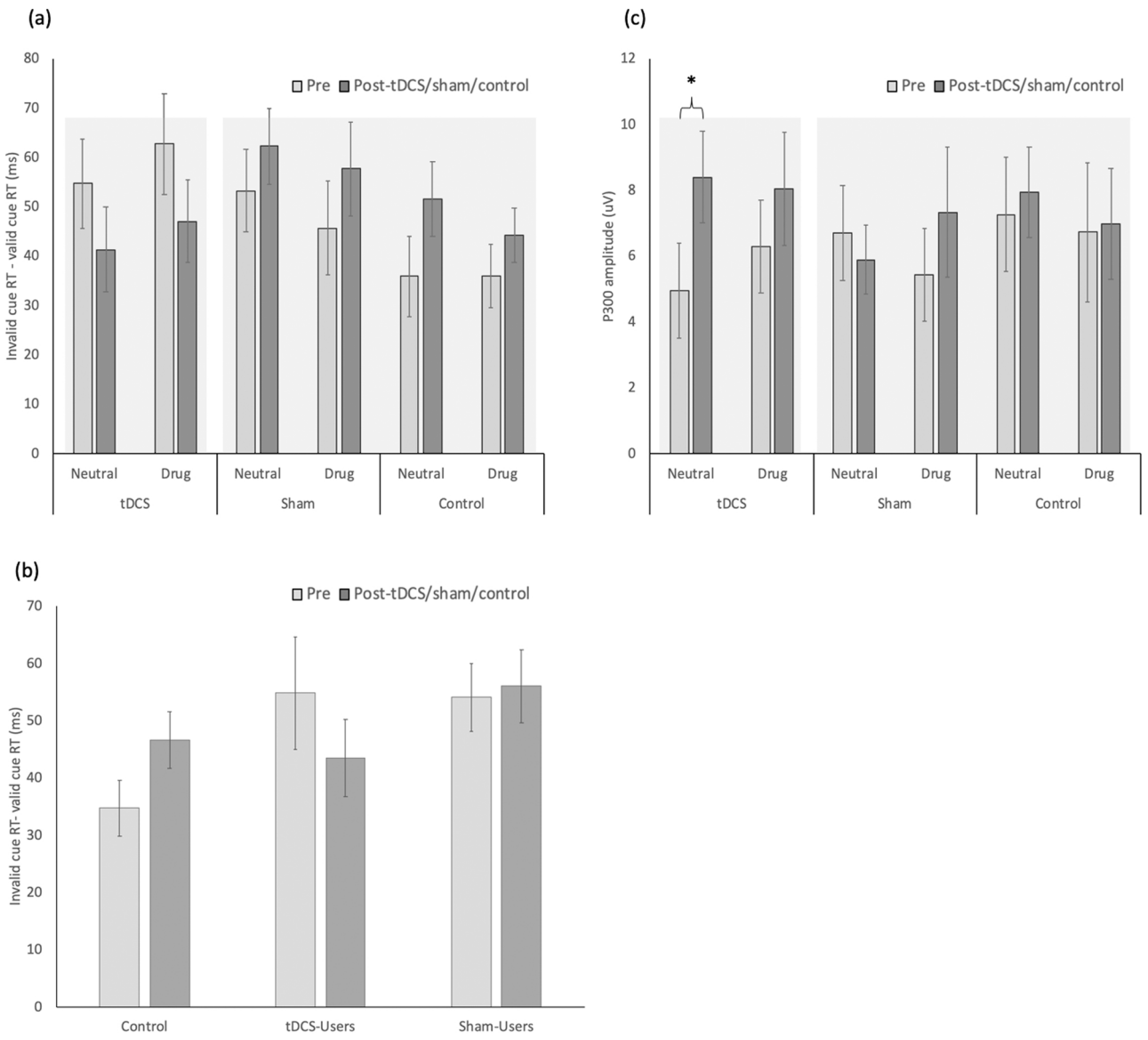

Fig. 3. Effects of tDCS on behavior and ERP measures. Error bars represent the standard errors of the means (S.E.M.). (a) The difference in the response times for invalidly versus validly cued targets (disengagement cost) for both drug-related and neutral cues. Note the general decrease seen with tDCS in abstinent users, compared to the opposite trend with both sham-tDCS and in control participants. (b) The data from (a) collapsed across cue type. The significant effect on performance relates to the increase seen in Control participants over time in contrast with a drop in the disengagement cost in the tDCS-user group. The cost in the Sham-User group was similar at both time-points. (c) P300 amplitude during task performance. There was a general increase with tDCS for both cue-types, and significantly so for neutral-cued targets. * $p < 0.05$.

again with factors of group (tDCS, sham, control), cue (drug, neutral), and time (a factor with two levels, one for 'pre', relating to pre-stimulation/sham/control, and one for 'post', relating to post-stimulation/sham/control). A significant effect was seen only for the cue x time x group interaction ($F(2,26) = 5.029$, $p = 0.014$) with no other significant effects, although the effect of time (pre- versus post-tDCS/sham/control) approached significance ($F(1,26) = 3.079$, $p = 0.091$). This interaction was investigated using Bonforroni-corrected t-test comparisons for P300 amplitudes pre- and post-tDCS/sham/control time points for each group and for drug and neutral cues. Results showed only a significant difference for the increase in P300 amplitude for the neutral cue condition for the drug-user group following tDCS ($p = 0.033$). The P300 amplitude was also increased in this group for the drug cue condition, but not significantly so (see Fig. 3 (c)).

3.3. Questionnaires

Questionnaire scores were analyzed with repeated measures ANOVA, again with factors of group (tDCS, sham, control), cue (drug, neutral), and time (pre- and post-stimulation/sham/control). Most of the questionnaires, and most of the sub-indices they represented, showed no significant differences. Exceptions to this were Negative Mood Regulation scores, which showed a main effect of pre- versus post-tDCS/sham/control ($F(1,17) = 9.904$, $p = 0.006$), with scores being higher for the post- than pre- condition. Additionally, Behavioral Inhibition Scale scores showed a similar main effect for pre- versus post-conditions ($F(1,17) = 14.512$, $p = 0.001$), with, in this case, scores being lower for the post- conditions. No other main effects or interactions were seen.

4. Discussion

This experiment investigated Posner cueing task performance with drug and neutral cues, along with the P300 ERP component associated with the onset of invalidly cued targets in the task. This was done before and after tDCS and sham stimulation in abstinent drug users and compared to data from control (non-drug user) participants to see whether tDCS delivered in recently abstinent drug users would produce effects on the P300 with the prediction that the amplitude of this component would become larger, and so show similar patterns to those seen in drug users more likely to maintain abstinence.

Performance on the Posner cuing task showed a significant interaction between group and pre/post intervention. This seemed to be driven by a fall in the overall difference between response times for invalid versus valid cues (the disengagement cost) in the tDCS stimulation condition, in contrast to an elevation in this measure in both the sham-tDCS and the control group. This is in conjunction with generally larger initial scores for the disengagement cost seen for the drug users (irrespective of tDCS group to which they were assigned), compared to the control participants. This pattern of results was consistent with a reduced cuing effect, irrespective of the nature of the cue (albeit only significantly so for neutral cues), in the tDCS group for the post- versus pre-tDCS measure, in comparison to increases in the cuing effect, generally, for the sham and control groups. The result, therefore, could be interpreted as reflecting more 'normal' performance in this group as a result of tDCS stimulation. This alone, of course, doesn't necessarily mean that any underlying abnormalities in the neural mechanisms of task performance in this group (should they exist) were normalized, but this is an issue at least partially addressed by the analysis of the P300 ERP component recorded during task performance.

The P300 ERP showed a significant interaction and *post-hoc* analysis showed this to be due to a significant increase in P300 amplitude for the tDCS group in the neutral cue condition. An increase was also seen for this group for the drug-cue condition, but this change was not significant. While this might be interpreted as meaning there was no meaningful change for the drug-cue condition, it seems relevant to note that this could be due to this component being larger than for the neutral cues in the pre-stimulation condition. This pattern of changes, overall, is encouraging given, for example, the reported correlations of lower P300 amplitudes in other addictions (such as alcoholism, see Enoch et al., 2001) and also the seeming pattern of P300 amplitude being a good indicator of relapse rate/speed (see Houston and Schlienz, 2018). It would be beneficial to see whether, on an individual level, changes in P300 due to tDCS relate more directly to beneficial effects in more clinically-relevant measures relating to abstinence from drug use, whether it is a general effect (i.e., is unaffected by whether cues are drug-related or not), or whether there is some other level of specificity of effect accounting for why significant effects were seen for neutral image cues, but not for drug-related image cues. Investigation of this would be beneficial in future studies.

There are, of course, a number of issues that exist in the current study in terms of experimental design and replicability or in terms of interpretability of results. This is particularly the case given some of the reported issues with studies employing tDCS in cognitive studies (see Horvath et al., 2015b). Although those concerns primarily relate to effects reported for single sessions of tDCS stimulation and in normal participants, it seems reasonable to bear these in mind for repeated stimulation regimes in 'non-normal' individuals. Consequently, erring on the side of caution when looking at data from a study employing tDCS and any effects on behavior and/or brain electrophysiology is prudent. Additionally, it is important to note the limited power of the current study due to the number of drug-user participants who took part. While this was partially due to the relatively strict criteria used for participant inclusion (i.e., only including individuals who had used amphetamines and no other substances) and a resulting low number of individuals taking part, further investigations would be useful to assess the reliability of the effects seen with the results here being more of a guide than allowing a definitive conclusion to be drawn. While there are some differences between conditions using drug-related and neutral cues in the present study, the potential for limits to these differences being a consequence of the short duration of cue presentation should also be borne in mind. Additionally, the absence of any changes in craving, as indicated by questionnaire scores, should be noted. This may be of importance given previous suggestions of links between abstinence and P300 amplitudes and whether it is dependent on the time of P300 modulation should be investigated. Finally, the lack of a completely blind experimental design (primarily for the control participants and the experimenter conducting the observations) should be borne in mind.

Despite these limitations, there seems to be grounds for optimism regarding the findings here. Primarily, the control conditions improve the general plausibility of the reported effects, with there being no changes in either the sham stimulation condition in recently abstinent drug-users or over a similar time period in the control (non-user) group, whereas the significant changes were seen in the group receiving 'real' tDCS. Additionally, the tDCS stimulation site(s) and parameters were based on those previously employed in a study by another group and that were reported to result in significant effects (Nakamura-Palacios et al., 2016). Of course, further and wider ranging investigation of this approach would be desirable, and, most specifically, in terms of whether the effects of stimulation are effective in helping to maintain abstinence from drug use across different addictions. In terms of beneficial experimental (and, therefore, potentially future therapeutic) refinements, consideration of what would be an 'optimal' stimulation level in terms of current/current density for maximizing and beneficial effects of tDCS would also be useful. Similarly, it may be that the stimulation schedule (e.g., daily, weekly) could be optimized, as could potential use of subsequent 'booster' tDCS stimulation sessions following the initial sessions of delivery. These all rely on stimulation producing an initial reliable, beneficial effect and would potentially necessitate investigation of many permutations of stimulation. While this may be possible to some extent, the aim of providing an effective, safe, and persistent aid to drug use abstinence should be the primary aim. There are some examples where this seems to have been achieved using transcranial magnetic stimulation (TMS) in depression, with repetitive TMS delivered twice a day, with a 15-minute interval between stimulations increasing efficacy (Enoch et al., 2001). However, there are relatively few similar examples in addiction and using tDCS in particular (but see Klauss et al., 2014). The results obtained here may represent one initial step in using more direct neurocognitive measures and applying these in the context of assessment of effectiveness of potential treatments in drug addiction. Further work to establish the reliability of the P300 as an indicator of therapeutic effectiveness of any tDCS delivered would also be useful.

4.1. Conclusions

This study evaluated the effects of one week of tDCS in recently abstinent amphetamine users on performance of a Posner cuing task and on the amplitude of the P300 ERP component obtained during task performance, a marker typically affected by addiction. Results were indicative of changes in performance such that tDCS caused behavior and electrophysiology of drug users to become more similar to normal (non-addict) individuals. Future work to assess the reliability of this effect, including by increasing participant numbers to increase the power of the study and its associated analysis, and whether it aids in maintaining drug-use abstinence would be useful.

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CRediT authorship contribution statement

Chiao-Yun Chen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Yu-Hua Liu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Neil G. Muggleton:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing.

Informed consent statement

Informed consent was obtained from all participants in the study.

Compliance with ethical standards

This study was approved by the Institutional Review Board of NCKUH and complied with the ethical standards of the Helsinki Declaration of 1975 and revised in 2008.

Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

Data Availability

Data is available upon reasonable request.

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