Brain Stimulation 12 (2019) 959–966

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Increased perseverative errors following high-definition transcranial direct current stimulation over the ventrolateral cortex during probabilistic reversal learning

Natalia Albein-Urios [a, *], Henry Chase [b], Luke Clark [c], Melissa Kirkovski [a], Charlotte Davies [a], Peter G. Enticott [a]

[a] Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Victoria, Australia
[b] Department of Psychiatry, University of Pittsburgh, PA, USA
[c] Centre for Gambling Research at UBC, Department of Psychology, University of British Columbia, Vancouver, Canada

ARTICLE INFO

Article history:
Received 17 September 2018
Received in revised form
6 February 2019
Accepted 18 February 2019
Available online 21 February 2019

Keywords:
Ventrolateral prefrontal cortex
Probabilistic reversal learning
High-definition transcranial direct current stimulation
Cathodal stimulation
Perseverative errors
Feedback-related negativity

ABSTRACT

Background: The prefrontal cortex regulates behavioural adaptation in response to feedback. However, the causal role of different prefrontal regions remains unclear, based on indirect evidence derived from functional neuroimaging. Neuroimaging studies show dorsomedial prefrontal activation during feedback monitoring, whereas the ventrolateral prefrontal cortex engages during behavioural adaptation (shifting).
Objective: We used high-definition transcranial direct current stimulation (HD-tDCS) to elucidate the roles of the ventrolateral prefrontal cortex (vlPFC) and the dorsomedial prefrontal cortex (dmPFC) in behaviour change, using a probabilistic reversal learning task (PRLT).
Method: Fifty-two healthy adults were randomly assigned to receive cathodal HD-tDCS to inhibit the vlPFC or the dmPFC versus sham stimulation, prior to completing the PRLT. The outcome measures were the number of perseverative errors and the electroencephalography (EEG) signals of feedback-related negativity (FRN) in the PRLT. We hypothesised that inhibition of the vlPFC would be specifically associated with more perseverative errors and weaker FRNs.
Results: We found that vlPFC inhibition was associated with higher perseverative errors compared to sham and dmPFC stimulation conditions. Although there were no statistically significant differences in FRN amplitudes, the effect sizes indicate an association between inhibition of the vlPFC and lower FRN amplitudes.
Conclusion: Our findings support a causal role of the vlPFC on feedback-based behavioural adaptation, which is critical for adaptive goal-driven behaviour.

Introduction

In a world of constant change, the ability to adapt to new situations is essential for survival and wellbeing. Reversal learning paradigms have been widely used in animals and humans to explore the neural basis of this *cognitive flexibility* [1]. Reversal learning requires individuals to flexibly adjust the responses from a previously reinforced stimulus, and switch responding to a newly reinforced stimulus. Traditionally, reversal learning tasks distinguish two stimuli, where one is rewarded and the other is not. Newer versions of this task include a probabilistic component to make the rule change more ambiguous, in which negative feedback is given to around 20% of the correct responses [1,2].

The use of probabilistic reversal learning (PRL) tasks in neuroimaging studies has revealed the involvement of ventral frontostriatal circuits [3]. In particular, the right ventrolateral prefrontal cortex (vlPFC) has been consistently involved in the process of inhibiting motor responses and re-orientation towards newly relevant stimuli [4]. Likewise, human brain lesion studies have evidenced the role of the vlPFC in inhibitory control [5]. Although the examination of patients with brain lesions provides the best evidence to investigate brain-behaviour relationships, lesion

* Corresponding author. School of Psychology, Deakin University, 221 Burwood Hwy, Burwood, Victoria, 3125, Australia.
E-mail address: natalia.albeinurios@deakin.edu.au (N. Albein-Urios).

https://doi.org/10.1016/j.brs.2019.02.013
1935-861X/

studies are limited by unknown premorbid factors, neuroplastic changes, and distal re-organization away from the lesion site [6].

Using functional MRI, Cools et al. (2002) [7] demonstrated that activation of the right vlPFC was specifically enhanced following the final reversal error of the PRL, before the participant shifts to the newly reinforced stimulus. Dorsomedial PFC, by contrast, was recruited more diffusely by negative feedback trials, including early (perseverative) reversal errors and probabilistic errors (correct responses that yield false feedback), implicating dmPFC in the processing of negative feedback rather than behavioural flexibility *per se*.

Similarly, EEG studies have shown that feedback-related negativity (FRN), an event-related potential generated at fronto-central electrode sites, is intimately linked with the outcome processes in PRL [8]. Increases in the amplitudes of the FRN in PRL have been generally associated with a negative prediction error, a discrepancy between the expected reward and its prediction (i.e., negative feedback) [9,10]. However, the elicitation of the FRN in PRL has been also found when outcomes are better than expected (i.e., positive feedback) [11] or when the outcomes reflect a signal of surprise [12].

Despite the ample scientific literature in reversal learning studies, to date the causal contribution of vlPFC in PRL has not been sufficiently explored. The use of non-invasive brain stimulation techniques provides an opportunity to investigate causal brain-behaviour associations [13]. Stimulation techniques such as transcranial direct current stimulation (tDCS) can be used to either enhance or temporarily disrupt neural activity in specific brain regions of interest [14]. TDCS consists of a weak electrical current that is passed through electrodes that are placed against the scalp. Typically, anodal-tDCS stimulation increases neural excitability in the underlying brain region, while cathodal-tDCS stimulation reduces neural excitability in the underlying region. For instance, anodal-tDCS stimulation over the ventral and dorsolateral prefrontal cortex (dlPFC) facilitates choosing a more advantageous decision-making strategy in the Iowa Gambling Task [15,16]. By contrast, cathodal-tDCS over the dlPFC has been shown to increase the number of incorrect responses in a cognitive conflict task [17]. A limitation of conventional tDCS is its lack of focality, with current induction occurring throughout large portions of the brain. A recently-developed technique, high definition tDCS (HD-tDCS), allows for more focal current delivery, and has causally demonstrated the role of the dlPFC in conflict adaptation during a visual flanker task [18].

In the current study, we sought to delineate the role of right vlPFC in PRL. We used cathodal HD-tDCS over the right vlPFC to probe its role on shifting behaviour indicated by the reversal trials of a PRL paradigm. We employed cathodal HD-tDCS over the dmPFC as an active control condition, as well as sham stimulation (half to vlPFC, half to dmPFC) as a baseline condition. The right vlPFC was stimulated in the experimental condition because functional neuroimaging of PRL indicates that this region is activated when shifting the previously rewarded response and updating to a new set of responses [4]. The dmPFC was stimulated as the active control region because of its presumed involvement in feedback conflict monitoring in PRL, but not specifically in the switching signal [19,20].

We hypothesised that participants receiving cathodal stimulation over the right vlPFC would commit more errors during reversal stages compared to both the active control and sham stimulation conditions. We also hypothesised that vlPFC stimulation would produce reduced FRN amplitudes during reversal trials and during the shift towards a new rewarded pattern of responses.

Materials and methods

Participants and design: Sixty-two right-handed volunteers were recruited from advertisements placed in the local community and on social media platforms. The selection criteria were: (i) aged between 18 and 30 years old, (ii) English as a first language, (iii) right-handedness, (iv) absence of history of current neurological or psychiatric disorders, and (v) Estimated IQ above 80—as measured by the Test of Premorbid Functioning (TOPF) [21]. Ten participants were excluded from the final sample: six due to meeting criteria for psychiatric disorder/s as measured by the Mini International Psychiatric Interview (M.I.N.I) [22], two participants for not meeting eligibility in the non-invasive brain stimulation safety screening due to neurological problems, and two due to problems during EEG recordings. The final sample comprised 52 participants [28 females, age mean (SD) = 22.02 (2.19)].

We used a randomized, double-blind, between-subjects design. Participants were randomly assigned to receive active cathodal-HD-tDCS stimulation to either vlPFC (n = 15) or dmPFC (n = 15) or sham (n = 22). Each participant was randomly allocated by an external researcher to the three conditions: vlPFC cathodal-HD-tDCS (experimental condition), dmPFC cathodal-HD-tDCS (active control condition), and sham- HD-tDCS (control condition).

High definition transcranial direct current stimulation (HD-tDCS; neuroConn, DC-Stimulator MC): We used HD-Explore and HD-Targets Software (Soterix Medical) to determine the intensity and focality of cathodal stimulation over the vlPFC and dmPFC. HD-tDCS setup allows current delivery with high spatial precision [23,24], which has been shown to result in more pronounced behavioural and neurophysiological effects than conventional tDCS [23,25].

We used a priori defined Montreal Neurological Institute (MNI) coordinates described in a previous fMRI-PRL study [7] to target the right vlPFC (coordinates *x*, *y*, *z* = 38, 24, −2; see Fig. 1). The same procedure was used to define the active control brain region, the dmPFC (coordinates *x*, *y*, *z* = 8, 32, 52).

For stimulation, two experienced researchers measured and used the four anatomical landmarks (i.e., nasion, inion and two pre-auricular points) to place the HD-tDCS electrodes according to the 10–20 system. A total of 2 milliamp (mA) current intensity was applied in the two active conditions through five 20 mm diameter circular rubber electrodes. For the vlPFC the electrode position and current intensity were: FP2 (0.9 mA), F6 (0.5 mA), FC6 (0.6 mA), T8 (−0.9 mA), FT8 (−1.1 mA). For the dmPFC the position and current intensity were: FZ (0.5 mA), FCZ (0.5 mA), CZ (0.5 mA), AF4 (0.5 mA), F2 (−2 mA) (See Fig. 1). For the HD-tDCS sham condition half of the participants (n = 11) had the electrodes positioned following the vlPFC montage, and the other half according to the dmPFC montage. An impedance check was carried out to ensure appropriate conductance. Before starting the stimulation, all impedance values were below 10 kΩ (neuroConn, 2014). The stimulation was delivered for 20 min with an initial ramp-up phase of 30 s and a ramp-down phase of 30 s in each of the three conditions.

During the ramp-up phase the electrical current was gradually increased, and in the ramp down period the electrical current was gradually decreased. During the sham stimulation condition, these ramp phases were essential to simulate the effect of an active stimulation condition.

Probabilistic reversal learning task (PRL): We used a probabilistic reversal learning paradigm adapted from Chase et al. (9). The task was administered on a desktop computer and responses were recorded using a standard keyboard. Participants were seated

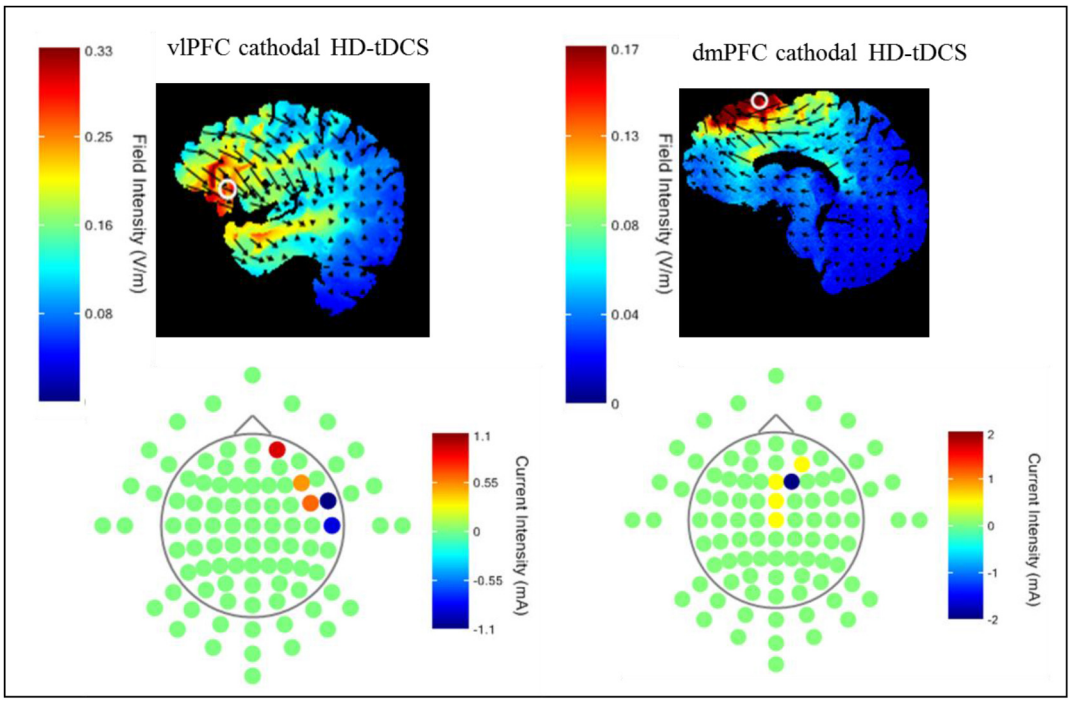

Fig. 1. Montage and Soterix modelling for direction and intensity of currents for high-definition cathodal stimulation of the right vlPFC and right dmPFC.

in a darkened room, with eyes 80 cm from the computer monitor (www.benq.us/product/monitor/XL2420TE/specifications).

On each trial, two Hiragana characters (black) were presented on either side of a central fixation point on a white background screen. Participants were instructed to choose one of the characters, receiving either a reward (green smiling face) or punishment (red sad face) feedback. The "correct" stimulus was rewarded on 80% of trials, whereas the "incorrect" stimulus was rewarded on 20% of trials. During the task, the rule changed intermittently and contingencies reversed so that the other stimulus was now (usually) correct. After contingency reversal, choosing the previously correct stimulus led to punishment on every trial until the participant selected the new correct stimulus. In this study, perseverative errors following the rule switch response were labelled "reversal errors," as an expression of cognitive inflexibility [1]. Participants had a short practice session followed by the completion of 10 blocks. Each block contained four reversals. On each trial, the stimuli were presented for 4000 ms, within which the response had to be made, otherwise a "too late" message was presented. Then, after a 1000 ms delay, feedback was presented for 500 ms. We analysed three main behavioural measures: 1. *Reversal errors* (number of errors relative to the total number of trials that occurred when participants repeatedly chose the previously rewarded stimulus after contingencies changed); 2. *Hits* (number of correct responses relative to the total number of trials), and; 3. *Other errors* (incorrect responses relative to the total number of trials that did not occur during reversal stages).

Procedures

The study was approved by the Human Research Ethics Committee of Deakin University (Australia), and all participants provided signed informed consent. Participants completed the psychiatric and medical screening as well as the non-invasive brain stimulation safety questionnaire. Eligible participants also completed a short sociodemographic assessment, the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [26] to measure trait reward and punishment sensitivity, and the IQ test, and were then randomly assigned to one of the three experimental conditions by a research assistant not involved in subsequent assessments. Two experienced researchers blind to the randomisation outcome performed the EEG and HD-tDCS setup and protocol.

First, participant's size and shape were measured, then following a systematic procedure consistent with a series of detailed instructions according to the 10–20 EEG system, the HD-tDCS electrodes for both stimulation conditions (i.e., vlPFC and dmPFC) were placed in their corresponding positions [27]. Each of the electrodes was secured in place using Ten20® conductive paste. After this, the EEG cap (www.easycap.de/) was carefully placed over the HD-tDCS electrodes by two experimenters to ensure they remained in place. An impedance check was then performed to ensure optimal values (<10 kΩ).

Then, after participants were fitted with the EEG cap, the EEG electrodes (Ag-AgCl) outside the stimulation area were gelled up with conductive gel. The stimulation was undertaken in a quiet room and participants were instructed to sit quietly while watching a fixation point displayed in the computer monitor during the stimulation period. Immediately after stimulation, two researchers carefully removed the HD-tDCS electrodes, cleaned the area with abrasive paste and alcohol swabs. Single silver–silver chloride (Ag-AgCl) sintered ring EEG electrodes were fastened to the corresponding area (where HD-tDCS electrodes were previously placed), conductive gel was applied, and ensured there was not any electrode bridging. This process and the task instructions were completed in a maximum of 10 min. If these tasks lasted less than 10 min, we instructed participants to wait until this time was completed to start the task. Participants then completed the PRL while undergoing EEG. A 64-channel SynAmpsRT amplifier (Compumedics Neuroscan, Charlotte, NC; http://compumedicsneuroscan.com) was used to record EEG data from 32 Ag/AgCl sintered electrodes placed in an elastic cap. Six additional

electrodes were attached to the left and right mastoid, to the outer canthi around the left and right eyes and above and below the left eye to measure electro-oculogram (EOG). The ground electrode was placed centrally on the forehead and the active reference electrode was placed on the right mastoid. Each electrode was adjusted to keep its impedance below 5kΩ. EEG data were common average referenced and recorded at a sampling rate of 1000 Hz. The PRL was administered during EEG recordings using E-Prime v2.0, Psychology Software Tools Inc. (http://www.pstnet.com/prime). EEG triggers were sent via parallel port to mark feedback onset during the PRL.

The duration of the task was approximately 25 min, but it varied depending on the accuracy in the participant's responses (i.e., higher number of 'other errors' outside reversal stages increased the number of trials). After performing the task, participants completed a post non-invasive brain stimulation safety questionnaire. The length of the session for each of the condition was approximately 2 h.

Data analysis

EEG data analysis: We focused our analyses on the FRN amplitude, a negative-going EEG waveform following feedback onset that is usually associated with the prediction error signal [28]. EEG data were pre-processed and analysed offline using Curry 7 Neuroimaging Suite. Offline high- and low-pass filtering were 0.1 and 30 Hz respectively. Eye-blink correction was conducted using a principal component analysis approach. Epochs were extracted at 200 ms baseline before and 500 ms after feedback presentation (700 ms in total). After epoching data, trials with voltage >70 μV were discarded, as these were likely to contain artifacts. The FRN amplitudes were estimated by using an average-base to peak extraction [9,29]. We averaged voltage measures over a fronto-central cluster comprising the following electrodes: F3, FZ, F4, FC5, FCZ, FC6, C3, CZ, C4. The lowest voltage peak was calculated in a time window from 240 ms to 290 ms post-feedback onset. The equivalent was performed for the highest peak in the preceding (160 ms–220 ms) and following (300 ms–420 ms) positive-going voltages. The average of the preceding and following highest peaks was then subtracted from the lowest peak. We averaged the epochs in each of the conditions to obtain an average waveform for each trial type and each participant. Overall, 80% of epochs were retained for analysis (averaged across all participants). In line with our study hypothesis FRN amplitudes were extracted from two trial types: 'reversal errors', measured during the reversal phase, and 'first positive after reversal', which coincides with the first correct response after behavioural switching in the reversal phase. These critical time points have been associated with increased brain activation within the vlPFC in neuroimaging studies [7,30].

Hypothesis testing. Data were analysed with SPSS version 24.0. We conducted one-way ANOVAs to compare the behavioural measures and the EEG signatures of the PRL between the three stimulation groups (vlPFC, dmPFC and sham). One-way ANOVAs were used on normally distributed data, and Kruskal-Wallis Test on data not normally distributed to determine differences in behavioural and psychophysiological data between the three stimulation groups; cathodal vlPFC and dmPFC HD-tDCS, and sham HD-tDCS. When one-way ANOVAs or Kruskal-Wallis tests yielded significant findings, we conducted paired contrasts using LSD and Mann-Whitney tests respectively. The FRN amplitude for 'reversal errors' and 'first positive after reversal' was analysed using a mixed ANOVA, with the within-subject factor trial type (two levels), and the between-subjects factor corresponding to the three stimulation conditions (vlPFC, dmPFC and sham). Both behavioural and electrophysiological data were screened for normality and outliers greater than two standard deviations from the mean. The latter were winsorised, and the appropriate procedure was adopted based on Tabachnick & Fidell [31]. Only in the electrophysiological data, a single outlier in the FRN amplitude of the variable 'first positive after reversal' was transformed.

Results

Descriptive analyses

The three groups were matched in terms of gender, years of education, and estimated intelligence (IQ). Groups were also matched in trait sensitivity to reward and punishment indicated by the SPSRQ (Table 1).

Behavioural measures

Reversal errors

We found a significant difference between the three groups on '*reversal errors*' in the Kruskal-Wallis Test ($\chi^2(2) = 9.169$, $p = 0.010$). The vlPFC group compared to the sham ($U = 91.000$, $z = -2.289$, $p = 0.022$), and dmPFC ($U = 41.000$, $z = -2.966$, $p = 0.002$) stimulation groups committed significantly more errors, while there was

Table 1
Mean, Standard Deviation (SD), F and χ^2 statistic, *p* values and Mann-Whitney paired contrasts (*U*) for descriptive, behavioural and feedback-related negativity (FRN) measures.

	vlPFC HD-tDCS		dmPFC HD-tDCS		Sham HD-tDCS		F/χ^2	*p*	*U*
	Mean	SD	Mean	SD	Mean	SD			
Descriptive measures									
Age	23.00	2.53	22.00	2.26	21.36	1.67	2.647	.081	
Years of education	15.93	1.09	15.60	0.91	15.22	0.81	2.616	.083	
Predicted IQ	109.00	8.23	106.93	11.67	109.72	9.65	.363	.697	
SPSRQ-punishment	8.26	4.83	9.73	4.00	11.40	4.01	2.469	.095	
SPSRQ-reward	9.06	3.55	9.53	3.97	9.18	4.23	.057	.944	
Behavioural measures									
Reversal errors	.120	.029	.076	.040	.086	.047	9.169	.010*	1 > 2** 1 > 3*
Other errors	.078	.033	.140	.076	.144	.106	3.974	.137	
Hits	.546	.033	.512	.060	.505	.064	2.548	.089	
FRN measures									
Reversal errors	−3.998	1.474	−5.045	1.901	−4.205	1.730	1.615	.209	
First positive	−2.861	1.406	−3.894	1.212	−3.803	1.807	2.159	.126	

Note. SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire; vlPFC: Ventrolateral prefrontal cortex; dmPFC: Dorsomedial prefrontal cortex; HD-tDCS: High-definition transcranial direct current stimulation; *$p < 0.05$; **$p < 0.01$.

no significant difference between the dmPFC and sham groups ($U = 144.500$, $z = -0.634$, $p = 0.531$; see Table 1).

Other errors

A Kruskal-Wallis Test did not show a significant difference in the 'other errors' variable across the three groups (χ^2 (2) = 3.974, $p = 0.137$).

Hits

A one-way ANOVA did not show differences on the 'hits' variable across the three stimulation groups (F (2, 49) = 2.548, $p = 0.089$).

Electrophysiological measures

We identified the typical FRN pattern characterised by a deflection occurring at approximately 200–350 ms after the presentation of feedback. There was a significant main effect for the effect of trial type, Wilk's Lambda = 0.862, $F(1, 49) = 7.856$, $p = 0.007$, $\eta_p^2 = 0.138$ with the three stimulation groups. Paired t tests were used to investigate this effect; As expected, FRN amplitude was largest on "reversal error" trials ($M = -4.387$, $SD = 1.734$) compared to "first positive after reversal" trials ($M = -3.558$, $SD = 1.575$; t (51) = −2.650, $p = 0.011$). The main effect of stimulation condition was not significant, $F(2, 49) = 2.964$, $p = 0.061$, $\eta_p^2 = 0.108$, and there was no significant interaction between the stimulation condition and the two variables, Wilk's Lambda = 0.973, $F(2, 49) = 0.679$, $p = 0.512$, $\eta_p^2 = 0.027$.

The FRN amplitudes of 'reversal errors' did not differ across the three stimulation groups (F (2, 49) = 1.615, $p = 0.209$).

No differences were found when comparing the FRN amplitude on the variable 'first positive after reversal' across the three stimulation groups after conducting a one-way ANOVA (F (2, 49) = 2.159, $p = 0.126$). However, the differences in FRN amplitude between the vlPFC group and the sham group showed a medium effect size, and the differences in FRN amplitude between the vlPFC and dmPFC stimulation group showed a large effect size (see Fig. 2).

Discussion

In this study we aimed to investigate the role of right vlPFC in reversal learning by using non-invasive brain stimulation. In support of our first hypothesis, we found that cathodal HD-tDCS over the right vlPFC increased perseverative reversal errors, but not other errors, during reversal learning. We also predicted electrophysiological changes after cathodal HD-tDCS stimulation over the vlPFC in reversal learning trial types. Although participants in the vlPFC group showed reduced FRN amplitudes when switching their response to a positive outcome compared to the sham and dmPFC stimulation group, these comparisons did not reach significance [$p < 0.1$]. Considering that the effect sizes indicated differences in FRN amplitudes in this variable between these groups, it is likely that this aspect of the study is not adequately powered. Cathodal stimulation over the dorsomedial prefrontal cortex (dmPFC) (the active control region) and sham stimulation did not impact in the number of reversal errors or FRN amplitudes. According to behavioural but not EEG signals, these findings provide preliminary causal evidence for the role of the vlPFC in cognitive flexibility after changes in reinforcement contingencies.

Our findings are consistent with previous neuroimaging research [7,32] and lesion studies [33,34] that demonstrate a key role of the right lateral PFC during reversal learning paradigms. In this study, we used the coordinates shown in Cools et al. [7], which corresponds to Brodmann area 47 but probably extends to lateral orbitofrontal aspects. These two regions are adjacent to one another, and consistently reported in the reversal learning literature [35]. In reversal paradigms, the vlPFC has been more commonly associated with stopping and shifting in response to negative feedback [36], and the lateral OFC has been shown to be relevant for modification of previously established stimulus-response associations [32].

The brain mechanisms involved in reversal learning have been mainly examined in animal studies, but rarely in humans. Interestingly, our findings seem to cohere with animal research. For instance, research in rodents has demonstrated that lesions over the lateral prefrontal cortex impair the ability to flexibly learn from reward schedules [37,38]. Riceberg & Shapiro [39] found that when choices are associated with reward outcomes, lesions over the lateral OFC interfered with lose-shift behaviours (characteristic in reversal learning), and therefore rats committed more perseverative errors. However, they remained intact in other forms of behavioural flexibility, and in some cases even showed an increase in performance [39,40]. In our study, putative inhibition of the vlPFC (i.e., via cathodal stimulation) resulted in participants committing more perseverative errors during reversal phases,

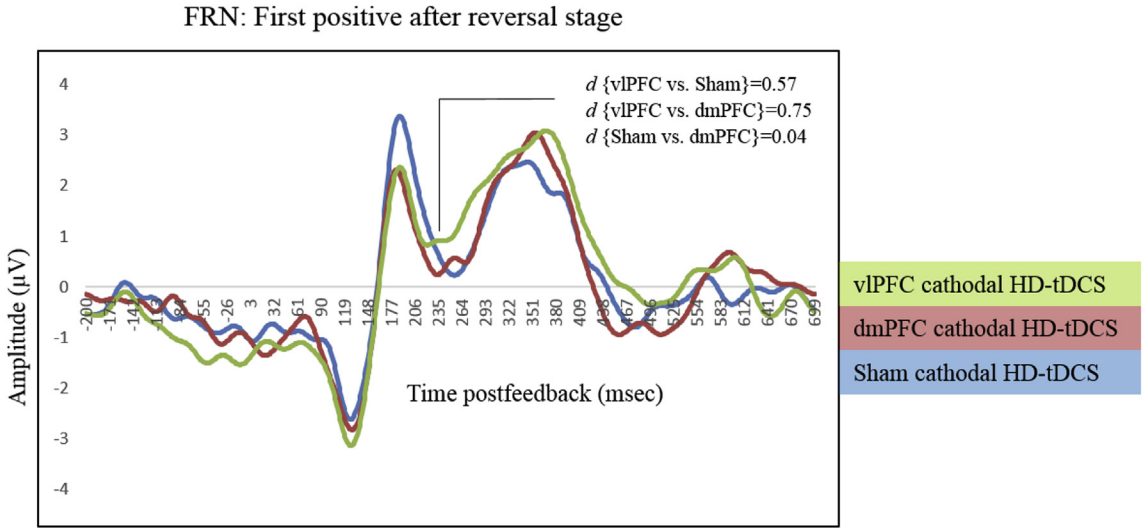

Fig. 2. Feedback-Related Negativity (FRN) amplitudes of first correct response after reversal stages and their Cohen's *d* effect size calculation corresponding to the three stimulation conditions: vlPFC cathodal HD-tDCS, dmPFC cathodal HD-tDCS, and Sham HD-tDCS. *Note. FRN amplitudes were calculated using an average-base to peak extraction.

although their rate of incorrect responses (outside the reversal phase) was reduced compared to the active control and sham groups as observed in the performance in the variable "other errors". This might indicate that cathodal HD-tDCS stimulation over the vlPFC selectively affects the PRLT trials that require a flexible adjustment of a previously learned sequence (reversal learning trials), without affecting those ones that only depend on feedback response (non-reversal learning trials). Also in line with our study results, research conducted with marmosets has associated lesions in the vlPFC with difficulties performing a series of discrimination reversals, and updating choices during probabilistic reversal learning paradigms [41–43].

In neuroimaging studies among healthy participants, the increase in signal in the vlPFC has been specifically associated with behavioural switching and establishment of the new pattern of responding [7,44]. These data are consistent with our predictions and also align with cross-species animal studies showing that damage to the vlPFC impairs reversal learning [45]. Cathodal stimulation over the vlPFC might temporarily disrupt the function of populations of neurons that update the reward value of choices during the reversal phase, resulting in shifting problems [14].

Reversal learning models have been also tested using electrophysiological recordings [28]. Particularly, FRN waves, which have been associated with dopaminergic signaling, are larger when punishment cannot be anticipated from the response or when feedback does not match reward expectations [11]. Previous research using similar versions of PRL have found that increased dopamine in the fronto-striatal circuits is related to increased sensitivity to learning from unexpected rewards with either a negative or positive valence [46]. In line with our hypothesis, we found reduced FRN amplitudes during 'first positive' events only in the VLPFC cathodal stimulation condition. These events occur when participants are attempting to adapt their behaviour to a new reward contingency. It is plausible that depletions in FRN waves might be the result of a temporary decreased neural response as a consequence of the inhibitory stimulation current [47,48]. No differences in FRN amplitude were found between the three stimulation conditions in the variable reversal errors. These findings are in agreement with the conclusions provided by Cools et al. [7], which revealed that the fMRI signal in the right vlPFC was greater during the final reversal error (final erroneous response before behavioural switching) than during all the previous reversal errors. Although in our study the final reversal error was not calculated, we hypothesised that, due to this attenuated signal during the reversal error trials, no observable differences would be detected in FRN amplitudes within the three stimulation conditions.

In this study, our use of cathodal stimulation over the dmPFC was intended to serve as a rigorous active control. Greater activity in dmPFC has been implicated in response conflict, independent of the value of the reward in both switch and non-switch trials [30,49]. In contrast to the vlPFC group, the dmPFC group did not differ from the sham group in their behavioural performance, suggesting that some aspects of learning from unexpected rewards and punishment-based learning are influenced by putative inhibition of the dmPFC via cathodal stimulation. Future research should continue to examine, through causal methods such as HD-tDCS, whether different aspects of reward and punishment-based learning are associated with related symptomatology in clinical populations (e.g., obsessive-compulsive disorder, autism spectrum disorder, etc.).

To the best of our knowledge this is the first study that uses HD-tDCS to unravel the mechanisms of reversal learning, however, some limitations need to be acknowledged. For instance, in this study we used the recommended tDCS parameters to optimise the stimulation effects, such as the intensity of the currents (i.e., 2 mA) and duration of stimulation (i.e., <30min) [27]. We also used a priori defined coordinates described in reversal learning studies supported by accurate tDCS software (Soterix Medical) to determine the position of the electrodes, as well as the intensity, direction and focality of the currents to obtain the best possible outcome. Nevertheless, it is known, that the effects of tDCS are complex and also depend on a range of other factors (e.g., cortical thickness, morphology, brain state) that are very difficult to control for. In addition, most of the previous modelling studies targeting the vlPFC have used conventional tDCS. Although in HD-tDCS the focality of the current delivered is increased versus tDCS, we cannot rule out the possibility that the observed behavioural effects might be partially due to the distributed stimulation effects in adjacent areas of the vlPFC. Thus, specific neural modulation to investigate the cathodal effects using HD-tDCS montages need further verification, and we cannot definitively evoke a cathodal-based explanation for these findings. In addition, the tendency to stay after positive feedback in the 20% option may have driven some perseverative errors. While the perseveration error index has been consistently obtained through the measurement of reversal errors in reversal learning paradigms, and associated with activation of the right vlPFC, a more detailed behavioural modelling will be required to account for any possible perseveration occurring during the task.

Conclusions

To the best of our knowledge this is the first non-invasive brain stimulation study to provide evidence for a causal role of the vlPFC in probabilistic reversal learning. Our results indicate that only stimulation over the right vlPFC induced changes in reversal learning performance. In this study, the modulatory effects on reversal learning suggest that this novel type of tDCS, HD-tDCS, is effective to modulate cognition in a regionally specific way. These findings lay foundation to explore beneficial effects of anodal HD-tDCS in ecologically relevant experimental contexts and in clinical populations with impaired cognitive flexibility. For instance, repetitive behaviours and interests, a core symptom in autism spectrum disorders (ASDs), and directly associated with cognitive flexibility impairments [50], has been linked with the insistence of choosing the previous rewarded stimuli in PRL paradigms [51]. This behavioural pattern in reversal paradigms also shows similarities with obsessive compulsive and addictive disorders [52,53]. Unravelling the causal neurobehavioural mechanisms of domains such as cognitive flexibility, raises the possibility of further exploring the potential benefits of non-invasive brain stimulation techniques in clinical contexts to contribute to reduce related symptomatology.

Declarations of interest

Luke Clark is the Director of the Centre for Gambling Research at UBC, which is supported by funding from the Province of British Columbia and the British Columbia Lottery Corporation (BCLC), a Canadian Crown Corporation. The BCLC and BC Government had no involvement in the design, conduct, or interpretation of the study, and impose no constraints on publishing. LC has received honoraria or travel reimbursements for invited talks from Svenska Spel (Sweden), National Association for Gambling Studies (Australia), and an award from the National Center for Responsible Gaming (US). He has not received any further direct or indirect payments from the gambling industry or groups substantially funded by gambling. He has received royalties from Cambridge Cognition Ltd. relating to neurocognitive testing.

Acknowledgments

This research was supported by the Faculty Research Development Grants, Deakin University (Australia). NAU was supported by a Faculty of Health Postdoctoral Fellowship Scheme from Deakin University (Australia). PGE was supported by a Future Fellowship from the Australian Research Council (FT160100077; Australia). We would like to thank the research team and the participants of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.02.013.

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