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High-definition tDCS alters impulsivity in a baseline-dependent manner

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ABSTRACT

In intertemporal choice (ITC), people discount future rewards in proportion to the time delay until reward receipt. Despite recent non-invasive brain stimulation studies suggesting a general causal link between dorsolateral prefrontal cortex (dlPFC) activity and ITC impulsivity, results regarding the functional specificity of dlPFC are mixed. We used high-definition transcranial direct current stimulation (HD-tDCS) to map changes in causal impulsivity through bi-directional modulation of left and right dlPFC during ITC. Model-free and model-based analyses demonstrated that anodal and cathodal stimulation of left dlPFC, but not right dlPFC, decreased and increased impulsivity, respectively. Critically, an individual differences analysis revealed that modulation of impulsivity was contingent on participants' baseline impulsivity. Overall, our results might reconcile the discrepancies in the existing literature and suggest a baseline-dependent role for left dlPFC during ITC.

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Introduction

It is well known that decisions are affected by the tradeoff between reward magnitude and time delay and, for the same reward magnitude, that people prefer immediate gratification over a time delay. Behavioral economics and psychology studies suggest that choosing between immediate and delayed rewards depends on the discounted subjective value (SV) of the delayed rewards. Popular models such as hyperbolic or quasi-hyperbolic have been proposed to explain and quantify individual differences in the degree to which people discount future rewards relative to immediate ones (i.e. impulsivity; Ainslie, 1975; Frederick et al., 2002; Kable and Glimcher, 2009; Rubinstein, 2003). Recently, nonhuman primate electrophysiology and human neuroimaging studies have started to probe the underlying neural correlates involved in the delay discounting process. More specifically, the SV of delayed rewards was recently shown to be encoded in the activity of value-related brain regions, particularly the ventral striatum and the ventromedial prefrontal cortex (vmPFC) (Ballard and Knutson, 2009; Cai et al., 2011; Kable and Glimcher, 2007, 2009; Peters and Buchel, 2009). The dorsolateral prefrontal cortex (dlPFC) is another brain area known to be involved in valuation tasks, and has been studied extensively in tasks that involve inhibitory control (Ballard and Knutson, 2009; Bickel et al., 2009; Hare et al., 2014; Jacobson et al., 2011; Juan and Muggleton, 2012; Kim et al., 2008; McClure et al., 2004; van den Bos et al., 2014). The dlPFC has been argued to be particularly important for evaluating delayed rewards (McClure et al., 2004); these two roles suggest the dlPFC might participate in separate neural networks for representing and processing immediate and delayed rewards. Alternatively, dlPFC might be involved more specifically in choice implementation. Evidence from fMRI (Hare et al., 2009; Luo et al., 2009) and repetitive transcranial magnetic stimulation (rTMS; Figner et al., 2010) suggests that dlPFC may override the temptation of immediate gratification and thus underlie the exertion of self-control during intertemporal decision-making.

It is now clear that dlPFC plays a pivotal role in intertemporal choice, though causal evidence from recent brain stimulation studies has painted a rather mixed picture in terms of its functional specificity (Cho et al., 2010, 2012; Essex et al., 2012; Figner et al., 2010; Hecht et al., 2013). For example, TMS of dlPFC has opposing effects on intertemporal preferences across studies, and

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mixed results have been reported in terms of hemisphere laterality (Cho et al., 2010, 2012; Essex et al., 2012; Figner et al., 2010). Similarly, bilateral transcranial direct current stimulation (tDCS) of the prefrontal cortex in delay discounting also yielded opposing effects on impulsivity change (Hecht et al., 2013; Kekic et al., 2014).

To address these conflicted findings, we systematically manipulated dlPFC activity using high-definition tDCS (HD-tDCS) in addition to conventional tDCS during an intertemporal choice task. We recruited three separate cohorts of subjects and applied conventional tDCS, HD-tDCS anodal, and HD-tDCS cathodal to each cohort. Subjects within each cohort received lateralized brain stimulation and sham stimulation on three different visits in a randomized order. Our design allowed us to replicate and extend previous conventional tDCS results (Hecht et al., 2013). In particular, by orthogonalizing stimulation site (left versus right dlPFC) and stimulation polarity (anodal versus cathodal) while using HD-tDCS, we exhaustively interrogated the functional specificity of dlPFC in ITC. We conjectured that brain stimulation to the left and right dlPFC would have asymmetric effects due to functional segregation of hemispheric laterality. Different stimulation polarities (anodal or cathodal) would have different modulation effects on neural activity (excitation or inhibition) (Filmer et al., 2014; Jacobson et al., 2012). Furthermore, the recruitment of subjects along the wide range of the impulsivity spectrum allowed us to test whether tDCS changes subjects' impulsivity in a homogeneous manner. Lastly, we also tested whether dlPFC was differentially involved in arbitrating reward options in immediate and delayed contexts. In the immediate context, one reward option in the choice set was available immediately and the alternative was delayed, while in the delayed context, both options were delayed. Given the hypothesized role of dlPFC in exerting self-control in ITC when immediate rewards are involved (Figner et al., 2010), we expected that dlPFC modulation might have different effects in the immediate and delayed contexts.

Materials and methods

Participants

117 healthy adults were recruited into 3 separate tDCS experiments (39 in each experiment; Exp. 1: 24 males, age 22.1 ± 2.0 years; Exp. 2A: 18 males, age 21.1 ± 1.8 years; Exp. 2B: 21 males, age 21.4 ± 2.0 years). All participants were right-handed and had no prior experience with tDCS (conventional or HD). None of the participants had a history of neurological or psychiatric problems. All participants gave informed written consent. Participants were paid based on their task performance (see details below). The study was approved by the Ethics Committee of the School of Psychological and Cognitive Sciences, Peking University.

Intertemporal choice (ITC) task

This study employed a randomized within-subject crossover design; participants in the three experiments completed three sessions of intertemporal choice tasks (Fig. 1A) under different types of tDCS manipulation of dlPFC. Each experimental session was separated by approximately 24 h. For each session, subjects completed 144 trials (12 blocks of 12 trials each). During each trial, participants were asked to make a choice between a sooner-smaller (SS) reward and a later-larger (LL) reward. The left-right positions of two options on the computer screen were randomized across trials, and participants were instructed to respond within 5 s. After responding, the chosen item was highlighted with a red rectangle. If participants failed to respond within 5 s, a warning sign reading, "Please respond faster" was displayed, and the task proceeded to the next trial (missed trials $<2\%$ for each participant).

The ITC task incorporated two different contexts that differed in the delay to the SS rewards. The first context was the "immediate context", in which the SS delay was fixed at "today". The second context was the "delayed context", in which the SS delay was fixed at 30 days. The difference in delays between LL and SS was selected from the time delay intervals (1, 3, 7, 14, 30, 90 days; Fig. 1B). For each trial block, delay intervals and contexts (immediate and delayed) were randomized across trials. The SS reward was fixed at 50 Chinese Yuan (about $8 USD). To accommodate a wide range of baseline impulsivity levels across subjects, the LL amounts between blocks were determined by a self-adaptive algorithm: the amount of the LL for each delay was independently adjusted to converge towards the same subjective value as the SS reward. We assumed that the subjective value (SV) of LL reward discounts along delay interval (D) following a hyperbolic model:

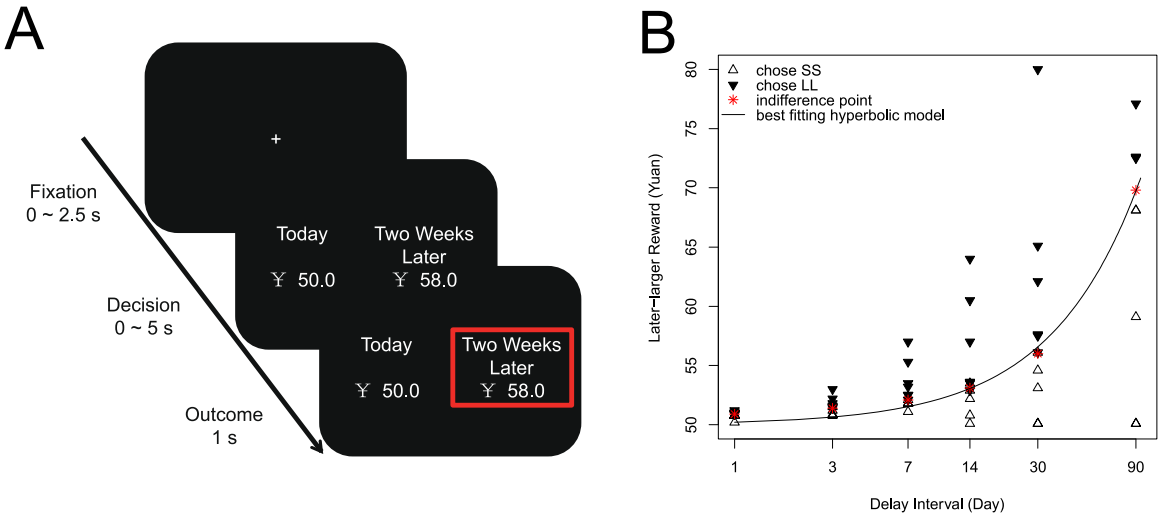

Fig. 1. Intertemporal choice (ITC) task and model fitting. (a) Schematic illustration of ITC task. For each trial, participants were required to choose between a sooner-smaller (SS) reward and later-larger (LL) reward within 5 s. (b) LL amounts, choices, and model fitting of a representative participant in the immediate context (i.e. SS reward available immediately). The LL amount was chosen according to a self-adaptive algorithm. SS choices are depicted as white triangles and LL as black triangles. The red stars indicate indifference points and the black line shows the best fitting hyperbolic model. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$SV = LL\ Amount/(1 + kD)$

The initial discount rates k were randomly set between 0.005 to 0.015 based on pilot studies and the existing literature (Rodriguez et al., 2015; van den Bos et al., 2014). If the participant chose the SS reward, k increased by 0.015 for the subsequent trial; if the participant chose the LL reward, k decreased by 0.015 for the subsequent trial. Each time the participant reversed his/her preference (chose the SS reward in the previous block but chose the LL reward in the current block, or vice versa), the step size was reduced by 0.005. Once the step size reached an amount smaller than 0.005, subsequent preference reversals resulted in step sizes reductions of 0.001. We also set the lower and upper bounds for the LL amount to 50.1 and 200, respectively. The average percent of choices for the SS rewards was 42.4% (SD= 9.8%).

Payment for each session was based on the choice of a randomly selected trial in the ITC task. To control for the influence of different methods of payment (i.e. cash for immediate reward and bank-transfer for delayed reward), all payments were implemented via "Alipay", which is a popular smartphone money transaction app in China. Subjects knew that they would receive immediate payments within seconds after the experimental session ended and future payments on the date specified by the time delay. To rule out the influence of payments from preceding sessions on subsequent sessions, we actually withheld the payment for the preceding sessions until the end of third session if the payment was specified at 0 and 1 day delays for the first session or 0 day delay (e.g. immediate reward) for the second session. We debriefed our subjects at the end of third session and none were aware of such manipulation.

Procedure

Left and right dlPFC were localized using the 10/20 EEG system at F3 and F4. In Experiment 1, participants performed the ITC task while receiving three different types of stimulation across sessions using conventional tDCS: (1) left anodal/right cathodal tDCS (F3+F4−), (2) left cathodal/right anodal tDCS (F3–F4+), and (3) sham stimulation. The session order was counterbalanced across participants. To avoid carry-over effects of tDCS, different

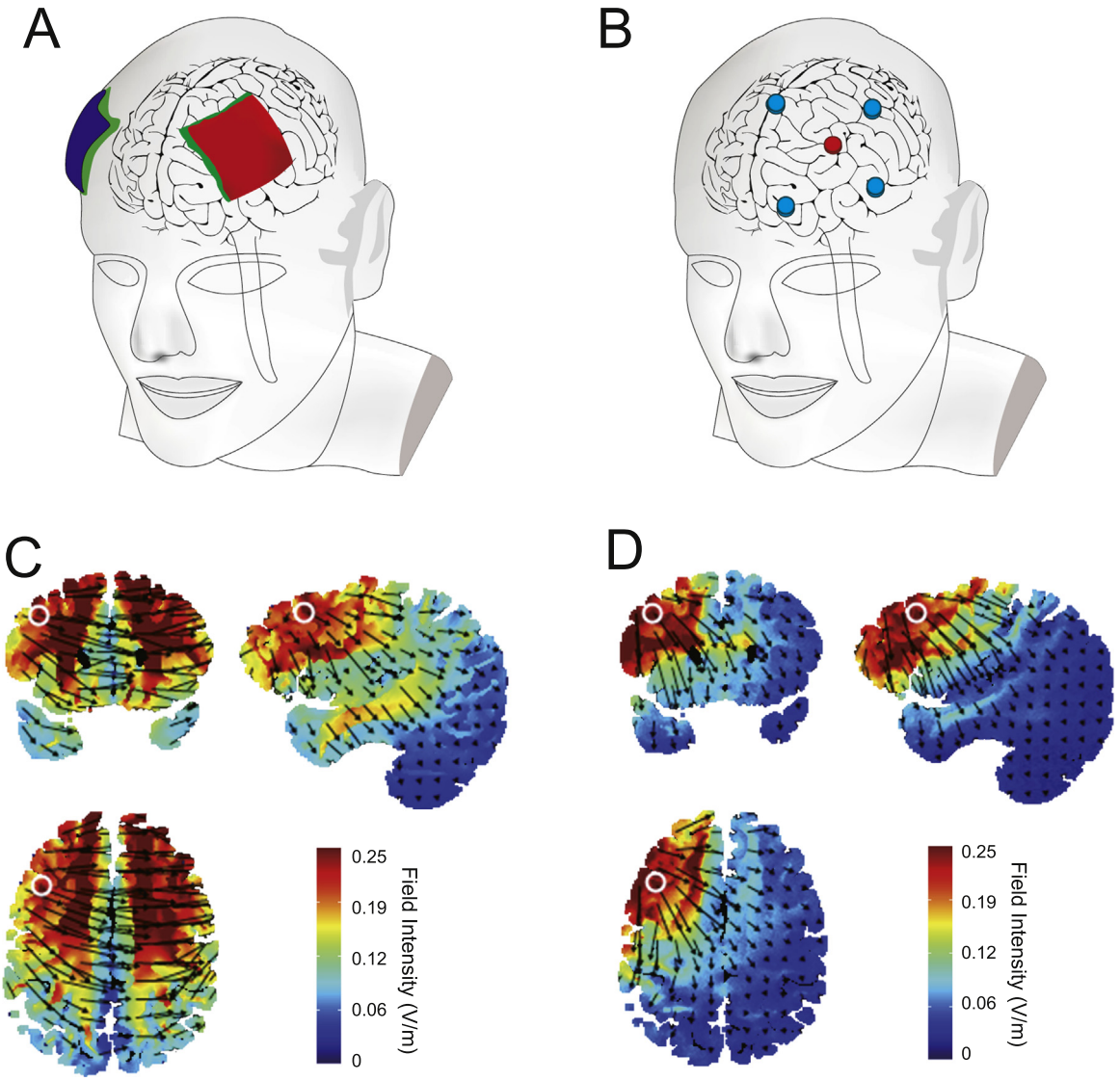

Fig. 2. tDCS protocols and electric field simulation. Schematic illustrations of conventional tDCS (a) and high-definition tDCS (b) electrode placements. Left and right dlPFC were localized using the 10/20 EEG system at F3 and F4, respectively. Electric field simulations were performed with the HD-explorer software (SoterixMedical, New York, USA). Simulated field intensity is indicated by the color bar. Arrows point in the direction of current flow, and the length indicates current flow intensity. Conventional tDCS (c) produces diffuse brain current flow. HD-tDCS (d) produces more focused current flow restricted within the ring of return electrodes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sessions were separated by one day (~24 h) for each participant (Nihonsugi et al., 2015).

HD-tDCS was used in Experiments 2A and 2B while participants completed the ITC task. There were three types of stimulation in Exp. 2A: (1) left anodal (F3+), (2) right anodal (F4+), and (3) sham stimulation. Stimulation in Exp. 2B reversed the central electrode polarity, resulting in (1) left cathodal (F3−), (2) right cathodal (F4−), and (3) sham stimulation. All other procedures for Exp. 2A and 2B were the same as in Exp. 1.

Conventional tDCS

Conventional tDCS was delivered with a battery-driven stimulator (SoterixMedical, Model 1300-A, New York) through a pair of electrodes housed in 5 × 7 cm saline-soaked sponge covers (Sarkis et al., 2014). Participants received three types of stimulation to dlPFC on different days: left anodal/right cathodal, left cathodal/right anodal, and sham stimulation. For left anodal/right cathodal stimulation, the center of the anode was placed over F3, and the center of the cathode was placed over F4 (F3+F4−); for left cathodal /right anodal stimulation, the center of the anode was placed over F4, and the center of the cathode was placed over F3 (F3−F4+; Fig. 2A). For active stimulation, participants received a constant current of 2.0 mA for ~20 min. Stimulation started 8 min before the task, and was delivered during the entire course of the task (~12 min) with an additional 30 s ramp-up at the beginning of stimulation and 30 s ramp-down at the end. Previous studies have shown that this intensity (0.057 mA/cm^2) and total charge (~0.0063 C/cm^2) are safe and well tolerated (Borckardt et al., 2012; Minhas et al., 2010; Villamar et al., 2013a). The placement of electrodes was the same for the sham and the active stimulation. However, for the sham stimulation, the initial 30 s ramp-up was immediately followed by the 30 s ramp-down, and there was no stimulation for the rest of the session (Douglas et al., 2015; Gandiga et al., 2006).

HD-tDCS

HD stimulation was delivered using a multi-channel stimulation adapter (SoterixMedical, 4 × 1-C3, New York) connected to the constant current stimulator used for conventional tDCS. Five Ag-AgCl sintered ring electrodes were held in plastic casings filled with conductive gel, embedded in an EEG cap, and attached to the adaptor device. Each electrode had ~4 cm^2 contact with the skull. The electrodes were arranged on the skull in a 4 × 1 ring configuration (Edwards et al., 2013; Villamar et al., 2013a). The return electrodes were spaced ~7.5 cm radially around the central electrode and at the corners of a square suggested by motor cortex HD-tDCS studies (Villamar et al., 2013a, 2013b). For left dlPFC stimulation, electrode locations corresponded roughly to C3, FT7, Fp1, and Fz, with the central electrode at F3 (Fig. 2B). For right dlPFC stimulation, the locations corresponded roughly to C4, FT8, Fp2, and Fz, with the central electrode at F4. The polarity of the current on the target brain area depended on the central electrode. We used central anodal stimulation for excitatory modulation, and central cathodal stimulation for inhibitory modulation suggested by motor cortex HD-tDCS studies (Filmer et al., 2014). The current intensity was 2.0 mA which created ~0.5 mA/cm^2 peak current density at the central electrode, and ~0.125 mA/cm^2 peak current density at the return electrodes. Procedures for active and sham HD-tDCS were the same as in conventional tDCS experiment. This procedure has been shown blindness effective for tDCS and HD-tDCS sham stimulation (Borckardt et al., 2012; Douglas et al., 2015; Gandiga et al., 2006; Gbadeyan et al., 2016; Heimrath et al., 2015; Nikolin et al., 2015). Though we did not explicitly solicit subjects' belief about whether each session was a sham or tDCS treatment session, no subject reported sensational difference among sessions in both conventional tDCS and HD-tDCS manipulations. HD-tDCS generates more focused stimulation than conventional tDCS, as shown in the simulated electrical fields (Caparelli-Daquer et al., 2012; Datta et al., 2009; Douglas et al., 2015; Kuo et al., 2013) (Fig. 2C and D). Although HD-tDCS is associated with stronger scalp sensations than conventional tDCS, it has been shown to be safe and tolerable with applications of up to 2.0 mA for 20 min (Borckardt et al., 2012; Kuo et al., 2013; Minhas et al., 2010). All the participants who participated in tDCS and HD-tDCS studies tolerated the stimulation well, and no adverse effects were reported.

Behavioral data analysis

Individual choice behavior was analyzed using the R statistical package (R Core Team, 2014) and Rstan (Stan Development Team, 2016). We used both model-free and model-based analyses to test for tDCS effects. For the model-free analysis, we estimated the indifference point at each delay by fitting a logistic function to the proportion of choices of the LL option as a function of the LL amount

$$logit\ P(chooseLL) = \beta_1\ LL\ amount + \beta_0$$

At this indifference point, we predicted subjects would choose the SS and LL option at the same frequency. This prediction also implies that LL rewards at the indifference point had the same SV as the SS option:

$$logit(0.5) = \beta_1 indifference\ point + \beta_0$$

Thus, we calculated indifference point according to parameters β_1 and β_0 that were fitted by the logistic curve:

$$indifference\ point = -\beta_0/\beta_1$$

Higher indifference points indicate greater impulsivity since they imply greater relative preference for SS rewards overall. We used a linear mixed model to fit parameters β_1 and β_0 ("lme4" package in R; Bates et al., 2014). For each experiment, LL amounts and participants' choices across the three experimental sessions were fed into one mixed model. The fixed effects of β_1 and β_0, and random effects of β_1 and β_0 at the subject and session levels were estimated separately for each time delay.

For the model-based analysis, we tested two influential models in temporal discounting literature: the standard hyperbolic model and the "as soon as possible" (ASAP) model (Kable and Glimcher, 2010; Mazur, 1987). For the model-based analysis in the immediate context, the ASAP model reduces to the standard hyperbolic model (Mazur, 1987), so we used the standard hyperbolic model discount factor to index each subject's impulsivity. The SV of the option with monetary amount A was assumed by the hyperbolic model

$$SV = \frac{A}{1 + kD}$$

where D is the delay of the option, A is the amount of the payment, and k is the subject-specific hyperbolic discount rate. A larger value of k indicates relatively greater impulsivity. For the delayed context, we tested the standard hyperbolic model with the ASAP model (Kable and Glimcher, 2010),

$$SV_{ASAP} = g(D_{ASAP})\frac{A}{1 + k_{ASAP}(D - D_{ASAP})}$$

where D_{ASAP} is the delay to the soonest currently available reward, $g(D_{ASAP})$ is a gain factor that is a function of delay to the soonest

available reward. In the ASAP model, SV declines hyperbolically relative to the soonest available reward, rather than with regard to the present. We compared the performance of these two models and found that the ASAP model captured subjects' behavior better at the group level (AIC for the ASAP model: 35503; AIC for the standard hyperbolic model: 35512). For the remainder of the text, we use the ASAP model to indicate subjects' impulsivity in the delayed context.

The discount rate k was fitted using the hierarchical Bayesian modeling package "hBayesDM" in R (Ahn et al., 2011, 2016). We assumed the logarithm of subjects' discount rates were drawn from a normal distribution: $\log(k) \sim N(\mu, \sigma)$ in each session. The probability of accepting the LL option was determined by the softmax function:

$$P(\text{choose LL}) = \left(1+e^{-b(SV_{LL}-SV_{SS})}\right)^{-1}$$

where SV_{SS} and SV_{LL} are the subjective value of the SS and LL options respectively, and b is a non-negative parameter representing the steepness of the psychometric function. Data for the immediate and delayed contexts were fitted separately.

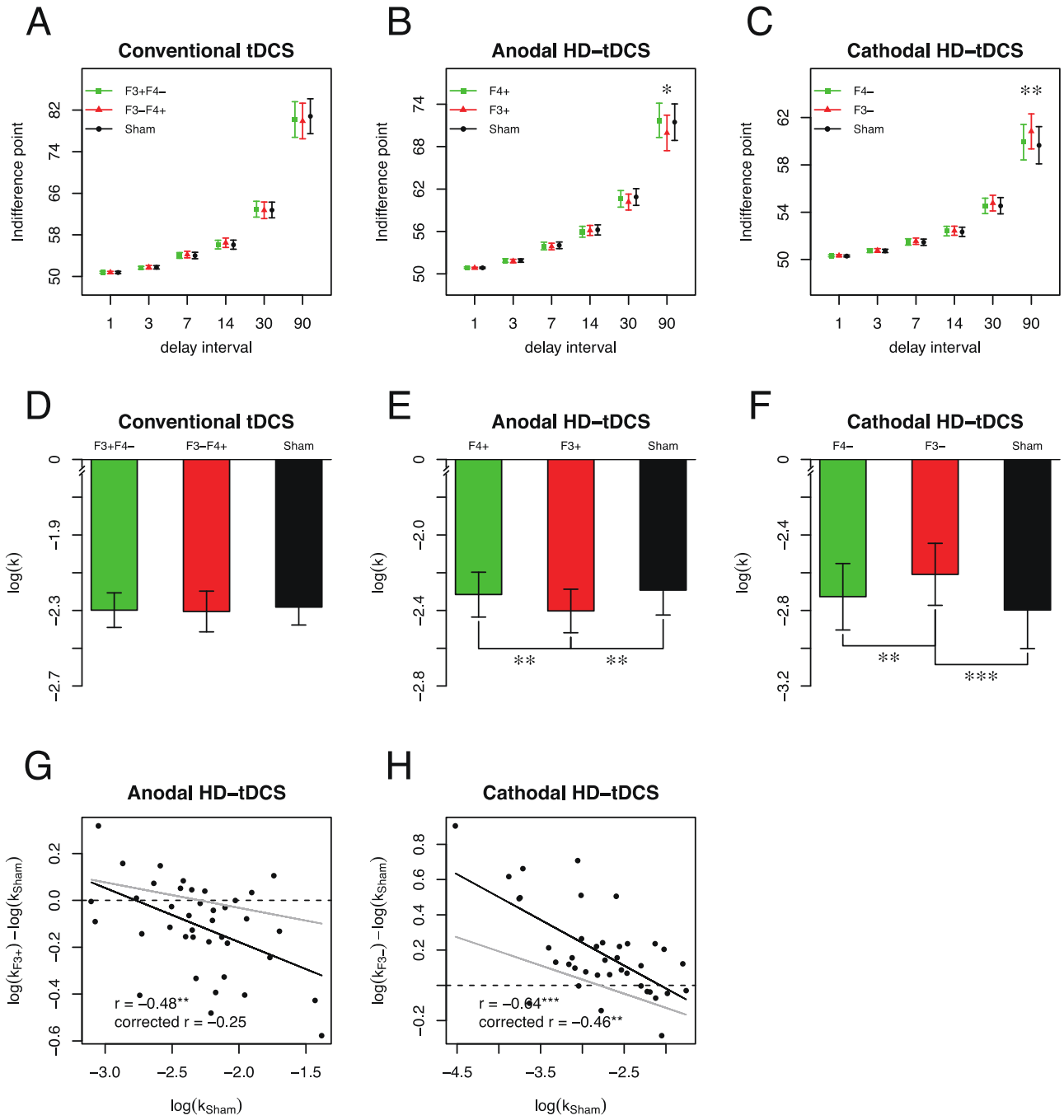

Fig. 3. Stimulation effects on indifference points and logarithm transformed discount rates ($\log(k)$) in the immediate context. (a,b,c) Stimulation effects on indifference points for conventional, anodal HD-tDCS and cathodal HD-tDCS. (d,e,f) Stimulation effects on $\log(k)$. (g,h) The effect of dlPFC HD-tDCS stimulation depends on baseline impulsivity. In both anodal and cathodal HD-tDCS manipulations, left dlPFC (F3) stimulation effects (difference between $\log(k)$ under F3 and sham stimulation) correlated with baseline impulsivity (black line). Gray lines were baseline dependent effects after correcting for regression to the mean effect. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < 0.001$; error bars represent 95% confidence intervals.

Results

Immediate context

Experiment 1. In the immediate context, choices were made between immediate and delayed rewards. In Exp. 1, we used conventional tDCS bilateral stimulation to test for the effects of F3+F4− and F3−F4+ in contrast to sham stimulation. We estimated each participant's indifference points and discount rates ($\log(k)$) in the F3+F4−, F3−F4+, and sham sessions. In the model-free analysis, we submitted subjects' indifference points to a repeated 2-way ANOVA analysis. The main effect of tDCS stimulation and stimulation by time delay interval interaction effect were not significant (Fig. 3A; main effect: $F_{(2,76)}=0.10$, $\eta^2=0.003$, $p=0.90$; interaction: $F_{(10,380)}=0.70$, $\eta^2=0.018$, $p=0.72$). For the model-based approach, we estimated each subject's delay discount rate k using the standard hyperbolic model described above. One-way ANOVA showed no differences across any of the stimulation type (Fig. 3D; $F_{(2,76)}=0.48$, $\eta^2=0.012$, $p=0.62$).

Experiment 2A and 2B. In Exp. 2A, all participants received anodal stimulation to left (F3+) dlPFC, right (F4+) dlPFC, and sham dlPFC stimulation across sessions via HD-tDCS. We compared the indifference points and the discount rates ($\log(k)$) across stimulation types. A two-way ANOVA analysis revealed a main effect of stimulation and an interaction between stimulation and delay interval on indifference points (Fig. 3B; main effect: $F_{(2,76)}=3.43$, $\eta^2=0.083$, $p=.038$; interaction: $F_{(10,380)}=4.04$, $\eta^2=0.096$, $p<.001$). A *post-hoc* one-way ANOVA at each time delay interval showed that the interaction was significant at the sixth delay interval (Fig. 3B; $F_{(2,76)}=5.77$, $\eta^2=0.13$, $p=.005$). Further paired *t*-tests at the sixth delay interval showed that F3+ produced lower indifferent points (i.e. greater patience) than sham and F4+ stimulations (Fig. 3B; F3+ versus sham: Δindifference point$=-1.52$, 95% CI$=[-2.64, -0.40]$, $t_{(38)}=-2.74$, $p=0.009$; F3+ versus F4+: Δ indifference point $=-1.78$, 95% CI$=[-3.04, -0.52]$, $t_{(38)}=-2.85$, $p=0.007$). There were no differences between F4+ and sham stimulations (Δ indifference point$=0.26$, 95% CI$=[-1.14, 1.66]$, $t_{(38)}=0.37$, $p=0.71$). Individual discount rates estimated using the model-based approach also showed that the discount rates ($\log(k)$) differed by stimulation type (Fig. 3E; $F_{(2,76)}=5.77$, $\eta^2=0.13$, $p=0.004$). *Post-hoc* paired *t*-tests showed that F3+ produced lower $\log(k)$ than sham and F4+ stimulations (F3+ versus sham: $\Delta\log(k)=-0.11$, 95% CI$=[-0.17, -0.047]$, $t_{(38)}=-3.54$, $p=0.001$; F3+ versus F4+: $\Delta\log(k)=-0.087$, 95% CI$=[-0.15, -0.023]$, $t_{(38)}=-2.77$, $p=0.009$), and there was no difference between F4+ and sham stimulations ($\Delta\log(k)=0.024$, 95% CI$=[-0.056, 0.10]$, $t_{(38)}=0.60$, $p=0.55$). The indifference points were only statistically different at later delays given variance in subjects' actual behavioral data at each delay. Indifference points simulated based on discount rates k and hyperbolic model also showed the same pattern (Fig. S1). Thus, both model-free and model-based model parameters revealed that HD-tDCS F3+ decreased impulsivity compared to sham and F4+.

In Exp. 2B, participants received cathodal stimulations to left (F3−) and right (F4−) dlPFC and sham stimulations across sessions via HD-tDCS. We performed a similar analysis as in Exp. 2A, and also found a main effect of stimulation and an interaction between stimulation and delay interval on indifference points (Fig. 3C; main effect: $F_{(2,76)}=3.73$, $\eta^2=0.089$, $p=.028$; interaction: $F_{(10,380)}=5.05$, $\eta^2=0.12$, $p<0.001$). This interaction effect, as shown by the post-hoc ANOVA analysis, was significant at the sixth delay interval (Fig. 3C; $F_{(2,76)}=6.26$, $\eta^2=0.14$, $p=0.003$). Paired *t*-tests showed that F3− produced a higher indifference points (e.g. reduced patience) than sham and F4− stimulations (Fig. 3C; F3− versus sham: Δindifference point$=1.18$, 95% CI$=[0.57, 1.78]$, $t_{(38)}=3.96$, $p<0.001$; F3− versus F4−: Δindifference point$=0.91$, 95% CI$=[0.21, 1.61]$, $t_{(38)}=2.65$, $p=0.01$). No difference between F4− and sham stimulations was observed (Δindifference point$=0.26$, 95% CI$=[-0.54,1.07]$, $t_{(38)}=0.66$, $p=0.51$). Hyperbolic discount rates were also different across stimulations (Fig. 3F; $F_{(2,76)}=8.36$, $\eta^2=0.18$, $p<0.001$). *Post-hoc* paired *t*-tests showed that F3− produced higher $\log(k)$ than sham and F4− stimulations (F3−versus sham: $\Delta\log(k)=0.19$, 95% CI$=[0.11, 0.27]$, $t_{(38)}=4.63$, $p<0.001$; F3− versus F4−: $\Delta\log(k)=0.12$, 95% CI$=[0.04, 0.19]$, $t_{(38)}=3.06$, $p=0.004$). There was no difference between F4− and sham stimulations ($\Delta\log(k)=0.07$, 95% CI$=[-0.05, 0.19]$, $t_{(38)}=1.21$, $p=0.23$). Similar to what we found in Experiment 2A, the indifference point and the discount rate analyses both demonstrated that HD-tDCS F3− increased impulsivity compared to sham and F4−.

Baseline-dependent effects

We reasoned that the effects of dlPFC tDCS may depend on the degree to which subjects engage dlPFC at baseline. Insofar as dlPFC activity correlates with delay discounting (Shamosh et al., 2008; van den Bos et al., 2014), the effect of tDCS should likewise correlates with subjects' baseline rate of delay discounting. To test for such an effect, we treated the $\log(k)$ value estimated during the sham condition ($\log(k)_{\text{sham}}$) as the baseline discount rates and then conducted a regression analysis to test for a relationship between baseline discounting and the impact of tDCS (i.e., the difference between $\log(k)$ estimated under left dlPFC (F3) stimulation and sham stimulation ($\log(k)_{F3}-\log(k)_{\text{sham}}$)). In Exp. 2A and Exp. 2B, the relative change $\log(k)_{F3}-\log(k)_{\text{sham}}$ was negatively correlated with the baseline discount rate $\log(k)_{\text{sham}}$ (black dots and black lines in Fig. 3G, H; Exp. 2A: $\beta=-0.23$, 95% CI$=[-0.37, -0.091]$, $p=0.002$; Exp. 2B: $\beta=-0.26$, 95% CI$=[-0.36, -0.16]$, $p<0.001$). To further differentiate the baseline-dependent effect from a potential confounding effect of regression to the mean, we first checked whether the variances of $\log(k)$ were different between F3 and sham tDCS. Different variances between measurements suggest differential effects on the group with initially low and high values beyond that expected from the regression effect (Galton, 1886; Hotelling and Secrist, 1933). In addition, we corrected for the regression to the mean effect in Exp. 2A and Exp. 2B by subtracting the variance that would be expected as a result of the regression to the mean effects (Kelly & Price, 2005). In Exp. 2B, variance of $\log(k)_{F3-}$ was significantly smaller than $\log(k)_{\text{sham}}$ ($t_{(37)}=3.49$, $p=0.001$; Pitman's (1939) test for the equality of variances in paired samples). As a comparison, variance of $\log(k)_{F4-}$ was not different from $\log(k)_{\text{sham}}$ ($t_{(37)}=1.62$, $p=0.13$). Regression between $\log(k)_{F3-}-\log(k)_{\text{sham}}$ and $\log(k)_{\text{sham}}$ but not between $\log(k)_{F4-}-\log(k)_{\text{sham}}$ and $\log(k)_{\text{sham}}$ survived after correction (F3−: gray line in Fig. 3H, $\beta=-0.16$, 95% CI$=[-0.26, -0.057]$, $p=0.003$; F4−: $\beta=-0.12$, 95% CI$=[-0.28, -0.048]$, $p=0.16$). However, in Exp. 2A, there was no variance difference between $\log(k)_{F3+}$ and $\log(k)_{\text{sham}}$ ($t_{(37)}=1.60$, $p=0.10$), or between $\log(k)_{F4+}$ and $\log(k)_{\text{sham}}$ ($t_{(37)}=1.07$, $p=0.29$). The corrected regression was not significant between $\log(k)_{F3+}-\log(k)_{\text{sham}}$ and $\log(k)_{\text{sham}}$ or between $\log(k)_{F4+}-\log(k)_{\text{sham}}$ and $\log(k)_{\text{sham}}$ (F3+: Fig. 3G, $\beta=-0.11$, 95% CI$=[-0.25, 0.03]$, $p=0.12$; F4+: $\beta=-0.080$, 95% CI$=[-0.26, 0.10]$, $p=0.37$). In summary, anodal and cathodal stimulation on the left dlPFC, but not the right dlPFC, were therefore causally related to the increase and decrease of the delay discount rate, respectively. Furthermore, the change of discount rate via F3 cathodal manipulation was correlated with subjects' baseline discount rate: subjects who were more patient in the sham session of ITC task were affected more by the cathodal stimulation (Fig. 3H).

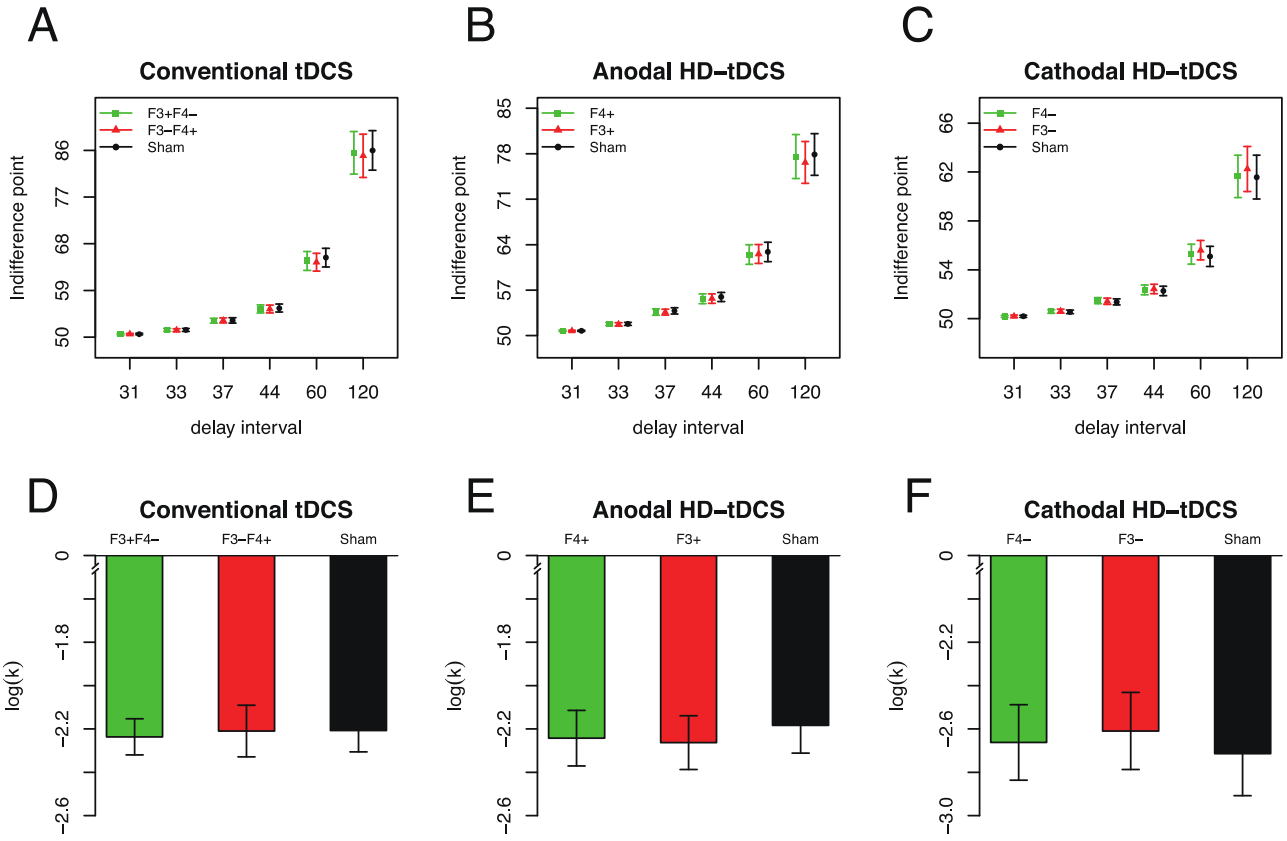

Fig. 4. tDCS stimulation effects on the indifference points and logarithm transformed discount rates (log(k)) in the delayed context. (a,b,c) treatment effects on the indifference points for conventional, anodal HD and cathodal HD tDCS respectively. In conventional tDCS (d), anodal HD-tDCS (e), or cathodal HD-tDCS (f) experiment, no significant treatment effect was detected on log(k). Error bars represent 95% confidence intervals.

Delayed context

Previous research using TMS suggests that dlPFC influences intertemporal decision-making only for choices involving immediate rewards (Figner et al., 2010). To systematically test for such an effect with tDCS, we included choice tasks under the delayed context in the experiments, in which both the SS and LL outcomes were delayed at least 30 days. We estimated each subject's indifference points at each delay interval, and we also estimated each participant's discount rate using the ASAP model (Kable and Glimcher, 2010) in the delayed context. Additionally, we compared subjects' indifference points and discount rates under different types of tDCS stimulations as we did for the immediate context. In the model-free indifference point testing, we did not find a main effect of stimulation or an interaction between stimulation and delay interval in Exp. 1, 2 A or 2B (Fig. 4A–C; main effect: $F_{(2,76)}=0.91$, $\eta^2=0.02$, $p=0.41$ (Exp. 1); $F_{(2,76)}=1.35$, $\eta^2=0.03$, $p=0.26$ (Exp. 2A); $F_{(2,76)}=2.60$, $\eta^2=0.06$, $p=0.08$ (Exp. 2B); interaction: $F_{(10,380)}=0.51$, $\eta^2=0.013$, $p=0.89$ (Exp. 1); $F_{(10,380)}=1.05$, $\eta^2=0.027$, $p=0.40$ (Exp. 2A); $F_{(10,380)}=1.72$, $\eta^2=0.043$, $p=0.07$ (Exp. 2B)). Differences of discount rates log(k) across stimulation types were not significant in Exp. 1 and 2A, or 2B (Fig. 4D–F; Exp. 1: $F_{(2,76)}=.70$, $\eta^2=0.018$, $p=0.50$; Exp. 2A: $F_{(2,76)}=2.72$, $\eta^2=0.067$, $p=0.072$; Exp. 2B: $F_{(2,76)}=2.86$, $\eta^2=0.070$, $p=0.063$). To compare tDCS effects under immediate and delayed contexts, we tested context and stimulation interactions on model-free and model-based parameters. A $2\times3\times6$ ANOVA (immediate & delay contexts, F3, F4 & sham stimulations, 6 time delay intervals) on indifference points showed no significant context and stimulation interaction in any experiment (Exp. 1: $p=0.88$; Exp. 2A: $p=0.88$; Exp. 2B: $p=0.98$). A 2×3 ANOVA on discount rates (log(k)) also failed to show significant difference of tDCS effect between immediate and delayed contexts (Exp. 1: $p=0.63$; Exp. 2A: $p=0.38$; Exp. 2B: $p=0.37$).

Discussion

We demonstrated that electric stimulation of left dlPFC causally influenced subject impulsivity for choices involving immediate rewards. We applied HD-tDCS while subjects completed an intertemporal choice task with both immediate and delayed contexts. Our findings were corroborated in three separate participant cohorts who underwent different types of stimulation (anodal, cathodal, and sham) across dlPFC sites (F3–F4, F3 only, and F4 only). In the immediate context, anodal HD-tDCS stimulation of left dlPFC reduced subjects' impulsivity while cathodal stimulation increased impulsivity. Furthermore, left dlPFC stimulation exerted its influence in a baseline-dependent manner, such that the effect of cathodal dlPFC stimulation was largest in subjects with low baseline discount rates (e.g. most patient, Fig. 3H).

Recent research in nonhuman primate electrophysiology and human neuroimaging studies suggests that brain valuation structures (vmPFC, ventral striatum, and posterior cingulate cortex) and brain areas involved in cognitive control and self-regulation (such as dlPFC) are critical to intertemporal decision-making processes (Ballard and Knutson, 2009; Cai et al., 2011; Kable and Glimcher, 2009; McClure, 2007; McClure et al., 2004; Peters and Buchel, 2009; van den Bos and McClure, 2013; van den Bos et al., 2014). Although the exact functional roles subserved by these brain regions are still under investigation, intact function of dlPFC is necessary for normal intertemporal decision-making (Kable and Glimcher, 2010; McClure, 2007; Sellitto et al., 2010; van den Bos and McClure, 2013; Wang et al., 2014). Recently, non-invasive TMS

and tDCS studies in humans have begun to unravel the causal link between dlPFC activity and intertemporal decision-making (Cho et al., 2010; Essex et al., 2012; Figner et al., 2010; Hecht et al., 2013; Kekic et al., 2014). However, results from these studies are mixed in terms of laterality of dlPFC function and the effects of different types of stimulation.

In the current study, we adopted a conventional tDCS protocol in Exp. 1, but we did not replicate the results of Hecht D *et al.,* (2013). This difference could potentially be explained by task design differences, such as self-adaptive versus fixed choice sets Current intensity should also considered when interpreting the ineffectiveness of our conventional tDCS experiment, which used a relatively large current intensity, 2 mA, compared to previous research, which used ~1 mA (Bogdanov et al., 2015; Hecht et al., 2013; Mengarelli et al., 2015). Recent evidence suggests that the enhancement of conventional tDCS current intensity does not necessarily increase the efficacy of stimulation, but instead it might shift the direction of excitability alterations (Batsikadze et al., 2013). Additionally, stimulation laterality in our conventional tDCS protocol, which stimulated both hemispheres with opposite polarity, may also contribute to the discrepancy between our current results and findings from previous tDCS research, in which unilateral stimulation was used (Fecteau et al., 2007; Mengarelli et al., 2015; Nihonsugi et al., 2015). To examine the effects of stimulation laterality, we thus conducted two additional studies (Exp. 2A and 2B) using high-definition unilateral stimulation in which the current stimulation was constrained within each hemisphere. This experimental design would also be expected to minimize the potential diffusive electric field created by conventional tDCS. Such a diffuse electrical effect may contaminate activity in vmPFC, a critical brain structure in evaluation and decision-making (Fig. 2C).

Results from Experiments 2A and 2B suggest the importance of left, but not right, dlPFC in intertemporal decision-making. These results help to resolve the debate over the laterality of dlPFC in intertemporal decision-making (Cho et al., 2010, 2012; Essex et al., 2012; Figner et al., 2010). Anodal and cathodal stimulation exhibited opposite modulation effect in the current study. As suggested by previous tDCS studies, anodal stimulation may excite activity of dlPFC thereby decreased the delay discounting impulsivity; cathodal stimulation may inhibit activity of dlPFC thereby increased the impulsivity (Filmer et al., 2014; Jacobson et al., 2012). However, we note that the task design did not allow us to delineate competing hypotheses as to whether dlPFC represents the value of delayed rewards or acts to suppress the temptation of immediate rewards (i.e., self-control; Hare et al., 2010; van den Bos and McClure, 2013). Future studies that combine functional imaging with HD-tDCS or TMS will be needed to investigate the functional consequences induced by modulating dlPFC activity on brain valuation structures such as vmPFC, ventral striatum, and posterior cingulate cortex.

In-depth investigation of subjects who received left dlPFC HD-tDCS stimulation revealed that the change of impulsivity levels depended on the individual subject's baseline impulsivity level. Participants with lower baseline discount rates (i.e. more patient) in ITC tasks were more affected by the cathodal HD-tDCS stimulation, which is suggested to inhibit neural activity, possibly due to floor effects (Fig. 3H). This baseline-dependent effect holds true even after correcting for regression to the mean (RTM), suggesting the efficacy of inhibiting left dlPFC is greater on more patient subjects who might have better self-control capability to start with (Hare et al., 2010; McClure et al., 2004). Due to the large individual variability in delay discounting impulsivity, previous research has adopted certain standards to filter out participants who deviate significantly from sample means (Essex et al., 2012; Peters and Buchel, 2009). This practice may limit the ability to detect the baseline-dependent correlation we identified.

The adaptive algorithm we used in the ITC task enabled us to characterize impulsivity across a wider range of discount rates than other approaches (hyperbolic k range from 3.0×10^{-5} to 0.076). Indeed, closer examination of our HD-anodal group showed a similar trend to the baseline-dependent effect (Fig. 3G). This effect was statistically insignificant, perhaps due to the low variance in baseline impulsivity levels (var.=0.17) compared to a more diverse distribution of impulsivity in the HD-cathodal group (var.=0.40). As our results indicate, subjects who were on the end of the impulsivity spectrum were the most influenced by the HD-tDCS stimulation. Particularly for studies with moderate to small sample sizes, this observed baseline dependence would be expected to produce the discrepancies that exist in the literature on brain stimulation and impulsivity change in ITC (e.g., Cho et al., 2012; Essex et al., 2012; Figner et al., 2010).

Interestingly, a recent study showed that the more automatic, model-free learning component was spared after a subject completed a cold pressor task (CPT) while the goal-directed, model-based learning component was dampened after induced stress, possibly mediated by working memory capacity (Otto et al., 2013). Taken together with our findings, these baseline-dependent studies might point to a general neural mechanism capable of accounting for vast individual variances in perception and valuation tasks (Otto et al., 2013; Weber et al., 2004). Previous imaging studies that focus on individual differences in delay discounting show that greater structural and functional connectivity between dlPFC and striatum is associated with increased patience (van den Bos et al., 2014), and that effective connectivity between dlPFC and vmPFC predicts between-subject differences in discount rates (Hare et al., 2014). Given that tDCS modulation can alter PFC activity and its connectivity with other subcortical regions (Weber et al., 2014), it is possible that the behavioral changes induced by HD-tDCS depend on the baseline activity of dlPFC and its connectivity with vmPFC and striatum.

Previous work has also shown that an individual's intertemporal choice behavior in the immediate and delayed contexts can be parsimoniously approximated by the ASAP model (Kable and Glimcher, 2010). Our choice data in the delayed context supports this idea. Model comparison showed that the ASAP model better accounted for our data than the standard hyperbolic model. We then specifically tested the ASAP model in our study. The manipulation of dlPFC activity via conventional or HD-tDCS did not have any significant impact on the ASAP discount rates or the model-free indifference points in the delayed context. While it still might be possible that the impulsivity change induced by tDCS and HD-tDCS was no different between immediate and delayed contexts (see Results), we stress that caution must be exerted while interpreting such null results. Discount rates in the conventional hyperbolic and ASAP models depict related yet different cognitive processes in the ITC task, thus rendering the direct comparison of discount rates between contexts less appropriate (Kable and Glimcher, 2010).

Though future research needs to be conducted about the role of dlPFC in ITC, the simplest interpretation given our data is that left dlPFC might be differentially involved in immediate and delayed contexts. Indeed, such an interpretation agrees with recent studies that examined the exact neural mechanisms at play in the immediate and delayed contexts; for example, subjective value representation of immediate and delayed rewards might be encoded in different brain areas (McClure et al., 2004; van den Bos and McClure, 2013). Excitation or inhibition of dlPFC may increase or decrease the SV of the delayed reward to a greater extent than the effects dlPFC modulation have on the immediate reward. However, in the delayed context, the SVs of the two delayed rewards may

change equivalently, resulting in invariant relative value differences and hence no change in preference. Another possibility is that dlPFC may carry out a self-control function that is not required for decisions involving two delayed rewards (Figner et al., 2010; Hare et al., 2010).

Conclusion

We provide direct evidence in establishing a causal link between HD-tDCS manipulated left dlPFC activity and significant behavioral change in intertemporal decision-making where immediate reward was involved. Anodal and cathodal HD-tDCS induced decreased and increased intertemporal discount rates, respectively. These mirroring effects depended on subjects' baseline impulsivity, such that participants with lower baseline impulsivity experienced greater relative change during left dlPFC inhibition. Our results might inform future neural models of ITC by providing a clear demonstration of the causal role of left dlPFC. The baseline dependent manner of the dlPFC manipulation effect also yields insight into why dlPFC manipulation biases behaviors in some cases but not in others (Otto et al., 2013; Weber et al., 2004).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2016.09.006.

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