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## Neuromodulation of risk and reward processing during decision making in individuals with general anxiety disorder (GAD)

Vahid Nejati<sup>1,2</sup>, Jamal Amani Rad<sup>3</sup> & Amir Hosein Hadian Rasanan<sup>4</sup>

Individuals with general anxiety disorder (GAD) have an impaired future-oriented processing and altered reward perception, which might involve the ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dIPFC). Twenty-nine adults with GAD performed the balloon analogue risk-taking task (BART) and delay discounting task (DDT) during five sessions of transcranial direct current stimulation (tDCS) with different stimulation conditions. The stimulation conditions were: anodal dIPFC (F3)/cathodal vmPFC (Fp2), anodal vmPFC (Fp2)/cathodal dIPFC (F3), anodal dIPFC (F3)/ cathodal right shoulder, anodal vmPFC (Fp2)/cathodal left shoulder, and sham stimulation. Cognitive modeling was used to extract process-based measures. The process-based modeling measures, rather than conventional outcome-based measures, showed a significant effect of stimulation condition. All real stimulation conditions improved the updating rate of prevalence, and risk taking in the BART. Moreover, for anodal dIPFC (F3)/cathodal vmPFC (Fp2), anodal vmPFC (Fp2)/cathodal dIPFC (F3), and anodal vmPFC (Fp2)/cathodal left shoulder stimulations we have observed an improvement in prior beliefs about the explosion. Also, for anodal dIPFC (F3)/cathodal vmPFC (Fp2), anodal dIPFC (F3)/cathodal right shoulder, anodal vmPFC (Fp2)/cathodal left shoulder we have observed more stable choice pattern. the DDT, exponential discounting rate and randomness were improved during anodal dIPFC and anodal vmPFC stimulation with extracranial return electrodes. Different roles of the targeted areas are discussed based on significant performance differences resulting from the specific electrode positions. The results suggest that different domains of reward processing are controlled by the vmPFC and dIPFC. The vmPFC is more relevant for value-based decision making with a positive expectation and chance-based randomness, whereas the dIPFC is more relevant for logic-based decision making.

**Keywords** General anxiety disorder (GAD), Ventromedial prefrontal cortex, Dorsolateral prefrontal cortex, Transcranial direct current stimulation, Reward processing, Risky decision making, Delay discounting

General anxiety disorder (GAD) is characterized by persistent, excessive, and unrealistic worry about a variety of events or activities, and is associated with restlessness, fatigue, irritability, muscle tension, and sleep disturbances<sup>1</sup>. GAD is a future-oriented emotional state characterized by worries about negative possibilities in the future<sup>2</sup>. Individuals with GAD cannot tolerate ambiguity and thus react negatively to uncertain information<sup>3,4</sup>. This increased uncertainty about the future in anxiety has been explained by several mechanisms: inflated estimates of threat cost and probability, hypervigilance to threat, deficient safety learning, behavioral and cognitive avoidance, and heightened reactivity to threat uncertainty<sup>2</sup>. This impairment reduces the subjective value of delayed or uncertain rewards and therefore impairs respective reward processing such as delay discounting and risky decision making.

Risky decision-making and delay discounting are two reward-based higher cognitive functions. Decisionmaking refers to the selection of the most beneficial choice from several alternatives with respect to its reward/ punishment aspects<sup>5</sup>. Delay discounting indicates the ability to postpone gratification and to prefer a larger later to a sooner smaller reward<sup>6</sup>. Both, risky decision-making and delay discounting require threat and reward

<sup>1</sup>Department of Psychology, Shahid Beheshti University Tehran, Tehran, Iran. <sup>2</sup>School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX, USA. <sup>3</sup>Choice Modelling Centre and Institute for Transport Studies, University of Leeds, Leeds, UK. <sup>4</sup>University of Basel, Basel, Switzerland. <sup>\Box</sup>email: nejati@sbu.ac.ir

processing. Relative anticipated reward and punishment have to be evaluated in both situations. For GAD, numerous studies described a steeper rate of discounting future rewards<sup>7,8</sup> and a biased decision making<sup>9-11</sup>.

The ventromedial prefrontal cortex (vmPFC) and the dorsolateral prefrontal cortex (dlPFC) are two main cortical structures in reward/punishment processing. Increased activity of the medial orbitofrontal cortex, as a subcomponent of the vmPFC, not only following receipt of reward, but also following successful avoidance of an aversive outcome has been shown in healthy individuals<sup>12</sup>. The vmPFC coordinates processes to minimize danger or threat and to maximize pleasure or reward<sup>13–15</sup>. Several functional neuroimaging studies describe a role of the vmPFC in reward-related computation, which depends on subjective values rather than objective properties of rewards<sup>16,17</sup>.

The dIPFC is involved in cognitive reappraisal for regulation of negative emotions<sup>18</sup>. The dIPFC coordinates an adaptive and contextually appropriate response to emotions via top-down regulation of the amygdala and ventral striatum<sup>19</sup>.

In individuals with GAD, reduced activity of the vmPFC leads to impaired safety-threat differentiation and reward-punishment perception<sup>20</sup>. The inability to discriminate reward from punishment and safety from threat makes the environment ambiguous and threatening for these individuals<sup>21</sup>.

Furthermore, neuroimaging studies described hypoactivity of the dlPFC<sup>22</sup> and the vmPFC<sup>20</sup> in GAD patients. In healthy individuals, the dlPFC decreases the experience of stress-related negative mood and anxiety and therefore regulates negative emotions<sup>18</sup> and the vmPFC reduces acute stress and facilitates reward processes<sup>23</sup>.

Non-invasive brain stimulation (NIBS) techniques provide an opportunity to modulate neural processes to study the causal contribution of neural structures to cognitive functions and behavior<sup>24</sup>. Main NIBS techniques include transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS). Transcranial direct current stimulation (tDCS), as a tES modality, alters neuronal resting membrane potentials via direct currents, and depending on the stimulation polarity, enhances or reduces excitability of the cortical target at a macroscale level<sup>25</sup>. tDCS over some minutes results in neuroplastic after-effects. The respective excitability and plasticity alterations induced by tDCS allow to alter various brain processes and cognitive functions via the modulation of cortical activity<sup>26,27</sup>.

The above-mentioned cortical areas involved in reward processing can be targeted with tDCS to study the specific roles of these areas in different domains of reward processing. Numerous tDCS studies described more conservative decision making and lower delay discounting during anodal stimulation over the dlPFC and the vmPFC<sup>28–35</sup>. In detail, some of these studies describe more conservative decision making with both anodal right/cathodal left dlPFC stimulation and reversed electrode positions<sup>28–30,35,36</sup>, anodal right/cathodal left dlPFC stimulation and reversed electrode positions<sup>28–30,35,36</sup>, anodal right/cathodal left dlPFC stimulation<sup>37–40</sup>, and anodal left dlPFC/cathodal right vmPFC stimulation<sup>33,34</sup>. However, one tDCS study applied cathodal or anodal tDCS over the left dlPFC in unipolar electrode arrangements, and report more risky decision making with anodal stimulation<sup>41</sup>. Another study used high definition-tDCS and found anodal left dlPFC with the reference electrodes over the AF3, F1, F5, FC3 and a reverse electrode position found that only cathodal left dlPFC reduced risk taking<sup>42</sup>. Finally , a tDCS study found a null effect of dlPFC stimulation on risky decision making in four stimulation conditions: right anodal/left cathodal, right cathodal/left anodal, and right or left anodal unipolar electrode arrangements<sup>43</sup>.

Decision making as a higher cognitive function is a multifactorial process with several subprocesses. Therefore, behavioral performance in standard laboratory decision tasks is the result of the interaction of several different underlying neurocognitive processes, including risk taking, risk aversion, reward and/or loss sensitivity, learning from past gains and losses, and/or erratic and impulsive choice processes<sup>44,45</sup>. The conventional approach to analyze behavioral performance does not allow us to break performance down into these underlying processes, nor does it even allow us to specifically identify the processes which have led to overall performance of a task<sup>46,47</sup>. The conventional approach to quantify performance of people in the balloon analogue risk task (BART) is to use the adjusted value (AV), the average number of pumps made by participants on unexploded balloons<sup>48</sup>, which correlates well with self-reported risky behaviors<sup>49</sup>. Cognitive modeling provides evidence for some latent neurocognitive processes determining decision making in this task, such as reward sensitivity and the ability to learn from positive/negative feedback, that are difficult to deduce directly from pure behavioral performance<sup>45,46,50</sup>. These latent parameters have been described at the neural levels. For instance, effective connectivity between the dorsolateral prefrontal cortex and ventromedial prefrontal cortex plays a critical role in predicting between-subject differences in the discount rate parameter<sup>51–53</sup>. Furthermore, given model-driven measurements, gamma as a measure BART, has a strong negative association with dIPFC activity and its effective structural connectivity to the vmPFC<sup>54-4</sup>

In sum, the conventional measures of risk taking and reward processing provide some information about the outcome of decision-making or delay discounting, but the behavior of the examinee during task performance while facing of reward and punishment as process-oriented measures remains elusive. During decision-making, moreover arousal or regret after gain or loss can direct the next selection.

To put in a nutshell, earlier accounts revealed the role of the dlPFC and the vmPFC in reward processing, the impaired reward processing in GAD, an altered activity of the dlPFC and the vmPFC in GAD, and the possibility of alteration of the vmPFC and the dlPFC activity with tDCS. Furthermore, cognitive modeling measures provide some processes-based measures that may be more informative compared to conventional outcome-oriented measures to investigation of decision making.

In the present study, we aimed to evaluate the role the dlPFC and the vmPFC in the process of risky decision making and delay discounting in individuals with anxiety. We aimed to evaluate the role of each area through excitation of one coupled with inhibition of the other compared to simultaneous stimulation of both areas and sham stimulation.

#### Materials and methods Participants

Twenty-nine individuals with GAD participated in the study. Eleven participants were not included in the data analysis because of at least one missing session. The 18 remaining participants had an age range between 20 and 40, mean  $20.35 \pm 6.83$ .

We used G\*Power<sup>58</sup> to determine the required sample size. Based on a power of 0.80, an alpha level of 0.05, and a large effect size (f=0.68) derived from tDCS effects on executive functions in anxiety obtained in our previous study<sup>59</sup>, the required sample size for the primary statistical test in this study was 17. All participants were diagnosed with GAD by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders 5th ed.<sup>60</sup>. The state-trait anxiety inventory was used to rate and confirm the diagnosis. Table 1 presents the demographic parameters of the participants in detail. Exclusion criteria were presence or history of psychiatric and/or neurologic comorbidities based on medical records and psychiatric interview. Participants were medication-naïve, non-smokers, right-handed, and had normal or corrected-to-normal vision. The procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. The study was approved by the ethical committee of Shahid Beheshti University.

#### The state-trait anxiety inventory (STAI)

The STAI is a 40-item inventory which consists of two parts, concerning trait and state anxiety<sup>61</sup>. Items are scored on a four-point Likert scale from one (not at all) to four (very much so). In the Persian version of the STAI, the Cronbach's alpha for internal consistency is 0.886 for trait anxiety and 0.846 for state anxiety. Retest-reliability is 0.765 for trait anxiety and 0.62 for state anxiety<sup>62</sup>.

#### Balloon analogue risk task (BART)

This computerized task is a measure of risky decision making<sup>48</sup>. It requires decision making under risk and reward/punishment anticipations<sup>63</sup>. Participants are instructed to pump up a balloon shown on a computer screen through pressing a button. Each button press increases the balloon size and a virtual monetary reward, 1000 RLS in the present study, appears on the balloon. Pumping can continue until explosion of the balloon. If the balloon explodes, the earned money shown on the balloon is lost. The explosion can occur at any size, but larger balloons are associated with a greater risk of explosion because of the balloon bursting probability which is  $p^{burst} = \frac{1}{128 - n^{pumps}}$ , where  $n^{pumps}$  is the number of pumps in the trial. Participants can choose during the

trial to press a button to "collect money", or to continue to pump. If they choose to collect the money, the earned money shown on the balloon is transferred to a permanent box and the next balloon appears. The task consists of 30 trials and takes about 5 min to perform. The conventional measures of this task are: (a) adjusted value (AV), the number of pumps of balloons which did not explode, and (b) the number of successfully pumped balloons (SPB). In addition to the conventional measures, the results of estimating the parameters of the four-parameter cognitive model fitted to the data are also reported here.

#### Delay discounting task (DDT)

The DDT is a monetary reward task that provides a choice between a small immediate, or large delayed reward. In this task, two choices are presented to the participant to choose, an immediate reward ( $V_i$ , Now) and a later larger reward ( $A_i$ , After  $D_i$ ). The main variable of this test is rate of discounting (K) which is calculated by the function Ki = (Ai-Vi)/Di.<sup>6</sup>. In the current study, eight V (102, 105, 125, 300, 700, 1350, 3000, 6500 KRLS) were presented with eight D (1 day, 1 week, 2 months, 6 months, 1 year, 5 years), randomly in 64 trials. The Ks as the main variable were calculated separately for each situation and the mean of Ks was calculated as K mean. Performing this task took about 5 min for our participants.

#### tDCS protocol

The ActivaDose transcranial stimulator (ActivaTek Inc., USA) was used for brain stimulation. An electrical direct current of 1.5 mA generated by the stimulator was applied through a pair of saline-soaked sponge electrodes with a size of  $25 \text{ cm}^2$  ( $5 \times 5$ ) for 20 min. The stimulation was applied in five separate sessions with one week interval. The electrodes were placed according to the 10–20 EEG international system. The stimulation conditions were: (a) anodal dlPFC (F3)/cathodal vmPFC (Fp2), (b) anodal vmPFC (Fp2)/cathodal dlPFC (F3), (c) anodal dlPFC (F3)/cathodal right shoulder, (d) anodal vmPFC (Fp2)/cathodal left shoulder, and (e) a sham stimulation condition with one of the above-mentioned electrode placements randomly chosen. For sham

Variables	M(sd)/description
Age (Years)	28.22 (8.29)
Education (Years*)	12.66 (4.14)
STAI—State	58.94 (10.01)
STAI—Trait	59.00 (11.76)
Gender (Female: Male)	11:7

**Table1**. Demographic characteristics of participants. Abbreviation: M, mean; sd, standard deviation; STAI,state-trait anxiety inventory; \*Number of formal academic years of education

stimulation, the electrical current was ramped up for 30 s to generate the same sensation as the active condition, and then turned off without participants' awareness<sup>64</sup>.

#### Procedure

This study had a single-blinded and crossover design. After participant selection and explanation of the procedure, participants signed a written informed consent form, and then the examiner explained the task instructions. The stimulation sessions were performed in a quiet room in a psychology clinic with a week ( $\pm 10$  h) interval to prevent carry-over effects. The order of stimulation and tasks was randomized across participants based on a randomization list. The participants were blinded to the stimulation condition. Five minutes after the beginning of stimulation, participants performed BART and DDT, which lasted for about 15 min. Both, tDCS and behavioral task instruction and supervision were performed by one researcher/author (S.K.). After each stimulation session, a side-effect checklist was completed<sup>65</sup>, and the participants guessed the type of the stimulation (real or sham).

#### Cognitive modeling

#### Four-parameter model for BART

In the four-parameter model<sup>66</sup>, two major assumptions are made about the behavior of the participants during BART performance. The first one is that the participants learn at each trial and then update the belief about the probability of the balloon bursting. The second assumption is that the participants decide about the optimal number of pumps before the onset of the trial. In this model the assumption is that the participants start with a prior belief about bursting of the balloon and update their belief at each trial based on the feedback received. The updating rule for this model which is constant during the trial k is as follow<sup>66,67</sup>:

$$p_k^{\mathrm{burst}} = 1 - \frac{\varphi + \eta {\sum_{i=0}^{k-1}} n_i^{\mathrm{success}}}{1 + \eta {\sum_{i=0}^{k-1}} n_i^{\mathrm{pumps}}} 0 < \varphi < 1, 0 < \eta,$$

where  $p_k^{\rm burst}$  shows the perceived probability that pumping the balloon in trial k will make the balloon explode,  $n_i^{\rm success}$  shows the number of successful pumps at i-th trial, which is equal to zero if the balloon explodes at the trial, and  $n_i^{\rm pumps}$  shows the number of pumps at the i-th trial. In the first trial  $\sum_{i=0}^{k-1}n_i^{\rm success}$  and  $\sum_{i=0}^{k-1}n_i^{\rm pumps}$  are equal to zero, and  $p_k^{\rm burst} = 1 - \varphi$ , therefore,  $\varphi$ , shows the prior belief of balloon explosion, and  $\eta$  is the belief updating rate from the feedback received. To be more precise, it can be said that the very smallness (the very largeness) of this parameter actually close to zero makes p-burst unaffected (to be strongly affected) by the feedback received from that trial, so that in the case of this parameter is very large, it can be seen that p-burst is fast approaching the observed probability of the explosion.

For the purpose of calculating the optimal number of pumps before each trial (i.e. the second assumption), the expected utility after pumps in trial k, can be obtained by  $^{66,67}$ :

$$U_{kl} = \left(1 - p_k^{\text{burst}}\right)^l (lr)^{\gamma},$$

in which r shows the amount of reward per successful pump and  $\gamma$  stands for risk-taking propensity. The optimal number of pumps can be calculated by finding the root of the first derivative of  $U_{\rm kl}$  with respect to  $\,$ . So, the optimal number of pumps in trial k which is denoted by  $v_{\rm k}$  can be computed as follows  $^{66,67}$ :

$$v_k = \frac{-\gamma}{\ln(1-p_k^{\rm burst})}, \gamma \ge 0.$$

Now for obtaining the probability of pumping the balloon in trial k for pump that is denoted by  $p_{kl}^{pump}$ , the optimal number of pumps  $v_k$  should be compared with the number of pumps as follows<sup>66,67</sup>:

$$p_{kl}^{\mathrm{pump}} = \frac{1}{1+\mathrm{e}^{\tau(l-v_k)}}, \tau \geq 0,$$

where  $\tau$  is the inverse temperature parameter which determines how deterministic (more consistent) or random the choice probability is; Lower values for  $\tau$  make the choice rule more deterministic.

For a simple overview of the parameters of this model, the free parameters of the revised four-parameter model and their implications are summarized in the Table  $2^{66,67}$ .

Now the only other important step left is to calculate the likelihood function to establish a bridge between the model and the observed data and to fit the model so that the parameters can be estimated and then interpreted. For this model, the probability of the data given the parameters,  $p(D|\phi, \eta, \gamma, \tau)$ , is given by:

$$p(D|\phi,\eta,\gamma,\tau) = \prod_{k=1}^{30} \prod_{l=1}^{l_k^{last}} \mathbf{p}_{kl}^{\mathrm{pump}} (1 - \mathbf{p}_{k,l_k^{last}+1}^{\mathrm{pump}})^{d_k},$$

Free parameter	Name	Interval	Cognitive interpretation
$\Phi(\text{Phi})$	Prior belief	[0, 1]	This parameter shows the initial belief of a participant that the balloon will not explode, it is a probability value
$\eta({\rm Eta})$	Updating	$[0, +\infty)$	$\eta \rightarrow 0$ : The subjective probability of bursting is affected by observation, no learning takes place $\eta \rightarrow +\infty$ : The participant learns quickly and the subjective probability of bursting tends to the observed probability of burst quickly
$\gamma(\text{Gamma})$	Risk taking	$[0, +\infty)$	$\gamma \to 0$ : The participant is very conservative $\gamma \to +\infty$ : The participant prefers a risky strategy
$\tau({\rm Tau})$	Inverse temperature	$[0, +\infty)$	$\tau \rightarrow 0$ : the participant behaves randomly $\tau \rightarrow +\infty$ : the participant behaves deterministically

Table 2. The parameters of four-parameter.

where  $l_k^{last}$  is the last number of pumping opportunities on trial k. Also here  $d_k$  can be one or zero, more precisely we can say that  $d_k$  on trial k will be equal to one if the subject decides to collect the money and transfer the money to the permanent box, and on the other hand  $d_k$  will be equal to zero if the balloon bursts in trial k.

#### Constant-sensitivity (CS) model for DD

Based on the utility-based approach, our present subjective reward value S(R, D) of an objective reward R at a given delay D, for an individual whose discounting rate is r (r > 0), is given by

$$S(R,D) = U(R) \cdot F(D),$$

where U(R) is a real-valued utility function relating objective rewards R to subjective values, which has similar properties as the utility function of prospect theory (Kahneman and Tversky 1979; Tversky and Kahneman 1992). However, the usual approach in the discount literature is to consider the subjective value function as linear by assuming the identity function for U(R), i.e. U(R) = R in which case U(R) is in units of Rials, Dollars, Pounds, Euros, etc. We also follow this approach in this research. To explain the discounting effect, the constant-sensitivity model (Ebert, Prelec, & Prelec, 2007) assumed that the discount function F(D) is a generalized exponential of subjective time,

$$F(D) = \exp\left(-(sD)^r\right),$$

where s(s > 0) is the impatience parameter that defines the boundary between the near (i.e. times shorter than 1/r) and far (i.e. times greater than 1/r) future. To be more precise, an immediate discounting of value in an individual is equivalent to having a greater impatience parameter. As we said before, in the DD task, two options are presented to the participant to choose from, an immediate reward (i.e. a smaller-sooner reward, let's denote it by SS) and a later larger reward (i.e. a later-lager reward, let's denote it by LL). In addition to the fact that the subject values of the two options are modeled with the exponential function mentioned above, a Sigmoid function is used to translate subjective values into the choice probability on trial t:

$$P(chooseLL) = \frac{1}{1 + \exp\left(-\beta \left[S_{LL(t)} - S_{SS(t)}\right]\right)}$$

where  $S_{SS(t)}$  and  $S_{LL(t)}$  are subjective values of the SS and LL options on trial t, and  $\beta$  is the inverse temperature parameter, which means that the higher values of  $\beta$  make the options appear more distinct, resulting in a more consistent choice, and lower values make the option more similar for the subject, leading the probability of selection to 0.5.

For a simple overview of the parameters of this model, the free parameters of the CS model and their implications are summarized in Table 3.

Similar to the BART modeling procedure, a maximum likelihood process is utilized for fitting this model on behavioral data and then the best fitted parameters for each individual are included in the further analysis.

#### Model fitting

To fit the models, we employed the hBayesDM package in Python. This package is developed based on Stan and utilizes a Monte Carlo Markov Chain (MCMC) technique to estimate the parameters. For each model, we ran four chains, with 1,000 warmup iterations and 1,000 sampling iterations per chain. To check the convergence of the chains, we used the Gelman-Rubin convergence diagnostic index ( $\hat{r} < 1.01$ ).

#### Data analysis

This study had a single-blind, complete crossover design. Data analyses were conducted using the statistical package SPSS for Windows, version 21. To explore the effect of tDCS on task performance, repeated measures one-factorial analyses of variance (ANOVA) were conducted for the within subject factor "Stimulation condition", 3 different conditions. Dependent variables, with respect to BART were the conventional measures

Free parameter	Name	Interval	Cognitive interpretation
r	Exponential discounting rate	$[0, +\infty)$	A higher r will result in more choices in favor of the smaller, sooner option because of the greater impact of the delay in the later option
s	Impatience	$[0, +\infty)$	Defines the boundary between the near (i.e. times shorter than $1/r$ ) and far (i.e. times greater than $1/r$ ) future
Beta	Inverse temperature	$[0, +\infty)$	$\tau \rightarrow 0$ : the participant behaves randomly $\tau \rightarrow +\infty$ : the participant behaves deterministically

#### Table 3. The parameters of constant sensitivity model.

	Conditions, M(SD)					Statistics			
Measures	dl/vm	vm/dl	dl/EC	vm/EC	Sham	df	F	Р	η <b>p</b> 2
Pain	0.21 (0.53)	0.26 (0.73)	0.21 (0.42)	0.52 (1.17)	0 (0)	4,72	1.95	0.112	0.098
Confusion	0.10 (0.31)	0.10 (0.31)	0.31 (1)	0 (0)	0.05(0.23)	4,72	1.04	0.391	0.055
Burning	1.74(1.15)	2.47(1.7)	2.26(1.24)	1.74(1.28)	0.89(0.57)	4,72	9.40	< 0.001	0.715
Itching	0.47(0.70)	0.79(1.44)	1.16(1.77)	0.42 (1.22)	0.05 (0.23)	4,72	2.33	0.103	0.383
Fatigue	0.32 (0.58)	0.16 (0.50)	0.47 (0.90)	0.37 (0.89)	0.05 (0.23)	4,72	1.32	0.308	0.260
Vertigo	0.58 (1.21)	0.37 (0.83)	0.42 (1.12)	0.63 (1.26)	0 (0)	4,72	1.92	0.159	0.339
Nausea	0.32 (1.16)	0.32 (0.94)	0.10 (0.31)	0.16 (0.50)	0 (0)	4,72	1.30	0.314	0.258

**Table 4**. Side effects of tDCS (means and sd) in the different stimulation conditions and the results of the respective ANOVAs are shown. Abbreviations: M, mean; SD, standard deviation; vm, ventromedial prefrontal cortex; dl, dorsolateral prefrontal cortex; EC, extracranial areas pre and post the dash indicate anodal and cathodal electrode placement respectively; df, degree of freedom; F, F-value; P, P-value; np2, partial eta squared

(AV, SPB) and the measures extracted from cognitive modeling BART (Phi, Eta, Gamma, Tau). With respect to DDT, conventional measures were Ks in different situations and cognitive modeling measures (R, S,  $\beta$ ). Mauchly, Levene, and Fisher's Least Significant Difference (LSD) tests were used for evaluation of Sphericity, normality and homogeneity of variance of the data, and Post hoc analyses. The degrees of freedom were corrected using the Greenhouse–Geisser method, if required. Session order and task order were integrated as covariates in an additional ANCOVA. A significance level of p < 0.05 was used for all statistical comparisons.

#### Results

All participants tolerated the stimulation without major side effects, except one who was excluded after the first session because of severe headache. Participants reported some degree of mild and tolerable itching, tingling and burning sensations under the electrodes during approximately the first 30 s of stimulation in each tDCS condition. Table 4 present means and standard deviations of side effects in different stimulation conditions. One-way ANOVAs showed no differences between conditions in pain ( $F_{4,72}=1.95$ , p=0.112,  $np^2=0.098$ ), confusion ( $F_{4,72}=1.04$ , p=0.391,  $np^2=0.098$ ), itching ( $F_{4,72}=2.33$ , p=0.103,  $np^2=0.383$ ), fatigue ( $F_{4,72}=1.32$ , p=0.308,  $np^2=0.260$ ), vertigo ( $F_{4,72}=1.92$ , p=0.159,  $np^2=0.339$ ) and nausea ( $F_{4,72}=1.30$ , p=0.314,  $np^2=258$ ), but significant differences in burning ( $F_{4,72}=9.40$ , p<0.001,  $np^2=0.715$ ). The LSD post hoc analysis showed fewer burning sensations in the sham, as compared to anodal vmPFC/cathodal dlPFC (mean difference (MD)=0.85, p<0.001), anodal dlPFC/cathodal vmPFC (MD=1.58, p<0.001), anodal dlPFC with extracranial cathodal electrode (MD=1.37, p<0.001), and anodal vmPFC with extracranial cathodal electrode (MD=0.85, p<0.001).

In the conventional outcome measures of the BART, the repeated measure ANOVA showed a non-significant main effect of stimulation for AV ( $F_{4,68} = 1.015$ , p = 0.406,  $\eta p^2 = 0.056$ ), PN ( $F_{4,68} = 1.52$ , p = 0.204,  $\eta p^2 = 0.082$ ), and also the value of Win ( $F_{4,68} = 0.541$ , p = 0.706,  $\eta p^2 = 0.031$ ), Figs. 1 and 2.

The analysis of the four-parameter modeling measures shows a significant difference between conditions with respect to prior beliefs about explosion (Phi) ( $F_{4,68} = 9764.310$ , p < 0.001,  $\eta p^2 = 0.998$ ), updating rate of prevalence (Eta) ( $F_{4,68} = 278.379$ , p < 0.001,  $\eta p^2 = 0.942$ ), risk taking (Gamma) ( $F_{4,68} = 2468.609$ , p < 0.001,  $\eta p^2 = 0.993$ ), as well as consistency (Tau) ( $F_{4,68} = 2497.289$ , p < 0.0001,  $\eta p^2 = 0.993$ ).

The LSD post hoc analysis revealed larger Phi during anodal vmPFC/cathodal dlPFC compared to anodal dlPFC/cathodal vmPFC stimulation (MD = 0.005, p < 0.001), larger Phi during anodal vmPFC stimulation with an extracranial return electrode (MD = 0.011, p < 0.001), and a larger Phi during anodal dlPFC stimulation with an extracranial return electrode (MD = 0.016, p < 0.001) and sham stimulation (MD = 0.011, p < 0.001). Also, the Phi during anodal vmPFC stimulation with an extracranial cathodal electrode was larger compared to anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.001), and sham (MD = 0.0004, p < 0.001). The Phi during sham stimulation was larger than anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.005, p < 0.001). Finally, Phi during anodal dlPFC/cathodal vmPFC stimulation was greater compared to anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.001, p < 0.001), and the anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.011, p < 0.001), and the anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.001), and the anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and sham stimulation (MD = 0.006, p < 0.001), Table 5.

For the Eta, the analysis showed significant main effects of stimulation ( $F_{4.68} = 278.379, p < 0.001, \eta p^2 = 0.942$ ) The LSD post hoc tests between stimulation conditions revealed a greater Eta during anodal dlPFC/cathodal







**Fig. 2.** DDT modeling parameters in different stimulation conditions. The point in the violin plot represents the median of the parameters, while the line indicates the 95% confidence interval. The width of the violin plot reflects the data distribution. Abbreviation: vm: ventromedial prefrontal cortex, dl: dorsolateral prefrontal cortex, EC: extracranial; areas pre and post the dash indicate anodal and cathodal electrode placement respectively. r = exponential discounting rate, s = impatience, Beta = inverse temperature, \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

Tests Measures	Sham M(sd)	dl/vm M(sd)	vm/dl M(sd)	dl/EC M(sd)	vm/EC M(sd)	df	F	Р	ηp <sup>2</sup>	
BART										
AV	30.66 (14.37)	31.76 (13.28)	34.30 (14.37)	29.20 (13.32)	33.49 (12.06)	4, 68	1.015	0.406	0.056	
PN	7.61 (3.94)	7.72 (3.79)	9.06 (4.11)	7.44 (3.78)	8.83 (2.79)	4, 68	1.52	0.204	0.082	
Earning	643,777.78 (237,922.27)	670,333.33 (218,202.01)	675,611.11 (229,590.20)	618,555.56 (210,144.83)	683,833.33 (195,831.94)	4,68	0.541	0.706	0.031	
Phi	0.969644 (0.000359)	0.975784 (0.000324)	0.980714 (0.000178)	0.965133 (0.000253)	0.970065 (0.000209)	4, 68	9764.310	< 0.0001	0.998	
Eta	0.000246 (0.000009)	0.000348 (0.000016)	0.000266 (0.000013)	0.000322 (0.000006)	0.000342 (0.000012)	4, 68	278.379	< 0.0001	0.942	
Gamma	6.814968 (0.091524)	5.232667 (0.078822)	5.011340 (0.052037)	5.889310 (0.046625)	5.949460 (0.037086)	4, 68	2468.609	< 0.0001	0.993	
Tau	0.024359 (0.000472)	0.025894 (0.000478)	0.020765 (0.000292)	0.032531 (0.000425)	0.026710 (0.000167)	4, 68	2497.289	< 0.0001	0.993	
DDT										
К	-0.226 (0.573)	0.243 (2.344)	-0.233 (0.483)	-0.039 (1.128)	-0.206 (0.831)	4, 72	0.613	0.654	0.033	
s	0.462 (0.201)	0.430 (0.148)	0.524 (0.212)	0.529 (0.207)	0.397 (0.145)	4, 72	7.031	< 0.001	0.281	
R	0.236 (0.206)	0.184 (0.163)	0.186 (0.180)	0.148 (0.191)	0.195 (0.169)	4, 72	8.909	< 0.001	0.331	
Beta	0.329 (0.210)	0.300 (0.226)	0.414 (0.331)	0.393 (0.292)	0.454 (0.249)	4, 72	7.881	< 0.001	0.305	

**Table 5**. Mean and standard deviation of measures and results of the ANOVA. Abbreviations: M, mean; SD, standard deviation; vm, ventromedial prefrontal cortex; dl, dorsolateral prefrontal cortex; ec, extracranial, areas pre and post the dash indicate anodal and cathodal electrode placement respectively; df, degrees of freedom; F, F-value; P, P-value; np2, partial eta squared

vmPFC stimulation compared to anodal vmPFC/cathodal dlPFC stimulation (MD=0.0001, p < 0.001) and the anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.00003, p < 0.001), but not anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.00001, p = 0.26). The Eta during anodal dlPFC/cathodal vmPFC stimulation was greater than sham stimulation (MD=0.0001, p < 0.001). The Eta during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001). The Eta during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001) and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001) was greater than anodal vmPFC/cathodal dlPFC stimulation. The Eta during anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001). Finally, Eta during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001). Finally, Eta during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001). Finally, Eta during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001) and anodal vmPFC/cathodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.0001, p < 0.001).

For the Gamma, the ANOVA analysis showed a significant main effect of stimulation ( $F_{4,68}$ =2468.609, p < 0.001,  $pp^2$ =0.993). The LSD post hoc comparisons between stimulation conditions revealed a greater Gamma during anodal dlPFC/cathodal vmPFC stimulation compared to anodal vmPFC/cathodal dlPFC stimulation (MD=0.221, p < 0.001). Also, the Gamma during anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.938, p < 0.001) and anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.878, p < 0.001) and sham stimulation (MD=1.804, p < 0.001) was grater compared to anodal vmPFC/cathodal dlPFC stimulation.

The Gamma during anodal vmPFC stimulation coupled with an extracranial cathodal electrode was grater compared to anodal dlPFC/cathodal vmPFC stimulation (MD=0.717, p < 0.001) and anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.06, p < 0.05). The Gamma during anodal dlPFC stimulation (MD=1.58, p < 0.001) was greater than anodal dlPFC/cathodal vmPFC stimulation. Finally, the Gamma during sham stimulation was larger than anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.926, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.926, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.866, p < 0.001).

For Tau, the analysis showed significant main effects of stimulation ( $F_{4,68} = 2497.289$ , p < 0.0001,  $\eta p^2 = 0.993$ ). The LSD post hoc analysis in stimulation condition revealed a greater Tau during anodal dlPFC/cathodal vmPFC stimulation compared to sham stimulation (MD = 0.002, p < 0.001). Also, the Tau during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.002, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.002, p < 0.001) was larger than sham, but the Tau during anodal dlPFC/cathodal vmPFC/cathodal dlPFC stimulation (MD = 0.004, p < 0.001). The Tau during anodal dlPFC/cathodal vmPFC stimulation (MD = 0.005, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.006, p < 0.001), and anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.002, p < 0.001), and anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD = 0.012, p < 0.001) was greater compared stimulation coupled with an extracranial cathodal electrode (MD = 0.012, p < 0.001) was greater compared

to anodal vmPFC/cathodal dlPFC stimulation. Also, the Tau during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.007, p < 0.001) and anodal vmPFC stimulation coupled with an extracranial cathodal electrode (MD=0.001, p < 0.001) was than anodal dlPFC/cathodal vmPFC stimulation. Finally, the Tau was greater during anodal dlPFC stimulation coupled with an extracranial cathodal electrode (MD=0.006, p < 0.001).

The results of data analysis of variance with repeated measures of the DDT showed a non-significant main effect of stimulation for the performance of the subjects in the delay-discounting task, which was performed on different stimulation positions ( $F_{4,72}$ =0.613, p=0.654,  $\eta$ p2=0.033). Results of the LSD post hoc analyses. The analysis of the three parameter modeling measures showed a significant difference between conditions with (R) ( $F_{4,72}$ =8.909, p<0.001,  $\eta$ p2=0.331), (S) ( $F_{4,72}$ =7.031, p<0.001,  $\eta$ p2=0.281), and (Beta) ( $F_{4,72}$ =7.881, p<0.001,  $\eta$ p2=0.305).

For R, the analysis showed significant main effects of stimulation (F4,72 = 8.909, p < 0.001,  $\eta p = 0.331$ ).

The LSD post hoc analysis in stimulation condition revealed a greater R during Sham stimulation compared to anodal dlPFC stimulation coupled with extracranial cathodal electrode (MD=0.088, p < 0.05). For S, the analysis showed significant main effects of stimulation (F4,72=7.031, p < 0.001,  $\eta p = 0.281$ ). The LSD post hoc analysis in stimulation condition revealed a greater S during anodal dlPFC stimulation coupled with extracranial cathodal electrode (MD=0.132, p < 0.05), and anodal vmPFC/cathodal dlPFC stimulation (MD=0.127, p < 0.001) compared to anodal vmPFC stimulation coupled with an extracranial cathodal electrode. For Beta, the analysis showed significant main effects of stimulation (F4,72=7.881, p < 0.001,  $\eta p = 0.305$ ). The LSD post hoc analysis in stimulation condition revealed a greater Beta during anodal vmPFC stimulation coupled with an extracranial cathodal electrode compared to sham (MD=0.125, p < 0.05), and anodal vmPFC stimulation coupled with an extracranial cathodal electrode to sham (MD=0.125, p < 0.05), and anodal vmPFC stimulation (MD=0.153, p < 0.05). The impact of tDCS on parameters of utilized computational models are exhibited in Fig. 2.

#### Discussion

In the present study, we aimed to explore the role of the dlPFC and the vmPFC in the process of reward processing. In general, the result showed a null effect of stimulation on conventional measures of BART and delay discounting but a significant effect on latent modeling measures. Therefore, the process, and not the outcome, of reward processing influenced by the stimulation of the vmPFC and the dlPFC.

In detail, the conventional results of BART showed no significant difference between different stimulation conditions for conventional measures, including earning, AV, and PN. Although we cannot draw conclusions about the psychopathology of GAD without comparing it to a healthy control group in our study, earlier tDCS studies described more conservative decision-making based on AV and earnings during anodal left dlPFC/ cathodal right vmPFC stimulation in healthy individuals<sup>33,39</sup>. It might be interpreted that the upregulation or downregulation of the impaired areas cannot influence performance during risky decision-making.

In modeling measures, Phi, a positive prior belief about explosion, was larger during all real compared to sham stimulation, except the anodal left dlPFC with an extracranial return electrode tDCS condition. The dlPFC governs behavior based on reward information, past outcomes, and previous decisions<sup>68,69</sup>. Furthermore, the dlPFC has been known as the neural correlates of belief updating in neuroimaging studies<sup>70,71</sup>. Therefore, the dlPFC is not involved in unrealistic optimistic view about the probability of explosion.

However, some studies described more positive ratings of negative stimuli during anodal left dlPFC stimulation<sup>72,73</sup> or improved resiliency as a positive adaptation in the context of risk or adversity<sup>74</sup>. Another study of our research group described more positive rating of negative stimuli and more negative rating of positive stimuli during anodal vmPFC/cathodal dlPFC stimulation (Nejati et al., 2021). This study attributed a modulatory role of the left dlPFC on rating of emotional valence. In the present study, positive prior beliefs are accompanied with a positive and unrealistic expectation about the balloon explosion. Thus, isolated stimulation of the dlPFC provides a more realistic, and not optimistic, state with respect to prior beliefs.

The vmPFC, with a putative role in valuation of reward, facilitates a positive bias in information processing<sup>75</sup>. The results of the present study showed that isolated stimulation of the vmPFC increased the positive prior beliefs. The results showed a higher Phi during anodal vmPFC compared to anodal dlPFC stimulation, both with an extracranial return electrode. Given the role of the dlPFC in updating and the role of the vmPFC in the valuation of information, reward valuation has more effect on the prior belief compared to updating. Indeed, updating prunes the unrealistic prior belief. This preference was confirmed by the higher Phi during anodal vmPFC/cathodal dlPFC stimulation compared to the reversed order of electrodes. Furthermore, Phi was larger during bipolar conditions compared to unipolar stimulation of the dlPFC or vmPFC with extracranial reference electrode. This finding might be explained in the light of realistic belief compared to unrealistic persimistic/optimistic belief. Meanwhile, in a mutual interaction, the vmPFC makes the positive beliefs and the dlPFC removes the unrealistic parts of the formed belief.

It is worth mentioning that the vmPFC and the dlPFC are hypoactive in GAD patients and it make difficult to use above mentioned studies with healthy participant for discussion. A tDCS study in GAD patients found fewer attention bias to threat-related stimuli during anodal stimulation of both, the left dlPFC and the right vmPFC, with an extracranial reference electrode<sup>59</sup>. With respect to the threat related attention bias in GAD patients, this improvement could be attributed to the more realistic interpretation accomplished by the dlPFC and more positive processing of the vmPFC.

The Eta, the updating or learning rate of explosion, was larger during all real conditions compared to sham stimulation, which shows the role of both dlPFC and vmPFC in updating and learning rates. Although learning and updating rates cannot be discerned in Eta, these might be discriminated at the neural level. The vmPFC is involves in learning, and the dlPFC predominantly in updating<sup>76</sup>. The former stores incoming information and

the latter deletes unwanted information. This could be confirmed by the regulatory role of the dlPFC on the vmPFC<sup>77</sup>. In the current study, in unipolar conditions, anodal stimulation of the vmPFC increased Eta more than anodal stimulation of the dlPFC, indicating a higher role of learning compared to updating in Eta per se. However, in the bipolar condition, a higher Eta during anodal dlPFC/cathodal vmPFC stimulation was found compared to the reversed order electrode placement, indicating more importance of updating compared to learning in Eta. With respect to unipolar condition, Eta was greater during anodal dlPFC/cathodal vmPFC, indicating a sort of active learning with higher executive, updating, component compared to passive learning with lower executive demand for Eta. It might be explained in the light of different role of the dlPFC and vmPFC in learning. It means that updating is more important than learning. In other words, updating makes learning more effective compared to increasing rate of learning. This relation has been described earlier in working memory performance<sup>78</sup>. The key role of the dlPFC in the updating of memory, has been described earlier through a neuroimaging<sup>76</sup> and neuromodulation studies<sup>70,79,80</sup>.

The Gamma, as an index of risk taking was smaller during all real conditions compared to sham stimulation, indicating the role of the dlPFC and vmPFC in regulation of risk taking. Gamma was larger during unipolar stimulation compared to bipolar conditions indicating the cooperative role of the dlPFC and the vmPFC in conservative decision making. In bipolar conditions, Gamma was greater during anodal dlPFC/cathodal vmPFC compared to anodal vmPFC/cathodal dlPFC. Earlier neuroimaging studies described the vmPFC decreased as the participants further expanded balloon during performing BART in healthy individuals<sup>55</sup>. They stated that decrease in the vmPFC activity during performing BART accompany with decreasing expected value.

However, the Gamma was greater during isolated stimulation of the vmPFC compared to isolated stimulation of the dlPFC. It might be explained by rule-based function of the dlPFC compared value-based function of the vmPFC. One tDCS study found decrease attitude toward risky behaviors after cathodal stimulation of the left dlPFC with extracranial return electrode in healthy adults<sup>81</sup>. Based on our search, the present study is the first tDCS study which compared anodal dlPFC and anodal vmPFC stimulation with extracranial reference electrode. Based on the result, it seems an optimal level of activity is required for normal activity of the vmPFC in risk taking behaviors, the inhibition of activity during anodal dlPFC/cathodal vmPFC and isolated excitation of the vmPFC increase risky decisions. Notably, the hypoactivity of the vmPFC in GAD should be taken into consideration in the interpretation of this finding. As mentioned earlier, the vmPFC is involved in subjective valuation of rewards and in the case of risky decision making it refers to the level of safeness. This activity as a baseline performance influences the impact of stimulation on the respective performance. A tDCS study found anodal left/cathodal right dlPFC stimulation decreased risk taking in smokers, but increased it in non-smokers<sup>35</sup>.

The Tau, as an index of randomness, was larger during the real stimulation conditions, except for anodal vmPFC/cathodal dlPFC, compared to sham stimulation, indicating a role of dlPFC and vmPFC in considering probability in decision-making. This role is more prominent for the dlPFC than the vmPFC based on the larger Tau in anodal dIPFC compared to anodal vmPFC stimulation conditions, both with extracranial return electrode positions. A similar finding was observed in bipolar conditions, larger Tau in anodal dlPFC/cathodal vmPFC compared to the reversed electrode placement. Earlier fMRI studies described the dlPFC and the vmPFC as a probability-sensitive area. An fMRI study in healthy adults described enhanced activity of the dorsal prefrontal regions during infrequent events and ventral prefrontal regions during frequent events in an oddball paradigm<sup>82</sup>. In the present study, we found larger Tau during unipolar conditions compared to bipolar condition, indicating the independent and facilitatory role of the vmPFC and dlPFC in randomness/probability learning. Randomness by definition could be defined in two way: (1) a special type of cause and (2) existence of multiple possibility or uncertainty<sup>83</sup>. In the former randomness perceives as a rule, governed by the dlPFC, and in the latter, it perceives as luck or chance, with a motivational/positive view, as a function of the vmPFC. Based on the results of unipolar conditions, the greater randomness in anodal dlPFC compared to anodal dlPFC, the logic-based role of the dlPFC is more decisive to make a random choice. However, these two functions of randomness are inclusive and larger Tau in unipolar stimulation compared to bipolar condition could be explained accordingly.

In the delay discounting task, K as a conventional measure of delay discounting or hyperbolic discounting rate was not significant in different stimulation conditions. In the modeling data, the R, as exponential discounting rate, was smaller during anodal stimulation of the dIPFC with extracranial reference electrode, compared to sham condition. This difference could be explained based on the logic of hyperbolic and exponential model to calculate K and R in order. The R is more sensitive than K, because of the importance of pure duration between smaller sooner and larger later choices, without considering the distance from now. An fMRI study found that the left dIPFC was more active in the selection of choices with delayed rewards<sup>51</sup>. The dIPFC is involved in temporal prediction of future events, particularly the time of reward, and activated in representation of an anticipated reward<sup>68,84,85</sup>.

The S as a measure of impatience was smaller during anodal vmPFC with an extracranial reference electrode compared to the anodal dlPFC with an extracranial reference electrode and anodal vmPFC/cathodal dlPFC. This finding is in line with the result of a tDCS study, which found lower resilience during anodal vmPFC coupled with cathodal dlPFC<sup>74</sup>.

The Beta, as an index of randomness, was increased during anodal stimulation of the vmPFC with extracranial return electrodes compared to sham condition. The vmPFC is involved in learning from outcome and larger Beta during stimulation of the vmPFC described lower randomness. A lesion study described an impairment in searching for information, considering the consequences of decisions, and shifting from their preference to the alternative in the vmPFC patients. This study described the role the vmPFC in delayed and probabilistic rewards<sup>86</sup>. The Beta in the delay discounting test is the same as BART conceptually. However, the nature of respective tasks makes them different functionally. The choices in the delay discounting are more uncertain because of delayed reward. Based on above-mentioned role of the dIPFC and vmPFC in logical and motivational

domain of randomness, the future-oriented uncertainty in delay discounting makes the motivational component more prominent.

#### Limitations and future directions

Some limitation should be taken into account. First, we used an exploratory single-blind design with sham control with relatively small sample of GAD patients without healthy control group to study the impact of psychopathology. Second, we target two prefrontal areas to investigate reward processing, the other cortical and even subcortical areas should be taken into account in the study of decision making. Third, we consider decision making and delay discounting as two candidate tasks of reward processing. Further studies can consider other decision making or delay discounting tasks or some other domains of reward processing such as planning, reward sensitivity, and reward processing. Fourth, this study utilizes a single computational model for each experiment to interpret the behavioral results. The models employed have been frequently used in empirical research. However, alternative competing models exist, such as the two-parameter model for the BART task and the hyperbolic discounting model for the DD task. Since different models incorporate distinct mechanisms for capturing human choice patterns, they may yield varying conclusions. Therefore, we should refrain from overinterpreting our results as general conclusions and acknowledge the need for further research. Additionally, it remains unclear which mechanisms are essential for explaining human choice behavior, and conducting model comparisons with larger datasets could provide valuable insights for drawing more generalized conclusions.

#### Conclusion

In conclusion, our study provides a new insight into the roles of the dlPFC and the vmPFC in reward processing, highlighting their distinct contributions to decision-making under risk. The findings indicate that while stimulation of these regions did not significantly alter conventional measures of risk-taking in tasks such as the BART and delay discounting, it did impact latent modeling measures, suggesting that the process of reward evaluation is more sensitive to neural modulation than the outcomes themselves. It could be interpreted as low sensitivity of outcome-related tasks in the study of risky decision-making in GAD. Future studies could consider incorporating measures of the decision-making process to evaluate the dynamics of decision-making.

The dlPFC appears to play a critical role in updating beliefs and regulating decision-making processes, whereas the vmPFC contributes to the valuation of rewards and the formation of positive biases in information processing. Notably, the interactions between these two areas underscore the importance of maintaining a balance in their activities for optimal decision-making, particularly in individuals with GAD, who exhibit hypoactivity in these regions. In essence, the vmPFC and dlPFC work in concert to navigate the complexities of decision-making. The vmPFC fosters an optimistic perspective, embracing the potential for positive outcomes and the inherent randomness of choices<sup>87</sup>. In contrast, the dlPFC acts as a critical evaluator, ensuring that this optimistic learning is tempered by a realistic appraisal of the information at hand. This dynamic interplay between value-based optimism and logic-driven realism not only enhances our understanding of decision-making processes but also highlights the need for a balanced approach in therapeutic interventions targeting decision-making deficits in various psychological conditions.

#### Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

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#### References

- 1. APA. American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (5th ed.). American Journal of Psychiatry (2013).
- Grupe, D. W. & Nitschke, J. B. Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nat. Rev. Neurosci.* 14, 488–501 (2013).
- 3. Carleton, R. N. Into the unknown: A review and synthesis of contemporary models involving uncertainty. J. Anxiety Disord. 39, 30–43 (2016).
- 4. Bishop, S. J. Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn. Sci. 11, 307-316 (2007).
- 5. Bechara, A. Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nat. Neurosci.* **8**, 1458–1463 (2005).
- Kirby, K. N. & Maraković, N. N. Delay-discounting probabilistic rewards: Rates decrease as amounts increase. *Psychon. Bull. Rev.* 3, 100–104 (1996).
- Xia, L., Gu, R., Zhang, D. & Luo, Y. Anxious individuals are impulsive decision-makers in the delay discounting task: An ERP study. Front. Behav. Neurosci. 11, 5 (2017).
- 8. Rounds, J. S., Beck, J. G. & Grant, D. M. Is the delay discounting paradigm useful in understanding social anxiety?. *Behav. Res. Ther.* **45**, 729–735 (2007).
- 9. Mitte, K. Anxiety and risky decision-making: The role of subjective probability and subjective costs of negative events. *Pers. Individ. Dif.* **43**, 243–253 (2007).
- 10. Nejati, V., Alipour, F. & Sharifi, M. Risk-taking comparison in adolescent girls with symptoms of anxiety, depression, stress and normal. *KAUMS J.* **20**, 566–573 (2017).
- 11. Niazi, L., Nazari, M. A., Nejati, V. & Hatami, J. Risky decision-making for self and others in anxiety state: An event-related potential study. *Adv. Cogn. Sci.* 17, 20–29 (2015).
- 12. Kim, H., Shimojo, S. & O'Doherty, J. P. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. *PLoS Biol.* **4**, e233 (2006).
- 13. Barbas, H. & Zikopoulos, B. The prefrontal cortex and flexible behavior. Neurosci. 13, 532-545 (2007).
- 14. Montague, P. R. & Berns, G. S. Neural economics and the biological substrates of valuation. Neuron 36, 265-284 (2002).

- 15. Williams, L. M. An integrative neuroscience model of "significance" processing. J. Integr. Neurosci. 5, 1-47 (2006).
- Padoa-Schioppa, C. & Assad, J. A. The representation of economic value in the orbitofrontal cortex is invariant for changes of menu. Nat. Neurosci. 11, 95–102 (2008).
- 17. Kable, J. W. & Glimcher, P. W. The neural correlates of subjective value during intertemporal choice. *Nat. Neurosci.* **10**, 1625–1633 (2007).
- Scult, M. A., Knodt, A. R., Swartz, J. R., Brigidi, B. D. & Hariri, A. R. Thinking and feeling: Individual differences in habitual emotion regulation and stress-related mood are associated with prefrontal executive control. *Clin. Psychol. Sci.* 5, 150–157 (2017).
- Heller, A. S. Cortical-subcortical interactions in depression: From animal models to human psychopathology. Front. Syst. Neurosci. 10, 20 (2016).
- 20. Via, E. et al. Ventromedial prefrontal cortex activity and pathological worry in generalised anxiety disorder. *Br. J. Psychiatry* **213**, 437–443 (2018).
- 21. Hazlett-Stevens, H. & Borkovec, T. D. Interpretive cues and ambiguity in generalized anxiety disorder. Behav. Res. Ther. 42, 881–892 (2004).
- Fitzgerald, K. D. et al. Reduced error-related activation of dorsolateral prefrontal cortex across pediatric anxiety disorders. J. Am. Acad. Child Adolesc. Psychiatry 52, 1183–1191 (2013).
- Hu, K. Neural activity to threat in ventromedial prefrontal cortex correlates with individual differences in anxiety and reward processing. *Neuropsychologia* 117, 566–573 (2018).
- Polania, R., Nitsche, M. A. & Ruff, C. C. Studying and modifying brain function with non-invasive brain stimulation. *Nat. Neurosci.* 21, 174–187 (2018).
- 25. Nitsche, M. A. et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul. 1, 206-223 (2008).
- Shin, Y.-I., Foerster, Á. & Nitsche, M. A. Reprint of: transcranial direct current stimulation (tDCS)–Application in neuropsychology. Neuropsychologia 74, 74–95 (2015).
- Nitsche, M. A. & Paulus, W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527, 633–639 (2000).
- 28. Beeli, G., Koeneke, S., Gasser, K. & Jancke, L. Brain stimulation modulates driving behavior. Behav. Brain Funct. 4, 1-7 (2008).
- 29. Fecteau, S. et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: A preliminary study. *Drug Alcohol. Depend.* **140**, 78–84 (2014).
- Gorini, A., Lucchiari, C., Russell-Edu, W. & Pravettoni, G. Modulation of risky choices in recently abstinent dependent cocaine users: A transcranial direct-current stimulation study. Front. Hum. Neurosci. 8, 661 (2014).
- 31. He, Q. et al. Anodal stimulation of the left DLPFC increases IGT scores and decreases delay discounting rate in healthy males. *Front. Psychol.* 7, 1421 (2016).
- 32. Manuel, A. L., Murray, N. W. G. & Piguet, O. Transcranial direct current stimulation (tDCS) over vmPFC modulates interactions between reward and emotion in delay discounting. *Sci. Rep.* **9**, 1–9 (2019).
- Nejati, V., Salehinejad, M. A. & Nitsche, M. A. Interaction of the left dorsolateral prefrontal cortex (I-DLPFC) and right orbitofrontal cortex (OFC) in hot and cold executive functions: Evidence from transcranial direct current stimulation (tDCS). Neuroscience 369, 109–123 (2018).
- 34. Nejati, V., Sarraj-Khorrami, A. & Nitsche, M. A. Transcranial direct current stimulation improves reward processing in children with ADHD. J. Atten. Disord. 25, 1623–1631 (2020).
- Pripfl, J., Neumann, R., Köhler, U. & Lamm, C. Effects of transcranial direct current stimulation on risky decision making are mediated by 'hot'and 'cold'decisions, personality, and hemisphere. *Eur. J. Neurosci.* 38, 3778–3785 (2013).
- 36. Ouellet, J. et al. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): A randomized and sham-controlled exploratory study. J. Psychiatr. Res. 69, 27–34 (2015).
- 37. Boggio, P. S. et al. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). *Drug Alcohol Depend.* **112**, 220–225 (2010).
- Cheng, G. L. F. & Lee, T. M. C. Altering risky decision-making: Influence of impulsivity on the neuromodulation of prefrontal cortex. Soc. Neurosci. 11, 353–364 (2016).
- Soyata, A. Z. et al. Effect of transcranial direct current stimulation on decision making and cognitive flexibility in gambling disorder. Eur. Arch. Psychiatry Clin. Neurosci. 269, 275–284 (2019).
- Ye, H., Chen, S., Huang, D., Wang, S. & Luo, J. Modulating activity in the prefrontal cortex changes decision-making for risky gains and losses: A transcranial direct current stimulation study. *Behav. Brain Res.* 286, 17–21 (2015).
- Ye, H. et al. Activation of the prefrontal cortex by unilateral transcranial direct current stimulation leads to an asymmetrical effect on risk preference in frames of gain and loss. Brain Res. 1648, 325–332 (2016).
- 42. Ye, H. et al. Transcranial direct current stimulation over prefrontal cortex diminishes degree of risk aversion. *Neurosci. Lett.* **598**, 18–22 (2015).
- Russo, R., Twyman, P., Cooper, N. R., Fitzgerald, P. B. & Wallace, D. When you can, scale up: Large-scale study shows no effect of tDCS in an ambiguous risk-taking task. *Neuropsychologia* 104, 133–143 (2017).
- Ahn, W. Y. et al. Decision-making in stimulant and opiate addicts in protracted abstinence: Evidence from computational modeling with pure users. Front. Psychol. 5, 1–15 (2014).
- Ahn, W. Y. & Busemeyer, J. R. Challenges and promises for translating computational tools into clinical practice. Curr. Opin. Behav. Sci. 11, 1–7 (2016).
- 46. Busemeyer, J. R. & Stout, J. C. A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychol. Assess.* 14, 253 (2002).
- Chan, T. W. S. et al. Differential impairments underlying decision making in anorexia nervosa and bulimia nervosa: A cognitive modeling analysis. Int. J. Eat. Disord. 47, 157–167 (2014).
- Lejuez, C. W. et al. Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). J. Exp. Psychol. Appl. 8, 75 (2002).
- Lejuez, C. W., Aklin, W. M., Zvolensky, M. J. & Pedulla, C. M. Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. J. Adolesc. 26, 475–479 (2003).
- Ahn, W. Y., Dai, J., Vassileva, J., Busemeyer, J. R. & Stout, J. C. Computational modeling for addiction medicine: From cognitive models to clinical applications. *Prog. Brain Res.* 224, 53–65 (2016).
- 51. Hare, T. A., Hakimi, S. & Rangel, A. Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting. *Front. Neurosci.* 8, 50 (2014).
- 52. Peters, J. & Büchel, C. The neural mechanisms of inter-temporal decision-making: Understanding variability. *Trends Cogn. Sci.* **15**, 227–239 (2011).
- Steinbeis, N., Haushofer, J., Fehr, E. & Singer, T. Development of behavioral control and associated vmPFC–DLPFC connectivity explains children's increased resistance to temptation in intertemporal choice. *Cereb. Cortex* 26, 32–42 (2016).
- 54. Tom, S. M., Fox, C. R., Trepel, C. & Poldrack, R. A. The neural basis of loss aversion in decision-making under risk. *Science*. 315, 515–518 (2007).
- 55. Schonberg, T. et al. Decreasing ventromedial prefrontal cortex activity during sequential risk-taking: An fMRI investigation of the balloon analog risk task. *Front. Neurosci.* **6**, 80 (2012).

- D'Alessandro, M., Gallitto, G., Greco, A. & Lombardi, L. A joint modelling approach to analyze risky decisions by means of diffusion tensor imaging and behavioural data. *Brain Sci.* 10, 138 (2020).
- 57. Quan, P. et al. Cerebellum anatomy predicts individual risk-taking behavior and risk tolerance. Neuroimage 254, 119148 (2022).
- Faul, F., Erdfelder, E., Buchner, A. & Lang, A.-G. G\* Power Version 3.1.7 [computer software]. Uiversität Kiel, Ger. (2013).
  Nejati, V., Khalaji, S., Goodarzi, H. & Nitsche, M. The role of ventromedial and dorsolateral prefrontal cortex in attention and
- Association, V., Khadaj, S., Goodari, H. & Hister, M. Inc Fole of ventionication and and solution plasma in dividuals with general anxiety disorder (GAD): A tDCS study. J. Psychiatr. Res. 144, 269–277 (2021).
  Association, A. P. Diagnostic and Statistical Manual of Mental Disorders (DSM-5\*) (American Psychiatric Pub, 2013).
- Association, A. P. Diagnostic and Statistical Manual of Mental Disorders (DSM-5<sup>-</sup>) (American Psychiatric Pub, 2013).
  Spielberger, C. D. State-trait anxiety inventory. Corsini Encycl. Psychol. https://doi.org/10.1002/9780470479216.corpsy0943 (2010).
- Abdoli, N. et al. Reliability and validity of Persian version of state-trait anxiety inventory among high school students. *East Asian Arch. Psychiatry* **30**, 44–47 (2020).
- Chan, R. C. K., Shum, D., Toulopoulou, T. & Chen, E. Y. H. Assessment of executive functions: Review of instruments and identification of critical issues. Arch. Clin. Neuropsychol. 23, 201–216 (2008).
- Palm, U. et al. Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimul.* 6, 690–695 (2013).
- 65. Brunoni, A. R. et al. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int. J. Neuropsychopharmacol.* **14**, 1133–1145 (2011).
- Wallsten, T. S., Pleskac, T. J. & Lejuez, C. W. Modeling behavior in a clinically diagnostic sequential risk-taking task. *Psychol. Rev.* 112, 862–880 (2005).
- 67. Park, H., Yang, J., Vassileva, J. & Ahn, W. The exponential weight updating model: A novel computational model for the Balloon Analogue Risk Task (2019). https://doi.org/10.31234/osf.io/sdzj4.
- Wallis, J. D. & Miller, E. K. Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. *Eur. J. Neurosci.* 18, 2069–2081 (2003).
- Barraclough, D. J., Conroy, M. L. & Lee, D. Prefrontal cortex and decision making in a mixed-strategy game. Nat. Neurosci. 7, 404–410 (2004).
- 70. Schulreich, S. & Schwabe, L. Causal role of the dorsolateral prefrontal cortex in belief updating under uncertainty. *Cereb. Cortex* 31, 184–200 (2021).
- 71. Huber, R. E., Klucharev, V. & Rieskamp, J. Neural correlates of informational cascades: Brain mechanisms of social influence on belief updating. Soc. Cogn. Affect. Neurosci. 10, 589–597 (2015).
- Boggio, P. S., Zaghi, S. & Fregni, F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47, 212–217 (2009).
- 73. Peña-Gómez, C., Vidal-Pineiro, D., Clemente, I. C., Pascual-Leone, Á. & Bartres-Faz, D. Down-regulation of negative emotional processing by transcranial direct current stimulation: Effects of personality characteristics. *PLoS ONE* **6**, e22812 (2011).
- Salehinejad, M. A., Nejati, V. & Derakhshan, M. Neural correlates of trait resiliency: Evidence from electrical stimulation of the dorsolateral prefrontal cortex (dLPFC) and orbitofrontal cortex (OFC). *Pers. Individ. Dif.* **106**, 209–216 (2017).
- Kuzmanovic, B., Rigoux, L. & Tittgemeyer, M. Influence of vmPFC on dmPFC predicts valence-guided belief formation. J. Neurosci. 38, 7996–8010 (2018).
- Kluen, L. M., Dandolo, L. C., Jocham, G. & Schwabe, L. Dorsolateral prefrontal cortex enables updating of established memories. *Cereb. Cortex* 29, 4154–4168 (2019).
- 77. Feeser, M., Prehn, K., Kazzer, P., Mungee, A. & Bajbouj, M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. *Brain Stimul.* 7, 105–112 (2014).
- Nejati, V., Salehinejad, M. A. & Sabayee, A. Impaired working memory updating affects memory for emotional and non-emotional materials the same way: Evidence from post-traumatic stress disorder (PTSD). Cogn. Process. 19, 53–62 (2018).
- 79. D'Ardenne, K. et al. Role of prefrontal cortex and the midbrain dopamine system in working memory updating. *Proc. Natl. Acad. Sci.* 109, 19900–19909 (2012).
- Basso, D., Ferrari, M. & Palladino, P. Prospective memory and working memory: Asymmetrical effects during frontal lobe TMS stimulation. *Neuropsychologia* 48, 3282–3290 (2010).
- 81. Wen, A. & Yoon, K. L. Depression and affective flexibility: A valence-specific bias. Behav. Res. Ther. 123, 103502 (2019).
- Casey, B. J. et al. Sensitivity of prefrontal cortex to changes in target probability: A functional MRI study. *Hum. Brain Mapp.* 13, 26–33 (2001).
- Batanero, C. Understanding randomness: Challenges for research and teaching. In CERME 9-Ninth Congress of the European Society for Research in Mathematics Education 34-49 (2015).
- Kobayashi, S., Lauwereyns, J., Koizumi, M., Sakagami, M. & Hikosaka, O. Influence of reward expectation on visuospatial processing in macaque lateral prefrontal cortex. J. Neurophysiol. 87, 1488–1498 (2002).
- Roesch, M. R. & Olson, C. R. Impact of expected reward on neuronal activity in prefrontal cortex, frontal and supplementary eye fields and premotor cortex. J. Neurophysiol. 90, 1766–1789 (2003).
- 86. Mok, J. N. Y. et al. Does ventromedial prefrontal cortex damage really increase impulsiveness? Delay and probability discounting in patients with focal lesions. *J. Cogn. Neurosci.* **33**, 1909–1927 (2021).
- 87. Luo, Q. & Shao, R. The positive and negative emotion functions related to loneliness: A systematic review of behavioural and neuroimaging studies. *Psychoradiology* **3**, kkad029 (2023).

#### Author contributions

V.N.: conceptualization, analysis, writing, and supervision. J.A.R.: modeling and visulaization. A.H.H.: modeling.

#### Declarations

#### **Competing interests**

The authors declare no competing interests.

#### Additional information

**Correspondence** and requests for materials should be addressed to V.N.

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