PCN Psychiatry and Clinical Neurosciences

REVIEW ARTICLE

Effects of transcranial direct current stimulation of prefrontal cortex on risk-taking behavior

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Aim: Recent cognitive neuroscience research shows that noninvasive brain stimulation can modify a wide range of behaviors in healthy people. Such regulation effects on human behaviors provide new insights into the neurobiology of cognitive processes and establish causal brain–behavior relations. Here, we aimed to examine the effects of transcranial electrical stimulation (TES) of the prefrontal cortex on risk-taking.

Methods: We performed a systematic search on the PubMed, Web of Science, and Cochrane databases with appropriate keywords for original studies reporting the use of TES to modulate risk-taking behavior in healthy individuals. Then, in the meta-analysis phase, a random-effects model was used to measure the pooled effect size (ES).

Results: Twenty articles were evaluated as eligible studies, including 16 articles on transcranial direct current stimulation (tDCS), two on transcranial alternating current stimulation, one on transcranial pulsed current stimulation, and one on high-definition tDCS. A meta-analysis showed a pooled estimated standardized ES of −0.20 (95% confidence interval [CI], −0.39 to −0.01), which indicates a small ES for active tDCS over the dorsolateral prefrontal cortex (DLPFC) in comparison to sham stimulation ($z = 2.31$, $P = 0.03$) in terms of less risky behaviors. Subgroup analysis showed that there is no significant ES for bilateral DLPFC stimulation ($d = -0.01$; 95%CI, −0.28 to 0.26), but a significant near-medium ES for unilateral DLPFC stimulation ($d = -0.41$; 95%CI, −0.71 to −0.10).

Conclusion: Our findings support a significant impact of neuroregulation of the DLPFC on risk-taking behavior in healthy individuals. Unilateral noninvasive electrical stimulation of the DLPFC can result in a conservative risk-averse response style, probably through modulating plasticity of the relevant brain networks, including cortical and subcortical structures, as well as increasing subcortical dopaminergic activity.

Keywords: *decision-making, dorsolateral prefrontal cortex, neuromodulation, risk-taking, transcranial electrical stimulation.*

http://onlinelibrary.wiley.com/doi/10.1111/pcn.13025/full

People are faced with different situations requiring decisions every day. Decisions involve a process of forming preferences based on the risks and benefits. Taking an excessively risky or very cautious approach can result in poor decisions that have unintended consequences. In an adaptive and sensible decision-making process, an individual may evaluate the risky and cautious behavioral choices and predict the potential outcomes to choose a decision based on his/her personality and desires.[1] Therefore, because of its immense importance, decision-making has attracted much attention in the fields of psychology, psychiatry, economy, and neuroscience. Clinical studies of patients with focal and well-defined brain lesions and, more recently, neuroimaging studies have considerably contributed to the comprehension of the neural substrates and functional neuroanatomy of decision-making.[2–5] These studies have implied the involvement of different brain regions in decision-making. The prefrontal cortex (PFC) is a main brain region that is part of a distributed bihemispheric cortico-subcortical network involved in decision-making.[6] It is composed of several highly interconnected regions called the dorsolateral PFC (DLPFC), medial PFC (mPFC), and orbitofrontal cortex (OFC), which are primarily responsible for executive functions or cognitive control.[7]

In recent years, noninvasive brain stimulation techniques have enabled the investigation of the behavioral outcomes of an externally induced activation or inhibition of the brain regions in healthy subjects or patients and have thus set up a causal relation between brain functions and behaviors without the inherent limitations of lesion studies. Transcranial electrical stimulation (TES) is a popular noninvasive brain stimulation technique that provides an effective, simple, and safe way to modulate cortical excitability and subsequently cognitive functions.[8] Transcranial direct current stimulation (tDCS) is the most common stimulation paradigm that applies a weak electric current flow from a positive (anode) to a negative (cathode) electrode. Anodal tDCS is supposed to raise cortical excitability and activity in the targeted brain region, whereas cathodal stimulation decreases it.[9] Beyond the target region, tDCS may change functional connectivity of the brain networks.[10] Moreover, transcranial alternating current stimulation (tACS) and transcranial pulsed current stimulation (tPCS) are the two common stimulation paradigms in TES. They deliver an alternating current with a sinusoidal, or other patterned, and pulsed waveform to alter the power and phase of brain oscillations. The frequency and relative phase are important parameters in tACS, and the frequency range and pulse duration are critical parameters in tPCS

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experiments.[11, 12] Using these TES modalities, particularly tDCS, to understand the underlying neural mechanisms involved in decision-making is one of the active research areas in cognitive neuroscience. Most studies have targeted the PFC, and particularly the DLPFC, during a risk task to assess the neurobiology of decision-making when decisions and choices are ambiguous. The purpose of the present study was to systematically review the current state of knowledge of the uses of TES techniques in risk-taking behaviors and risky decision-making.

Methods

An extensive literature search was performed on the PubMed, Web of Science, and Central Cochrane databases with English-language articles from 1 January 2000 to 15 January 2019, irrespective of country of origin or publication source. We were looking for human studies conducted in healthy subjects, without regard to sex, age, or study design, reporting the effects of TES techniques on risk-taking behaviors and risky decision-making. The search terms included TES modalities ('tDCS', 'tACS', 'tPCS', 'tRNS', and 'transcranial electrical stimulation'), brain stimulation-related keywords ('transcranial', 'cortical stimulation', 'noninvasive brain stimulation', 'neurostimulation', and 'neuromodulation'), and behavior-related keywords ('risk', 'risky', 'decision-making', 'risk-taking', 'risky behavior', and 'choice behavior'). Also, a combination of these keywords was used to search relevant human studies.

Two independent reviewers conducted the early stage of screening based on the titles and abstracts of the papers; they excluded duplicate and non-relevant articles, and selected eligible studies. Exclusion criteria were as follows: (i) non-peer-reviewed papers and book chapters; (ii) commentaries and letters to editors; (iii) review articles; (iv) case reports; (v) study protocols; (vi) hypothesis articles; (vii) non-human studies; and (viii) studies with non-healthy subjects. Methodological assessments of studies were performed by the Consolidated Standards of Reporting Trials (CONSORT) checklist (http://www.consortstatement.org/). After removal of irrelevant studies, two reviewers extracted important data from each included study, such as author name, publication year, study design (randomization, blinding, and control status), intervention group, control group, TES techniques, brain target, technical parameters for stimulation, outcome measure, and obtained results.

Data Analysis

All statistical analysis was performed using STATA/MP 14.1 for Mac (StataCorp, College Station, TX, USA). We quantified the effect of the DLPFC electrical stimulation based on the difference in performance between tDCS and sham conditions using a standardized measure of effect size (ES). Mean adjusted values (Balloon Analog Risk Task [BART]), along with SD, were used in the calculation of the standardized mean difference and 95% confidence interval (95%CI) for each study. Cohen's *d* was used as a measure of ES. Subsequently, the ES needed to be pooled into a measure of the ES across studies. A random-effects model was used to measure the pooled ES, weighted by the inverse variance method. However, when a study utilizes one control group and several intervention groups, the data obtained from the control group are utilized to calculate more than one ES. Thus, these ES are correlated to each other and we should consider this multiple comparison issue while computing the variance. Therefore, to compute a pooled ES, we created at least one synthetic ES for each study (the number of ES was based on the number of control groups in each study), defined as the combined mean that is calculated as the weighted mean across intervention groups.[13] The χ^2-test was used to assess heterogeneity of ES and the I^2 statistic was used to quantify heterogeneity between studies, with the values of 25%, 50%, and 75% reflecting a small, medium, and large degree of heterogeneity, respectively.[14] Also, publication bias was assessed by funnel plots with Egger's test. For all statistical analyses, the level of significance was set at 0.05.

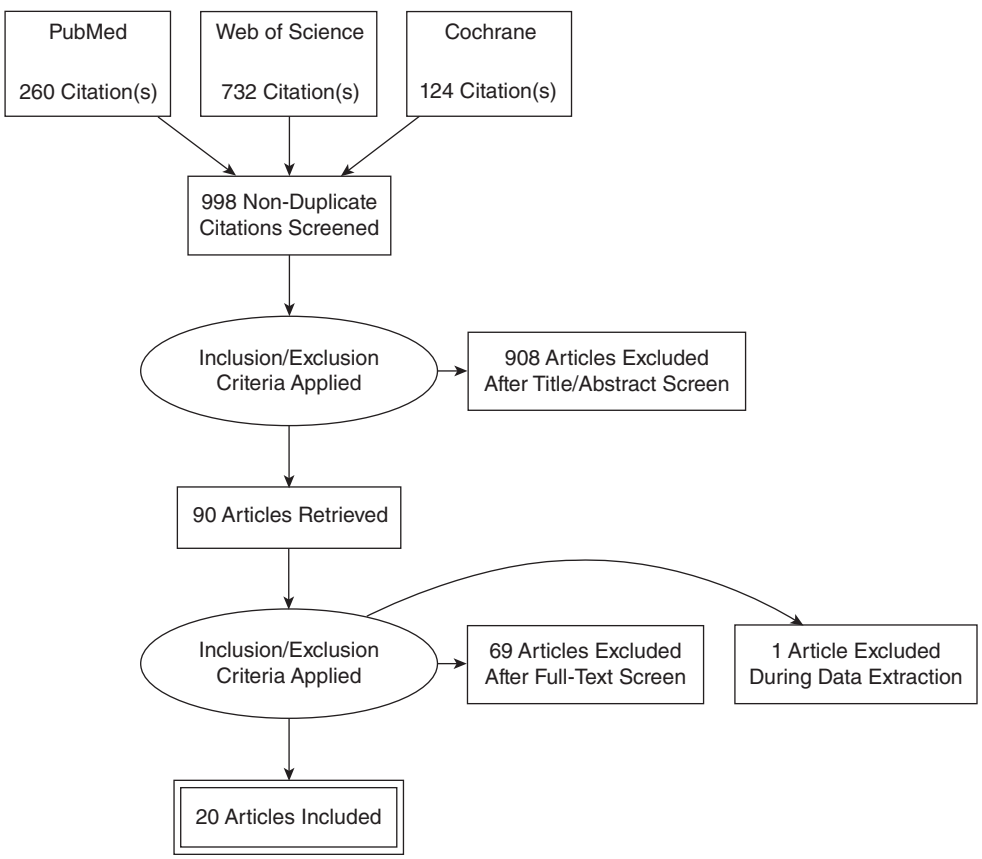

Fig.1 Flow diagram and process of identification, screening, and eligibility assessment of studies on the subject of transcranial electrical stimulation effects on risk-taking behaviors.

Table 1 Study and sample characteristics for included studies

Authors (year)	TES technique	Design				*N* Intervention (mean age in years)	*N* Control (mean age in years)	Sex	Risk of bias
		Study	Randomization	Blinding	Control				
Fecteau *et al.* (2007)[18]	tDCS	RCT (between-subject)	Yes	Double	Sham	12; 12	12	11 M; 25 F	Low
Fecteau *et al.* (2007)[19] – Study 1	tDCS	RCT (between-subject)	Yes	Double	Sham	10; 10	10	9 M; 26 F	Low
Fecteau *et al.* (2007)[19] – Study 2	tDCS	RCT (between-subject)	Yes	Double	Sham	6; 6	10	1 M; 11 F	Low
Beeli *et al.* (2008)[15]	tDCS	Open label	No	No	No	24 (24.1 ± 2.7)	—	24 M	High
Boggio *et al.* (2010)[16]	tDCS	RCT (between-subject)	Yes	Double	Sham	10 (69.4 ± 8.9); 9 (68.9 ± 12.6)	9 (67.0 ± 9.0)	3 M; 25 F	Low
Sela *et al.* (2012)[31]	tACS	RCT (between-subject)	Yes	Double	Sham	8 (22.8 ± 1.5); 8 (23.6 ± 2.07)	8 (25.0 ± 3.5)	13 M; 14 F	Low
Minati *et al.* (2012)[22]	tDCS	RCT (between-subject)	Yes	Double	Sham	16 (22.3 ± 3.2); 15 (20.9 ± 1.0)	16 (21.8 ± 2.5)	47 F	Low
Pripfl *et al.* (2013)[30]	tDCS	RCT (within-subject)	Yes	Not reported	Sham	36 (21.7)	36 (21.7)	11 M; 25 F	Medium
Cheng and Lee (2016)[17]	tDCS	RCT (within-subject)	Yes	Single (only participants)	Sham	16 (20.9 ± 2.8)	16 (20.9 ± 2.8)	6 M; 10 F	Low
Morales-Quezada *et al.* (2015)[33]	tPCS	RCT (between-subject)	Yes	Double	Sham	15 (30.5 ± 7.5)	15 (28.4 ± 5.1)	13 M; 17 F	Low
Ye *et al.* (2015)[26]	tDCS	RCT (between-subject)	Yes	Not reported	Sham	20; 20	20	25 M; 35 F	Medium
Ye *et al.* (2016)[27]	tDCS	RCT (between-subject)	Yes	Single (only participants)	Sham	20; 20; 20; 20	20	36 M; 64 F	Low
Yaple *et al.* (2017)[32]	tACS	RCT (between-subject)	Yes	No	Sham	17 (20.5 ± 2.5); 17 (21.1 ± 2.7)	17 (20.5 ± 2.5); 17 (21.1 ± 2.7)	13 M; 21 F	Medium
Russo *et al.* (2017)[24] – Study 1	tDCS	RCT (between-subject)	Yes	Double	Sham	41; 43	33	49 M; 68 F	Low
Russo *et al.* (2017)[24] – Study 2	tDCS	RCT (between-subject)	Yes	Double	Sham	16; 16; 11; 11	16; 11	30 M; 51 F	Low
Gilmore *et al.* (2018)[20]	tDCS	RCT (between-group)	Yes	Single (only participants)	Sham	15 (60.4 ± 6.6)	15 (58.3 ± 7.6)	Not reported	Medium
Guo *et al.* (2018)[34]	HD-tDCS	RCT (between-group)	Yes	Single (only participants)	Sham	20 (21.3 ± 3.8); 16 (19.2 ± 0.9)	22 (20.4 ± 3.9)	21 M; 37 F	Low
Yang *et al.* (2017)[25]	tDCS	RCT (between-group)	Yes	Single (only participants)	Sham	48	24	42 M; 30 F	Low
Huang *et al.* (2017)[21]	tDCS	RCT (between-group)	Yes	Single (only participants)	Sham	120	30	68 M; 82 F	Low
Zheng *et al.* (2017)[29]	tDCS	RCT (between-group)	Yes	Single (only participants)	Sham	30 (21.3); 30 (21.4)	30 (21.2)	44 M; 46 F	Low
Zhang (2018)[28]	tDCS	RCT (between-group)	No	No	Sham	30 (21.3); 30 (21.4)	30 (21.3)	45 M; 45 F	High
Nejati *et al.* (2018)[23]	tDCS	RCT (within-subject)	Yes	Single (only participants)	Sham	24 (26.7 ± 1.8)	24 (26.7 ± 1.8)	24 M	Low

HD-tDCS, high-definition transcranial direct current stimulation; RCT, randomized controlled trial; TES, transcranial electrical stimulation; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tPCS, transcranial pulsed current stimulation.

Results

Synthesized findings

As shown in Figure 1, this systematic search in the three above-mentioned databases yielded 998 unique original articles. Two independent reviewers excluded 908 records according to their titles and abstracts during the early stage of screening. Finally, 70 records were excluded during the full-text screening and data extraction, and 20 articles were evaluated as eligible studies: including 16 articles on tDCS,[15–30] two on tACS,[31, 32] one on tPCS,[33] and one on high-definition tDCS.[34] One of these articles was open label[15] and the remaining 19 were randomized controlled trials. Among these 19 controlled trials, three used a within-subject design and the remaining 16 used a between-subject design. In total, 784 healthy adult volunteers, including men and women, underwent TES methods in these trials. Sixteen (80%) studies had a low risk of bias and only two had a high risk due to non-randomization and non-blinding problems. Table 1 summarizes the study designs and participant descriptions for the included studies.

Although there were differences in some details of stimulation parameters, no major difference existed between studies in respect to the stimulation protocols. Most studies targeted the DLPFC unilaterally or bilaterally, and two trials selected the OFC for delivery of stimulation. In most studies, the current stimulation and the electrode size were 2 mA and 35 cm^2, respectively. However, some trials also assessed 1-mA and 1.5-mA currents and used other electrode sizes, including 25 cm^2. Furthermore, in most cases, the duration of stimulation was 15 min and 20 min. Table 2 summarizes the stimulation parameters for the included trials.

Table 2 Stimulation parameters, outcome measures, and results for included studies

Authors (year)	Anode site for tDCS/target electrode for tACS	Cathode site for tDCS/reference electrode for tACS	Current (mA)	Frequency (Hz)	Electrode size (cm^2)	Duration (min)	Montage	Outcome measures	Results
Fecteau *et al.* (2007)[18]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35	<15	Bilateral	A gambling task	Reduced risky behaviors after anodal stimulation over rDLPFC compared with the other groups
Fecteau *et al.* (2007)[19] – Study 1	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35	<15	Bilateral	BART	Reduced risky behaviors after bilateral stimulation over the DLPFC compared to the sham
Fecteau *et al.* (2007)[19] – Study 2	lDLPFC; rDLPFC	Right supraorbital; left supraorbital	2	—	35	<15	Unilateral	BART	No difference in decision-making behaviors after unilateral stimulation over the DLPFC
Beeli *et al.* (2008)[15]	lDLPFC; rDLPFC; ipsilateral mastoid	lDLPFC; rDLPFC; ipsilateral mastoid	1	—	35	15	Unilateral	A driving task	Reduced risky behaviors after anodal stimulation over right or left DLPFC
Boggio *et al.* (2010)[16]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35	15	Bilateral	A gambling task	Increased risky behaviors after left anodal/right cathodal stimulation over the DLPFC
Sela *et al.* (2012)[31]	lDLPFC; rDLPFC	Left temporal; right temporal	1	6.5	25	15	Unilateral	BART	Increased risky behaviors after left hemispheric stimulation over the DLPFC
Minati *et al.* (2012)[22]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	Not reported	20.5 ± 4.1	Bilateral	A gambling task	No differences in risk propensity after stimulation over the DLPFC
Pripfl *et al.* (2013)[30]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	0.45	—	5.3 anode/ 35 cathode	15	Bilateral	CCT	Reduced risky behaviors after anodal left/ cathodal right stimulation in the cold version of the CCT in both smokers and non-smokers; reduced risky behaviors and increased risky behaviors after right anodal/left cathodal stimulation in smokers and non-smokers, respectively, in the hot version of the CCT
Cheng and Lee (2016)[17]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35	19	Bilateral	RGT; BART	Reduced risky behaviors after right anodal/left cathodal stimulation that was more prominent in more impulsive subjects
Morales-Quezada *et al.* (2015)[33]	Earlobe	Earlobe	2	1–5	—	20	Bilateral	BART	No differences in risk propensity after stimulation
Ye *et al.* (2015)[26]	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35	15	Bilateral	The Risk Measurement Table	Increased risky behaviors in the gain frame and reduced risky behaviors in the loss frame after right anodal/left cathodal stimulation over the DLPFC
Ye *et al.* (2016)[27]	rDLPFC; lDLPFC; parietal	rDLPFC; lDLPFC; parietal	2	—	35	15	Unilateral	The Risk Measurement Table	Increased risky behaviors in the gain frame and reduced risky behaviors

Table 2. (*Continued*)

Authors (year)	Anode site for tDCS/target electrode for tACS	Cathode site for tDCS/reference electrode for tACS	Current (mA)	Frequency (Hz)	Electrode size (cm^2)	Duration (min)	Montage	Outcome measures	Results
									in the loss frame after right anodal/left cathodal stimulation over the DLPFC
Yaple *et al.* (2017)[32]	rDLPFC; lDLPFC	Ipsilateral deltoid	1	5; 10; 20; 40	35	40	Unilateral	A neuro-economic risky decision-making task	Increased risky behaviors after left hemispheric stimulation over the DLPFC
Russo *et al.* (2017)[24] – Study 1	lDLPFC; rDLPFC	rDLPFC; lDLPFC	2	—	35; 25	30	Bilateral	BART	No differences in risk propensity after stimulation
Russo *et al.* (2017)[24] – Study 2	lDLPFC; rDLPFC	rDLPFC; lDLPFC/ contralateral supraorbital	2	—	35	20	Bilateral/ unilateral	BART	No differences in risk propensity after stimulation
Gilmore *et al.* (2018)[20]	rDLPFC	lDLPFC	2	—	25	25	Bilateral	BART; Risk Task	Reduced risky behaviors after active tDCS compared to sham
Guo *et al.* (2018)[34]	lDLPFC	Left frontal (AF3, F1, F5, and FC3)	1.5	—	4	20	Unilateral	BART	Reduced risky behaviors after active tDCS compared to sham
Yang *et al.* (2017)[25]	lDLPFC; rDLPFC; rOFC; lOFC	rDLPFC; lDLPFC; lOFC; rOFC	2	—	35	20	Bilateral	Risk/Ambiguity Decision-Making Task	Increased risky behaviors after right anodal/left cathodal stimulation over the DLPFC; reduced risky behaviors after right anodal/left cathodal stimulation over OFC; and reversed effects after stimulation over two regions
Huang *et al.* (2017)[21]	rDLPFC; lDLPFC; parietal	rDLPFC; lDLPFC; parietal	2	—	35	15	Unilateral	The Risk Measurement Table	Reduced risky behaviors in the gain frame after left anodal tDCS and increased risky behaviors in the loss frame after right cathodal tDCS
Zheng *et al.* (2017)[29]	rDLPFC; occipital	rDLPFC; occipital	2	—	35	20	Unilateral	A risk game	Reduced risky behaviors after right anodal stimulation over the DLPFC
Zhang (2018)[28]	rDLPFC; occipital	rDLPFC; occipital	2	—	Not reported	20	Unilateral	A financing risk investment task	Reduced risky behaviors after right anodal stimulation over the DLPFC
Nejati *et al.* (2018)[23]	lDLPFC; rOFC	lDLPFC; rOFC	1.5	—	35	20	Bilateral	BART	Reduced risky behaviors after left anodal stimulation over the DLPFC and right anodal stimulation over OFC

BART, Balloon Analog Risk Task; CCT, Columbia Card Task; DLPFC, dorsolateral prefrontal cortex; lDLPFC, left dorsolateral prefrontal cortex; lOFC, left orbitofrontal cortex; OFC, orbitofrontal cortex; rDLPFC, right dorsolateral prefrontal cortex; RGT, Risky-Gains Task; rOFC. right orbitofrontal cortex; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation.

In these studies, the BART, risk-measurement table, and gambling tasks were administered to measure risk-taking behavior and decisions under risk. Among these, the BART is the most commonly used task to rate risk-taking behavior, so we performed the meta-analysis based on this outcome. The BART is dependent upon learning from experience-based decision-making that has convergent validity with real-world risk-related situations.[35] Performance on the BART is proven to be linked to the occurrence of real-world risk behaviors, such as criminal behaviors, substance use, and self-report assessments of risk-related constructs, including impulsivity, sensation-seeking, and deficiency in behavioral constraints.[36] Here, meta-analysis is performed based on the average number of adjusted

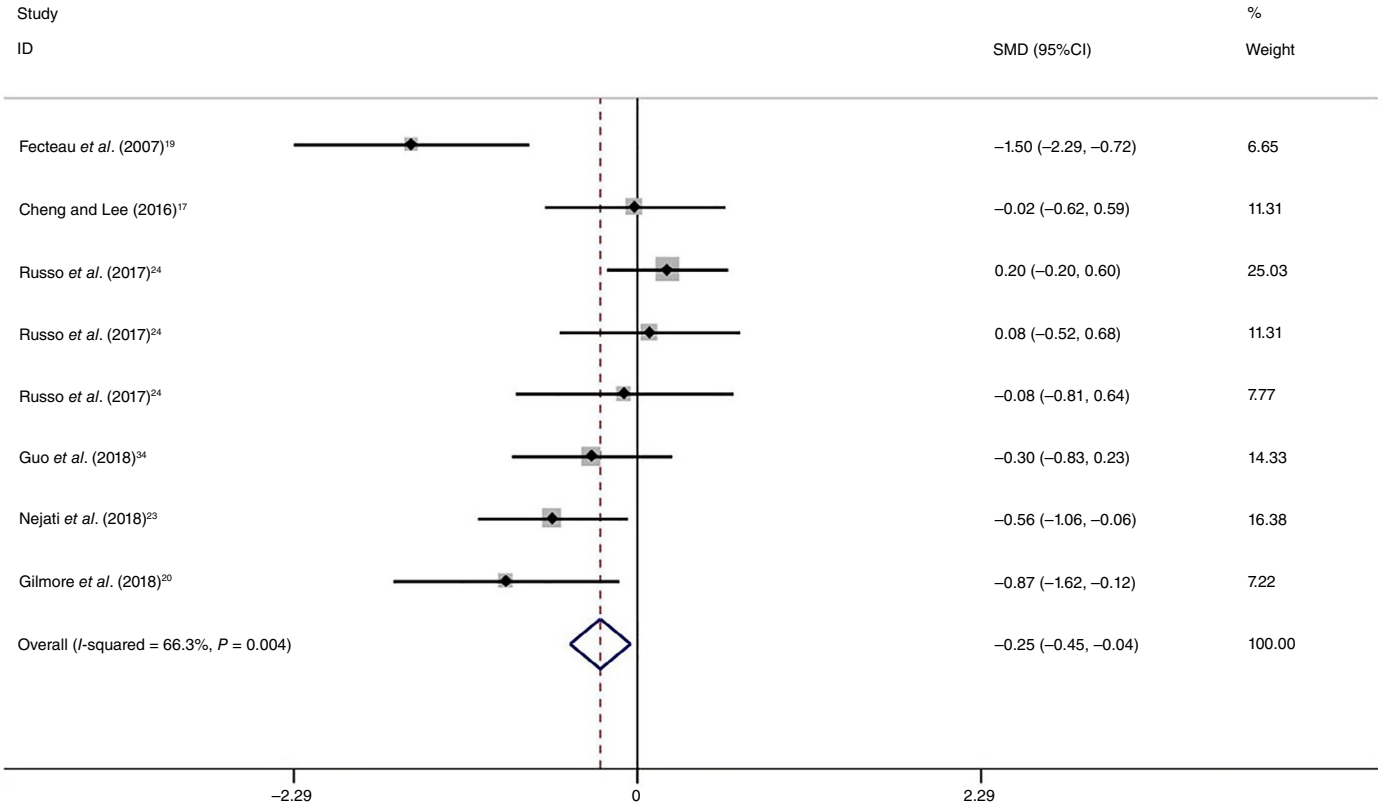

Fig.2 Pooled estimate of standardized mean difference (SMD) for transcranial direct current stimulation effects on risk-taking behaviors. CI, confidence interval.

pumps (or adjusted value) score from the BART. This score is a non-punitive and more adaptive index of the form of risk-taking propensity and behavior. Low scores of adjusted value are suggestive of low-risk behaviors.

At the quantitative analysis stage, a total of six studies and 17 clinical trials performed on 17 separate healthy samples were included in the meta-analysis. Mean values and SD of adjusted values were extracted for both intervention and sham groups. As mentioned, we created at least one synthetic ES for each study based on the number of control groups. In total, eight synthetic ES were computed for meta-analysis. Figure 2 shows the results obtained from the random effect analysis for risk-taking propensity. Findings revealed a significant effect of tDCS on risk-taking behavior overall in terms of the adjusted values (BART). The analysis showed a pooled estimated standardized ES (Cohen's d) of −0.25 (95%CI, −0.45 to −0.04), which indicates a small ES for active tDCS over the DLPFC in comparison to sham stimulation ($z = 2.40$, $P = 0.017$). However, the heterogeneity test was significant for pooling all trials ($I^2 = 66.30\%$, d.f. = 7, $P < 0.05$). This heterogeneity can be attributed either to the different parameters and protocols of stimulation, or outlier results from different original studies. Eleven trials used bilateral DLPFC stimulation and the other six trials used unilateral DLPFC stimulation. Also, we performed Egger's test to assess any potential publication bias, which revealed no significant publication bias ($P = 0.091$).

Furthermore, we performed a subgroup analysis by the montage of stimulation (unilateral and bilateral DLPFC [Figure 3] without those two outliers). The results of this subgroup analysis showed that there is no significant ES for bilateral DLPFC stimulation ($d = −0.18$; 95%CI, −0.45 to 0.08), but a significant near-medium ES for unilateral DLPFC stimulation ($d = −0.41$; 95%CI, −0.71 to −0.10). The heterogeneity test was significant for bilateral stimulation ($I^2 = 89.6\%$, d.f. = 4, $P < 0.01$), but not significant for unilateral stimulation ($I^2 = 0.0\%$, d.f. = 3, $P = 0.64$). In the bilateral subgroup, one study (Fecteau *et al.*[19]) seems to influence the excessive heterogeneity levels and can be considered as an outlier. Egger's test also showed a significant publication bias caused by this study ($P = 0.016$). After excluding this study, we conducted Egger's test again; there was no significant bias this time ($P = 0.15$). Then, we repeated this subgroup analysis. Figure 4 confirms the results of Figure 3, but here, the heterogeneity of the bilateral subgroup is no longer significant ($I^2 = 51.5\%$, d.f. = 3, $P = 0.1$). This subgroup analysis and subsequent Egger's test showed that some of the results of the study by Fecteau *et al.*[19] have publication bias. Therefore, the overall results obtained from this analysis are more valid than the initial overall result, which was described in the previous paragraph. So, let us modify the result of overall analysis as follows. The overall analysis showed a pooled estimated standardized ES (Cohen's d) of −0.20 (95%CI, −0.39 to −0.01), which indicates a small ES for active tDCS over the DLPFC in comparison to sham stimulation ($z = 2.31$, $P = 0.03$). Interestingly, the heterogeneity test was not significant here for pooling all trials ($I^2 = 39.2\%$, d.f. = 7, $P = 0.118$). Moreover, we performed a further subgroup analysis to determine the optimal approach (the optimal way to stimulate the DLPFC) for affecting risk-taking propensity using tDCS. However, given that the number of trials in each protocol category was insufficient, the ES was not significant for any of the stimulation protocols.

Discussion

The present study provides a systematic review and meta-analysis to estimate the efficacy of non-invasive TES to modulate risk-taking behaviors and risky decision-making. The random effect meta-analysis of eight synthetic trials revealed a significant ES supporting DLPFC electrical neuromodulation noninvasively, compared to sham TES in terms of reduction of risky behaviors and risk-taking propensity. Based on results of the subgroup analysis, the effect of tDCS is

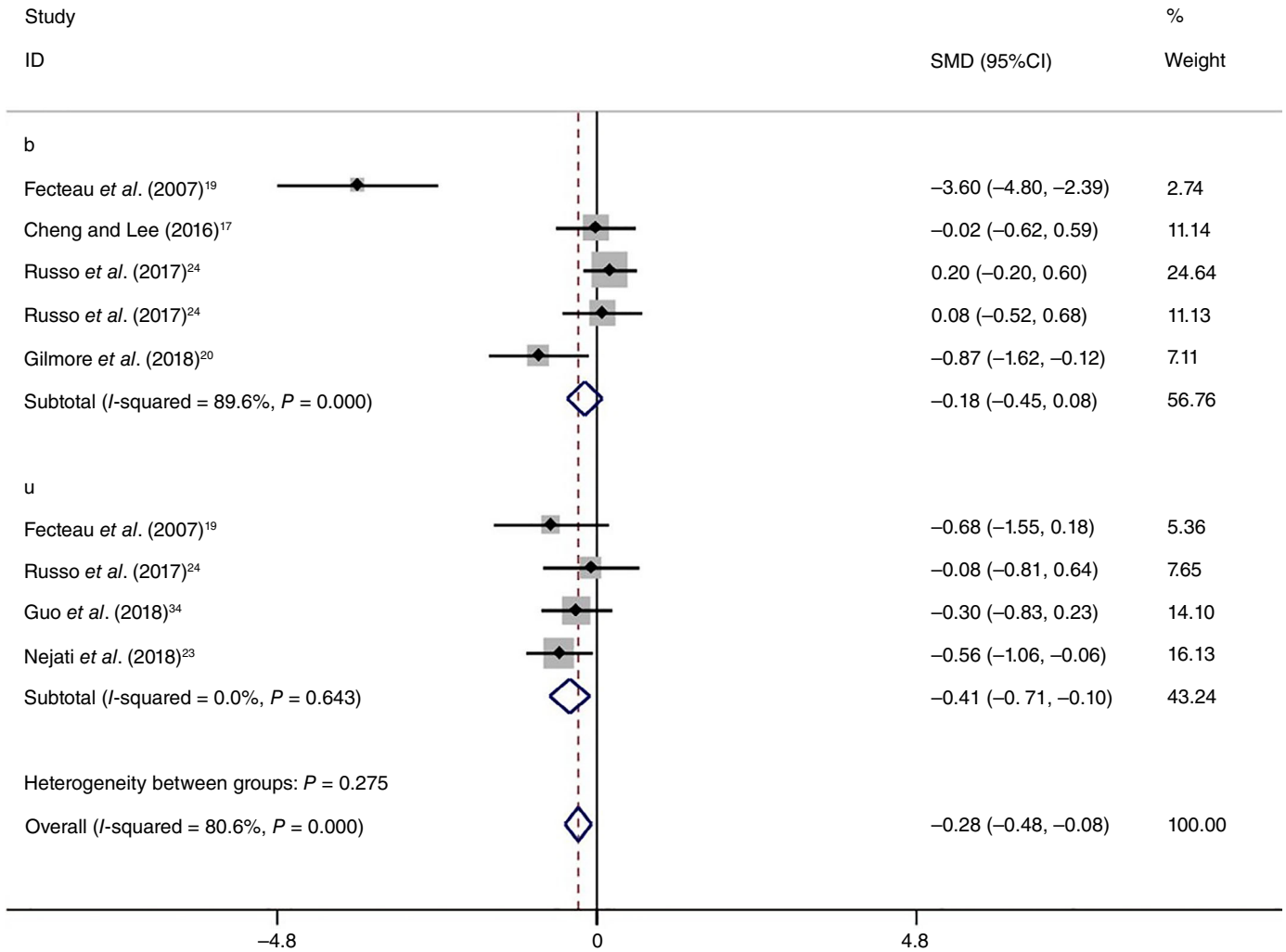

Fig.3 Pooled estimate of standardized mean difference (SMD) for transcranial direct current stimulation effects on risk-taking behaviors after sub-grouping by unilateral or bilateral protocols, without those two outlier studies specified in Figure 2. CI, confidence interval.

specific to the montage of DLPFC stimulation (bilateral or unilateral). In other words, bilateral stimulation over the DLPFC showed no significant ES, whereas the unilateral DLPFC stimulation significantly affected risk-taking behavior. In fact, this type of stimulation results in lower scores of adjusted values (BART) and, therefore, a conservative risk-averse response style compared to sham tDCS. It should be noted that although original studies have failed to alter risky behaviors using unilateral DLPFC stimulation, the result of the meta-analysis suggests that this type of brain stimulation may influence risky decision-making. This significance can be attributed to the increase in sample size and consequently the power of the study. Therefore, further studies with large sample sizes are needed to investigate the actual effect of unilateral DLPFC stimulation.

Recent cognitive neuroscience studies show that noninvasive brain stimulation, such as tDCS, can modify a wide range of behaviors in healthy people.[37] Such regulation effects on human behaviors provide new insights into the neurobiology of cognitive processes and, contrary to lesion studies, establish causal brain–behavior relations. Decision-making (particularly risk-taking propensity) is a complex type of behavior that is proved in this meta-analysis study to be modulated to a more cautious behavior with brain stimulation over the DLPFC using tDCS. In fact, the application of tDCS over the DLPFC likely modulates plasticity of the relevant brain networks, including the cortical and subcortical structures.[38–40] As a vital brain region in different cognitive processes, the DLPFC has been demonstrated to be a region associated with risky decision-making.[41, 42] However, different and contradictory results have been reported about the lateralization of DLPFC function in risk-taking and decision-making behaviors. A lesion study reported abnormal risk-taking behavior in patients with a right ventromedial PFC lesion compared to patients with a lesion in left side and healthy people.[43] Two other studies also found evidence of abnormal risk-taking behavior in patients with a left ventromedial PFC lesion.[44, 45] This dispersion is also seen in neuroimaging studies. A meta-analysis of the functional neuroimaging studies showed that bilateral activation of the PFC (mainly the OFC and DLPFC) is engaged in ambiguous and risky decision-making.[46] In another meta-analysis study of functional magnetic resonance imaging (fMRI) experiments, Mohr *et al*.[47] indicated that the right DLPFC is activated for decision risk, not for anticipation risk. In fact, the right DLPFC is associated with valuing choice options during decision-making. In an fMRI study, Heekeren *et al*.[48] indicated that the left DLPFC is activated during risky decision-making. However, recent fMRI studies demonstrated that the right DLPFC activity mediates less risky decision-making.[49, 50] These diverse results have also been reported in brain stimulation studies. Therefore, although it is difficult to conclude from these different results, both sides of the DLPFC appear to be involved, but not in a same way, in risk-taking behavior depending on the task and modality

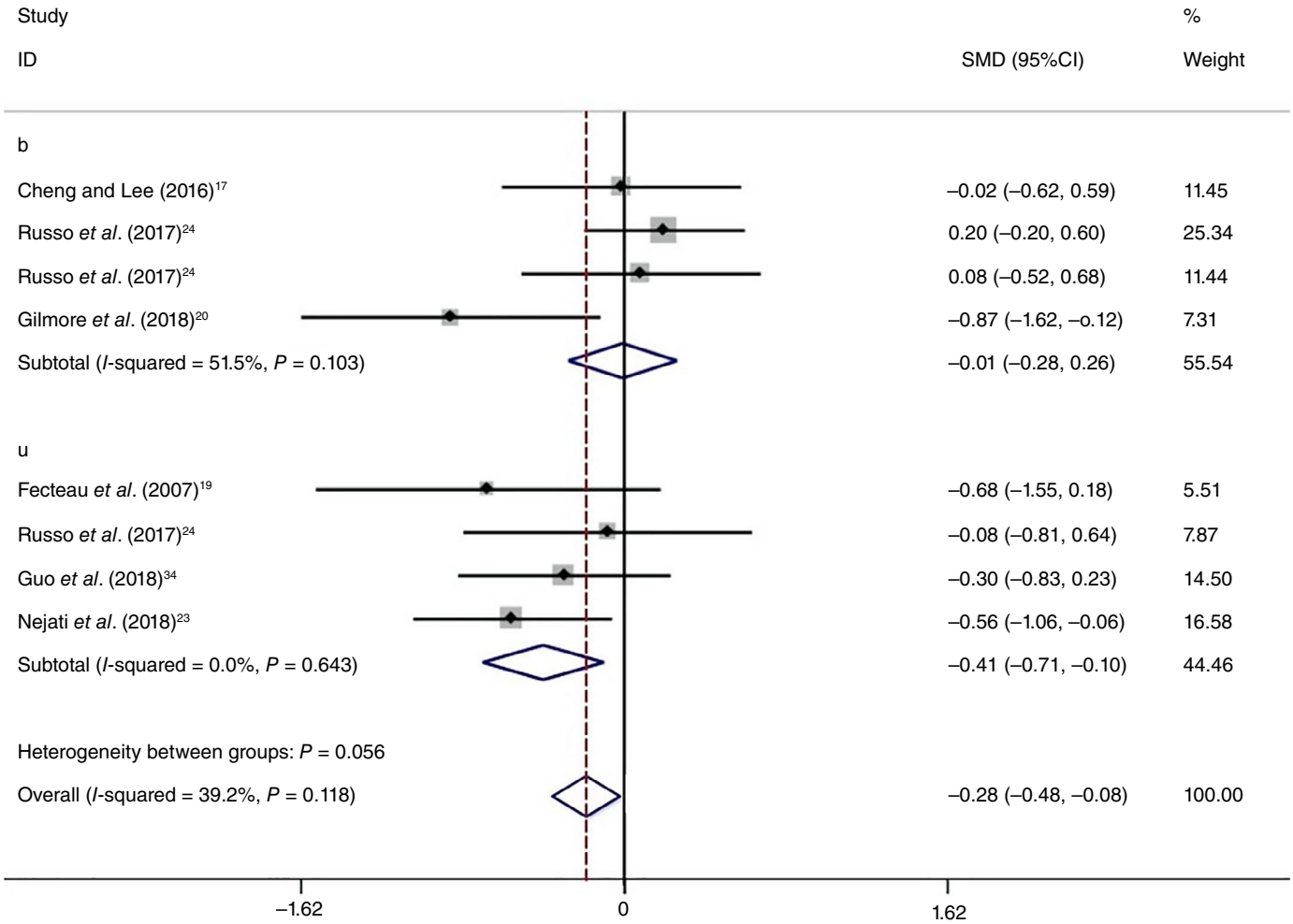

Fig.4 Pooled estimate of standardized mean difference (SMD) for transcranial direct current stimulation effects on risk-taking behaviors after sub-grouping by unilateral or bilateral protocols, without the outlier study in the bilateral subgroup. According to the results of publication bias analyses, the overall result obtained here was considered as the main overall result. CI, confidence interval.

used. This conclusion is in line with the results of our meta-analysis. Our findings demonstrate that unilateral tDCS techniques can lead to less risk-taking in decision-making. In other words, facilitation (or suppression) of activity in the left DLPFC and suppression (or facilitation) of activity in the right DLPFC make healthy people choose low-risk prospects more often. It should be noted, however, that this conclusion is limited to the tDCS technique and BART task.

It is well established that risky decision-making involves a corticolimbic brain network, including prefrontal regions, ventral striatum, amygdala, and insula.[49, 51] Responses to rewards may affect decision-making by supporting a balance between goal-directed behavior, directed by the PFC, and reward-seeking, originating in ventral striatum activity.[52] Actually, decisions under risks are determined, to some extent, by motivational states that indicate the ventral striatum activity and by evaluation and preservation of goal states, supported by activity in the PFC.[53] A critical neurotransmitter system that plays the role of an interface between limbic (i.e., midbrain) and frontal regions is the mesocorticolimbic dopamine system.[54] In fact, the PFC can affect striatal activity via different signaling pathways, including mesocortical glutamatergic projections that increase tonic striatal dopamine release. In the situations of decision-making involving reward and risk, these interactions can be defined in an activity-dependent plasticity framework that is controlled by differences in striatal dopamine release.[55] Neuroimaging studies, mostly using PET scans, have demonstrated that less risky decision-making is associated with greater right, but not left, ventral striatal dopamine release.[56, 57] On the other hand, tDCS to the DLPFC has been shown to enhance dopamine release in the right ventral striatum.[58, 59] Therefore, two conclusions can be drawn here. First, since tDCS can influence presynaptic and postsynaptic striatal dopamine receptors by modulation of DLPFC activation, differences in striatal dopamine release may change the computational properties of frontostriatal brain circuits during risky decision-making. Second, risky decision-making may associate with a predominantly right lateralized neural network, which is consistent with our findings regarding the significant effect of unilateral stimulation on risk-taking behaviors.

As mentioned, there is a significant heterogeneity between studies overall, and between bilateral stimulation protocols caused by two outlier trials. These two outliers also led to a significant publication bias generally. Although trial designs and populations under study (healthy people) are often similar, differences in the technical details of stimulation methods may serve as heterogeneity or bias sources, such as the location of the anode and cathode electrodes, current intensity, electrode size, and duration of stimulation. These are all factors that critically influence the effects of neuromodulation interventions. In addition, another important issue to note is the small or medium ES obtained in the results. Most included studies applied a single-session stimulation of 13–20 min when participants completed the BART. The effects of this short-lasting anodal and cathodal tDCS administration are primarily limited to changes in resting membrane

potentials of neurons during stimulation, which may last for up to 90 min afterward, with small alterations in synaptic plasticity.[60] Therefore, it can be expected that repetitive stimulation (i.e., cumulative effects) will lead to larger effects on synaptic modulation and thus to a larger ES.

The capacity of affecting processes involved in decision-making is of great interest, as such processes are important parts of human emotional and social functioning or even dysfunctioning. As a result, potential clinical relevance of these neuromodulation findings can be considered for patients with abnormal risk-taking behaviors. Abnormal decision-making behaviors toward more risky choices have been reported in patients with a lesion in the PFC,[61] addictive disorders,[4, 62–64] borderline personality disorder, [65, 66] and Parkinson's disease.[67, 68] For instance, patients with nicotine addiction make more risky choices[35] and patients with opiate and amphetamine addiction show higher sensitivity to reward in risk tasks.[69] Given previous great efforts to develop noninvasive brain stimulation-based clinical protocols to alleviate symptoms, such as mood elevation, by the application of repetitive transcranial magnetic stimulation over the DLPFC in depressed patients,[70] future clinical protocols can be developed based on these cognitive neuroscience findings to regulate risk-taking behaviors in different clinical populations. To this end, further research is needed to consider other brain areas involved in risk-taking and decision-making processes. One of the less studied regions of the brain is the OFC. Neuroimaging studies have demonstrated that the OFC is activated in situations involving risk-taking.[71, 72] Clinical studies have also reported an OFC dysfunction in impulsive or risky behaviors and psychiatric disorders, such as eating disorders,[73] addiction, [74] and obsessive–compulsive disorder.[75] Although some studies have targeted the OFC, there is still little evidence of the effect of stimulating this region on risk behaviors, and further research is needed to examine this issue closely.

According to the results reported in the included studies, we conducted a meta-analysis only for the BART and the average number of adjusted pumps, which is a limitation in the present work. Furthermore, low cumulative sample size in overall analysis and especially in subgroup analyses is another limitation of this research, which is caused by the low sample size in the eligible original studies. This is, along with the heterogeneity and bias, one of the main factors limiting the possibility of clearly evaluating the effects of neuromodulation for risk-taking behavior.

Conclusion

In general, the findings of the current meta-analysis research support a significant impact of neuroregulation and neuromodulation of the DLPFC on risk-taking behavior in healthy individuals. This is the first meta-analysis study proving that neuromodulation can actually result in more prudent choices in decision-making in healthy individuals. According to the obtained results, unilateral noninvasive electrical stimulation of the DLPFC can result in a conservative risk-averse response style, probably through modulating plasticity of the relevant brain networks, including cortical (other frontal areas, such as the ventromedial PFC) and subcortical (striatum, hippocampus, amygdala, and insula) structures, as well as increasing subcortical dopaminergic activity. Future clinical trials can be designed based on these cognitive neuroscience findings to regulate risk-taking behaviors in different clinical populations. To do this, however, the neuropathology of different clinical populations must be carefully considered, and then appropriate neuromodulatory protocols should be examined based on neurophysiology and symptoms specific to each disease as well as ethical considerations.

Disclosure statement

All authors claim that there are no conflicts of interest.

Author contributions

All authors contributed to the conception and design of the study. H.Z. and S-A.M. conducted the search processes. A.K., H.Z., and S-A.M. participated in screening, assessments, and data-extraction processes. H.Z. and S-A.M. performed the statistical analyses. A.K., G.P.J., and M.R.M. discussed the results and wrote the manuscript. All authors read and approved the finalized manuscript.

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