*European Psychiatry*

**www.cambridge.org/epa**

# Prefrontal cortex stimulation prevents stress-induced HPA axis reactivity in people at familial risk of schizophrenia

Ondine Adam[1,2], Mélanie Perret[1,2], Louis Simon[1,2,3], Clément Dondé[4,5,6,7], Véronique Raverot[8,9], William Vallet[1,2], Marine Mondino[1,2] and Jérôme Brunelin[1,2]

[1]Le Vinatier Psychiatrie Universitaire Lyon Métropole, Bron, France; [2]CNRS, INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028 UMR5292, PsyR2 Team, Université Claude Bernard Lyon 1, Bron, France; [3]Psychiatric Emergency Service, Hospices Civils de Lyon, Lyon, France; [4]Université Grenoble Alpes, Grenoble, France; [5]INSERM U1216, Grenoble, France; [6]Psychiatry Department, CHU Grenoble Alpes, Grenoble, France; [7]Psychiatry Department, Centre Hospitalier Alpes-Isère, Saint-Egrève, France; [8]CNRS, INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028, WAKING Team, Université Claude Bernard Lyon 1, Bron, France and [9]Centre de biologie et de pathologie Est, Hospices Civils de Lyon, Groupement Hospitalier Est, LBMMS, Lyon, France

**Research Article**

**Cite this article:** Adam O, Perret M, Simon L, Dondé C, Raverot V, Vallet W, Mondino M, Brunelin J (2025). Prefrontal cortex stimulation prevents stress-induced HPA axis reactivity in people at familial risk of schizophrenia. *European Psychiatry*, **68**(1), e55, 1–8 https://doi.org/10.1192/j.eurpsy.2025.2455

Received: 03 February 2025
Revised: 24 March 2025
Accepted: 30 March 2025

**Keywords:**
at risk; cortisol; schizophrenia; stress; tDCS

**Corresponding author:**
Jérôme Brunelin;
Email: jerome.brunelin@ch-le-vinatier.fr

## Abstract

**Background.** Schizophrenia is a multifactorial disorder with a range of risk factors. Dysregulation in the systems involved in the stress response is a key component of its pathophysiology. Individuals at risk of developing schizophrenia exhibit hyperreactivity to stress and altered cognitive performance, both known as vulnerability markers. This study aims to determine whether stimulation of the prefrontal cortex can reduce reactivity to stress in unaffected siblings of patients with schizophrenia.

**Methods.** In a randomized, sham-controlled trial, 27 participants were assigned to receive either active ($n$ = 14) or sham ($n$ = 13) transcranial direct current stimulation (tDCS) over the prefrontal cortex for 30 min during exposure to an acute stressor. The stress response was measured biologically, via salivary cortisol levels, and cognitively, through a reality monitoring task, which serves as an intermediate cognitive vulnerability marker.

**Results.** In contrast to the sham condition, active stimulation significantly reduced cortisol release in response to stress ($F_{(9,216)} = 1.972$; $p = 0.04$) and prevented stress-induced impairment in reality monitoring ($F_{(1,23)} = 9.954$; $p = 0.004$).

**Conclusions.** These findings suggest that tDCS should be a promising tool for reducing stress-induced biological and cognitive reactivity in a population at risk of schizophrenia.

## Introduction

Schizophrenia accounts for a significant proportion of the global burden of mental disorders in terms of years lived with disability, despite its relatively low prevalence [1]. Although the etiology of schizophrenia remains incompletely understood, there is an increasing body of evidence indicating a multifactorial pathology involving both environmental and genetic components. The role of genetics has been highlighted by the progressive increase in the risk of developing the disease with the genetic proximity of an individual to a patient [2]. Siblings of patients are therefore considered to be at an elevated risk, displaying a tenfold increase in the likelihood of developing schizophrenia compared to the general population. They also exhibited reduced cognitive performance at an intermediate level between the deficits observed in patients and the performance observed in healthy individuals. Deficits have been observed in a range of broad cognitive domains, such as working memory, attention, and executive function [3–6], as well as in specific cognitive processes associated with psychotic symptoms, such as reality monitoring. Reality monitoring is a cognitive process that enables individuals to differentiate between memories of imagined events and memories of perceived real events [7, 8].

However, the heritability of schizophrenia is limited to 80% [9], thereby suggesting the presence of non-genetic risk factors. In this regard, the neural diathesis-stress model of schizophrenia posits that, in addition to the neurodevelopmental part, the interplay between genetic vulnerability and environmental stressors is responsible for the triggering of neurodegenerative processes, which in turn increase the risk of developing this pathology [10]. Indeed, evidence indicates an association between stress exposure and increased risk of schizophrenia, particularly in vulnerable populations [11–13].

Alterations in the systems involved in the stress response [14–19], particularly in the activity of the hypothalamic–pituitary–adrenal (HPA) axis, the main effector of the stress response [20], have been frequently reported in patients with schizophrenia. The basal concentrations of



EUROPEAN PSYCHIATRIC ASSOCIATION

cortisol, a reliable marker of HPA axis activation, have been found to be systematically increased in patients with first-episode psychosis or established schizophrenia [21, 22], as well as in clinical high-risk individuals with attenuated symptoms [23]. Abnormalities have also been observed in the HPA axis stress reactivity. Patients with schizophrenia or first-episode psychosis exhibited diminished reactivity, as evidenced by reduced cortisol release [21, 24], whereas individuals with prodromes showed HPA axis hyperreactivity, characterized by exaggerated cortisol release [25, 26]. Remarkably, hyperreactivity to stress has also been reported in unaffected first-degree relatives of patients with schizophrenia [18, 27], suggesting that hyperreactivity could be an endophenotype of schizophrenia. Moreover, altered brain network dynamics during stressful situations have recently been documented in siblings of patients [28]. These impairments would reflect the interactions between genes and the environment, positioning the activation of stress effector systems such as the HPA axis as a core component of the physiopathology of schizophrenia [10].

Among the brain regions involved in the regulation of the stress response, the prefrontal cortex exerts an inhibitory influence on the HPA axis through indirect neuronal connections [29]. However, stress can disrupt the functioning and integrity of the prefrontal cortex [30]. Recent studies have suggested that stimulation of the prefrontal cortex using non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), can reduce stress-related cortisol release in healthy individuals, thereby reinforcing the prefrontal cortex's regulatory influence over the HPA axis [31]. tDCS is a promising tool that delivers a weak electric current, modulating the activity of cortical regions beneath the stimulation electrodes [32–34] and interconnected brain regions with the stimulated area [35]. Additionally, prefrontal cortex stimulation with tDCS has been demonstrated to modulate cognitive processes, including working memory [36] and reality monitoring [37]. The repeated application of tDCS has been associated with improvements in various symptoms across different pathologies, particularly in patients with schizophrenia and depression [38]. It has been postulated that these beneficial effects on stress-related disorders may be mediated by the impact of the prefrontal cortex (PFC) stimulation on the HPA axis activity [39]. This brain region is therefore a prime target for reducing the stress response in individuals with dysfunctional stress response systems. In siblings of patients with schizophrenia, enhancing prefrontal cortex activity could help restore inhibitory control over an exacerbated response, the latter being a potential contributor to the physiopathology of this disorder.

In this context, we aimed to evaluate the physiological and behavioral effects of stimulating the PFC using tDCS in first-degree relatives of patients with schizophrenia when confronted with an acute stressful situation. We hypothesized that active PFC stimulation, compared to sham stimulation, would prevent the effects of stress, and that we would be able to measure these effects at two different levels: (i) a physiological level by restraining the stress-induced release of cortisol, the end product of the HPA axis, and (ii) a cognitive level by preventing stress-induced changes in reality monitoring performances, which are known to be affected by acute stress exposure [40, 41].

## Methods

### Participants

We conducted a randomized, sham-controlled, triple-blind trial involving 28 participants. The participants were first-degree relatives, unaffected siblings of patients diagnosed with schizophrenia, aged between 18 and 30 years. Exclusion criteria were: a current diagnosis or history of a psychiatric (interview with a psychiatrist), somatic or neurological disorder; current any medication treatment (excluding contraception); pregnancy or breastfeeding; and contra-indications to tDCS (including head trauma, metal implants in the head, history of stroke, or unexplained loss of consciousness).

Participants were randomly assigned to receive either a sham or active tDCS session (randomization ratio of 1:1 with varying block sizes, 2, 4, and 6). The sample size was calculated a priori to have 80% power with a hypothesized 35% elevation of cortisol in the active group and 80% in the sham group, based on the results of a previous study in 30 healthy volunteers using the same design and outcomes [42]. Due to missing data (insufficient saliva in 8 out of the 10 collected samples), a participant was not included in the analysis. The final analysis sample consisted of 27 participants, 14 in the active group and 13 in the sham group. To minimize the influence of sex hormones, females were included during the first phase of the menstrual cycle.

The participants were recruited from the siblings of patients who were hospitalized at Le Vinatier Hospital (Bron, France) between 2019 and 2023. All participants gave written informed consent before taking part in this study. This study complied with the Declaration of Helsinki for trials involving human participants and has received approval from a local ethics committee (Comité de Protection des Personnes Est IV, France, A00850, on April 10, 2017). The study protocol was pre-registered on a public database (https://clinicaltrials.gov/, NCT03217357, on July 5, 2017).

### Overview of the experimental procedure

All experimental sessions took place in the morning, with participants arriving at 8:30 am. To minimize inter-individual variations associated with the nychthemeral cortisol cycle, the stress induction protocol began between 10:30 and 11 am for all participants. Upon arrival at the laboratory, participants completed a series of self-report questionnaires, which were followed by a computerized reality monitoring task. An initial saliva sample was then collected as the basal sample. Subsequently, a 30-min tDCS session was initiated, followed by the beginning of the instruction and anticipation phase of the MAST protocol, as done in a previous study conducted with healthy volunteers [42]. Six saliva samples were collected at 5-min intervals during the tDCS session (Figure 1). After the stimulation period, three additional samples were collected at 15-min intervals while participants filled in the self-report questionnaires and the computerized reality monitoring task a second time.

### Transcranial direct current stimulation

The tDCS was administered using a DC-plus Stimulator (NeuroConn GmbH, Germany). The current was delivered through two 3 × 3 cm electrodes. Because of the key role of the PFC in stress regulation [29, 30], the electrodes were placed following the 10/20 international EEG electrode placement system, with the anode over F3 and the cathode over F4 (corresponding to the left and right PFC, respectively). A conductive paste (Ten20, Weaver and Company, USA) was applied to the surface of the electrodes in contact with the skin. Stimulation was administered for 30 min at 2 mA, with a 30-s ramp-up and ramp-down periods. The stimulation parameters (30 min, 2 mA) and electrode montage were selected based on our previous studies, in which tDCS not only reduced stress reactivity in healthy volunteers [42], but also improved

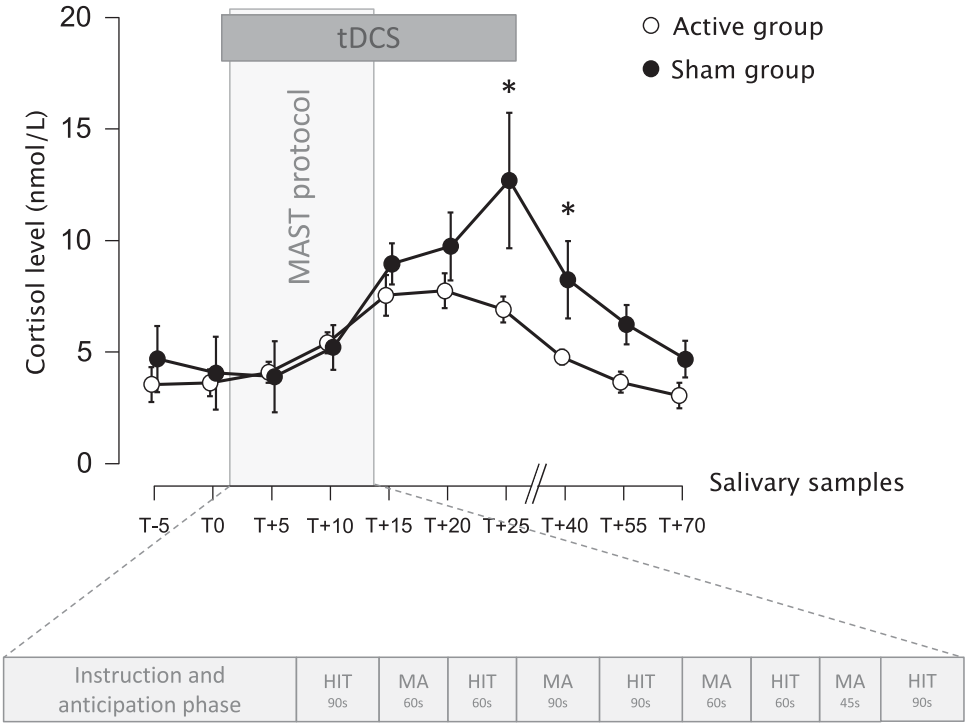


**Figure 1.** Variations in cortisol concentrations during the experimental protocol. The timing of the collection of salivary samples was noted in relation to the onset of the stimulation (tDCS) and stress (MAST) periods (*T0*). The repeated-measures ANOVA revealed a significant interaction between Time and Group. The mean cortisol levels increased to 241% of the basal level in the active group, as compared to 385% in the sham group. MAST protocol = Maastricht Acute Stress Test, which includes the Hand Immersion Test (HIT) in 8°C cold water and Mental Arithmetic (MA) stress tasks and their duration. *$p < 0.05$ (T+25 and T+40).

cognition [43] and alleviated symptoms in patients with major depression [44]. Sham stimulation consisted of applying a 2-mA current only during the first minute of the stimulation period (with 30 s ramp up/ramp down). Blinding was ensured using the "Study Mode" of the tDCS device, which allows the entry of an individual's five-digit code corresponding to either active or sham stimulation. The device then delivers the stimulation (active or sham, based on the code) without the knowledge of the person administering the stimulation or the participant. Each code was assigned to a participant by a third party, thus ensuring blinding of participants, experimenters, and statisticians.

### Stress induction protocol

Stress was induced using an adapted version of the Maastricht Acute Stress Test (MAST, [45]), which combines psychogenic and physical stressors that we previously used in a study with the same design [42]. After 5 min of anticipation, during which the experimenter informed the participant that the stress exposure was imminent, the participant was subjected to alternating periods of different durations of both hand immersion in water at 8 °C, which constituted a physical stressor, and mental arithmetic, which constituted a psychogenic stressor, for 10 min (see Figure 1 for details of the period's duration). The order of presentation and the duration of the physical and mental stressors were the same for each subject, while the participants were not informed of the duration of each sequence. During the mental arithmetic periods, participants were required to perform subtractions (e.g., counting backward from 3125 in steps of 17) in the quickest possible time without making any mistakes. Whenever they hesitated or made a mistake, the experimenter provided negative feedback and restarted the trial from the beginning.

### Reality monitoring

Reality monitoring performance was assessed before and after the stress protocol using a computerized version of the task previously developed and validated in the lab [46]. The task consisted of a presentation phase immediately followed by a test phase. In the presentation phase, 16 words were displayed on a computer screen in a sequential order for a duration of 3 s each, with each word preceded by an instruction presented for 3 s. The instructions were either to "*Imagine hearing the following word*" for half of the words or to "*Listen to the following word*" for the other half. In the subsequent test phase, participants were presented with 24 words in succession, including the 16 words from the presentation phase (8 imagined and 8 heard) and 8 new words. Participants were asked to determine the source of each word (i.e., "Imagined," "Heard," or "New"). To acquaint themselves with the task requirements and to ensure proper understanding of the instructions, all participants completed a short training session prior to the main task. Two distinct lists of 24 words were used to avoid any learning effect between the pre- and post-stress and stimulation assessments.

### Outcomes

The primary outcome used to assess the reactivity to stress was cortisol levels, which were estimated by measuring salivary cortisol concentration. Salivary cortisol is a reliable marker of cortisol variations observed in the blood [47], thus allowing us to avoid

the stress associated with blood sampling. A total of 10 saliva samples were collected throughout the course of the experiment to monitor the kinetics of cortisol release. Saliva was sampled using Salivettes® (Sarstedt, Germany). The Salivettes were then centrifuged and stored at −20 °C until analysis. Cortisol levels were determined by liquid chromatography coupled with tandem mass spectrometry relative to reference values [48].

Stress reactivity was also assessed by cognitive measures, comparing reality monitoring performance before and after the period of stress and stimulation. Reality monitoring performance was assessed as the total number of correct responses for each task condition: imagined words (range 0–8), heard words (range 0–8), and new words (range 0–8).

Finally, schizotypal personality was assessed at baseline using the Schizotypal Personality Questionnaire (SPQ) [49] to control this parameter, which could influence cortisol levels. The level of depressive symptoms was assessed using the 13-item self-reported Beck Depression Inventory (BDI) [50].

To assess the safety of tDCS in siblings of patients with schizophrenia, participants were asked to report any side effects they had experienced, based on the criteria established by Antal and colleagues [51]. Moreover, they rated the potential pain associated with the electrical current application using a visual analog scale. Blinding was assessed at the end of the session by both the experimenter and the participants (guessing method).

### Statistical analyses

All statistical analyses were performed using JASP (version 0.16.03, JASP team, 2022). Distribution normality and homogeneity of variances assumptions were controlled with the Shapiro–Wilk test and Levene's test, respectively. Baseline sociodemographic and clinical characteristics, as well as tDCS safety data of both groups, were compared using Fisher's exact tests for qualitative variables, and bilateral Student's *t*-test or Mann–Whitney *U* test for quantitative variables. A Welch correction was applied when a deviation from the assumption of equal variance was detected.

As primary analysis, we conducted a repeated-measure analysis of variance (rmANOVA) on cortisol concentration with Time (10 time points corresponding to the 10 saliva samples) and Group (active, sham) as factors. Age was introduced as a covariate in the analysis. Missing cortisol data (insufficient quantities of saliva to measure cortisol) were imputed using spline interpolation.

To evaluate the effects on reality monitoring performance, a rmANOVA was performed on the number of correct responses, with Time (pre- and post-stimulation) and Task Condition (hear, imagine, or new) as within-subject factors, and Group (active, sham) as a between-subject factor.

The alpha level was set at .05, and partial eta squared ($\eta_p^2$) was reported as the measure of effect size.

## Results

Active and sham groups were comparable at baseline concerning socio-demographic and clinical characteristics (Table 1).

### tDCS effects on cortisol release

The rmANOVA revealed a significant main effect of Time ($F_{(9,216)} = 2.174$; $p = 0.025$; $\eta_p^2 = 0.083$) and a significant interaction between group and time ($F_{(9,216)} = 1.972$; $p = 0.044$; $\eta_p^2 = 0.076$) (Figure 1). No significant effect of age ($F_{(1,24)} = 4.063$; $p = 0.055$; $\eta_p^2 = 0.145$), group ($F_{(1,24)} = 2.651$; $p = 0.117$; $\eta_p^2 = 0.099$), or Time × Age interaction ($F_{(9,\ 216)} = 1.509$, $p = 0.146$, $\eta_p^2 = 0.059$) was observed. Post-hoc comparisons were conducted between the active and sham groups at each time point to further examine the significant Time × Group interaction. Significant differences in cortisol elevation were observed at time points 7 (T+25) and 8 (T+40), with the active group showing lower cortisol increases than the sham group (Mean Difference = −8.385, SE = 2.670, $t = -3.140$, $p = 0.002$, Cohen's $d = -1.285$ for time point 7; Mean Difference = −6.422, SE = 2.670, $t = -2.405$, $p = 0.019$, Cohen's $d = -0.984$ for time point 8). No other time points showed statistically significant differences (all $p_{corr} < 0.05$). The mean cortisol levels increased to 241% of the basal level in the active group, as compared to 385% in the sham group (Figure 1).

**Table 1.** Sociodemographic and clinical data of the participants

| | Active group | | Sham group | | |
|---|---|---|---|---|---|
| | Mean (SD) | *n* | Mean (SD) | *n* | *p*-Value |
| *n* total | | 14 | | 13 | |
| Age (years) | 22.3 (3.4) | | 24.7 (3.4) | | 0.09 |
| Sex (F/M) | | 11/3 | | 9/4 | 0.67 |
| Laterality (R/L) | | 11/3 | | 13/0 | 0.22 |
| Education (years) | 14.6 (2.7) | | 14.6 (2.7) | | 0.94 |
| $BDI_{13}$ | 3.6 (3.6) | | 2.4 (2.3) | | 0.33 |
| SPQ | 12.1 (10.5) | | 12.4 (7.9) | | 0.93 |

Abbreviations: $BDI_{13}$, Beck Depression Inventory; SD, standard deviation; SPQ, Schizotypal Personality Questionnaire; *p* values, Fisher's exact test (sex and laterality) and Student's *t*-test for other variables.

### tDCS effects on reality monitoring

Two participants were excluded from these analyses due to missing data, resulting in 25 participants, divided between the active ($n = 13$) and sham ($n = 12$) groups.

The rmANOVA revealed a significant interaction between Time and Group ($F_{(1,23)} = 9.954$; $p = 0.004$; $\eta_p^2 = 0.302$; Figure 2), and a significant interaction between Task and Group ($F_{(2,46)} = 3.349$; $p = 0.044$; $\eta_p^2 = 0.127$). No significant interactions were observed between Time and Task ($F_{(2,46)} = 1.931$; $p = 0.16$; $\eta_p^2 = 0.077$) and between Time, Group, and Task ($F_{(2,46)} = 0.953$; $p = 0.39$; $\eta_p^2 = 0.040$). The rmANOVA revealed a significant main effect of Task ($F_{(2,46)} = 45.317$, $p < 0.001$, $\eta_p^2 = 0.663$). No significant main effects were found for Time ($F_{(1,23)} = 1.741$, $p = 0.200$, $\eta_p^2 = 0.070$) or Group ($F(1,23) = 0.002$, $p = 0.964$, $\eta_p^2 = 0.0001$).

Post hoc analyses for the interaction between Time and Group indicated a significant reduction in the number of correct responses between pre- and post-stimulation in the sham group (Mean Difference = 0.750, SE = 0.242, $t = 3.102$, Cohen's $d = 0.552$, $p = 0.005$; Figure 2). The active group showed no statistically significant change in performance over time (Mean Difference = −0.308, SE = 0.232, $t = -1.325$, Cohen's $d = -0.227$, $p = 0.198$). Findings suggested that active tDCS may prevent stress-induced effects on reality monitoring performance. This effect seems driven by a 22% decrease in the recognition of imagined words in the sham group (8% for heard words), whereas a 5% increase in performance was observed in the active group (14% for heard words).

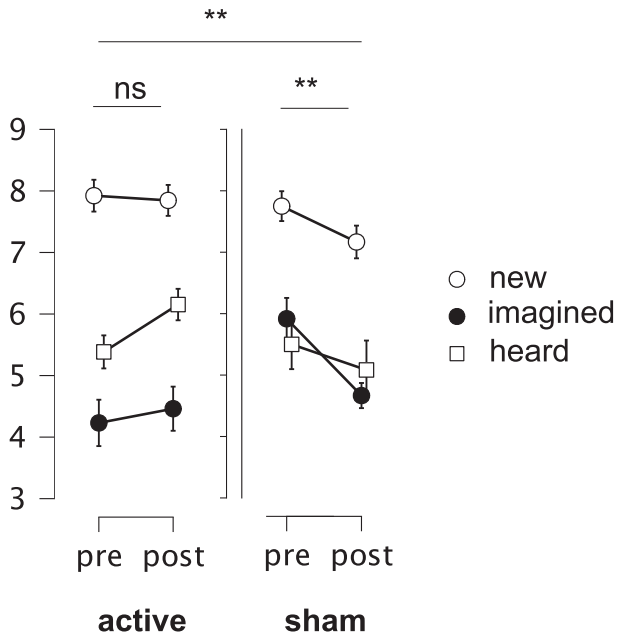


**Figure 2.** Variations in reality monitoring performances (number of correct responses). There was a significant interaction between Time (pre- and post-stress) and Group (active or sham tDCS). We observed a significant reduction in the number of correct responses between pre- and post-exclusively in the sham group, regardless of the task condition (imagined, heard, or new). $^{**}p < 0.01$; ns, not significant.

### *Safety and blinding*

Stimulation was well tolerated by all participants, with mild discomfort reported in both groups during application. Self-reported pain induced by tDCS, assessed on a Visual Analog Scale (VAS) from 0 to 10, showed no significant difference between the groups: the sham group reported an average pain level of 3.8 (SD = 3.2), while the active group reported an average of 2.8 (SD = 2.8) ($p = 0.38$). Similarly, no significant difference was observed in the frequency of tDCS-related side effects between the groups ($p = 0.33$).

Regarding blinding, neither the participants (log OR = −0.54, $p = 0.71$) nor the experimenters (log OR = −1.64, $p = 0.07$) were able to correctly identify the stimulation condition to which the participant had been subjected.

## Discussion

This randomized sham-controlled study investigated the impact of bifrontal tDCS on stress reactivity in unaffected siblings of patients with schizophrenia. To the best of our knowledge, this is the first study to investigate this paradigm in a population at risk of psychosis, which is thought to present an exaggerated response to stress. A single session of tDCS over the prefrontal cortex (PFC) delivered during acute stress resulted in a reduction in stress-induced cortisol release and cognitive changes in participants who received active stimulation compared to those who received sham stimulation. These findings suggest that tDCS may attenuate both biological and cognitive responses to stress, which are known to be hyperactive in people at risk for schizophrenia. For example, in a comparable study using tDCS during stress exposure with the MAST protocol conducted in healthy volunteers [42], we observed a mean increase in cortisol of 179.8% in the sham group and a 138.5% increase in the active group. In contrast, in the current study conducted in unaffected siblings of patients with schizophrenia, we observed a 385% increase in cortisol in the sham group and a 241% increase in the active group, in support of the hypothesis of stress hyper-responsiveness in this population (see Figure 1).

The observed effects on cortisol release suggested that tDCS may enhance the inhibitory control of the prefrontal cortex over the HPA axis stress reactivity in acute stress situations. These results are consistent with lesion studies, which have identified the prefrontal cortex as playing a crucial role in stress regulation [52], through indirect inhibitory projections on the paraventricular nucleus of the hypothalamus [29]. These findings are also consistent with other noninvasive brain stimulation studies that have reported a reduction in stress-induced cortisol release following a single session of brain stimulation over the PFC in healthy volunteers [31]. In stressful situations, the performance of executive functions is disrupted [42, 53, 54], which also suggests an alteration in the activity of the prefrontal cortex. This region might then no longer be able to exert its inhibitory control over the HPA axis. Assuming that tDCS may have increased the PFC excitability in the current study, the inhibitory control of the PFC over the effector structures of the stress response could be reinforced, exerting its influence from the onset of stress. Our results suggested that this improved regulation of the stress response would manifest itself in a reduced release of cortisol by the HPA axis.

In addition to inhibiting stress-induced cortisol release, tDCS appears to mitigate the adverse effects of stress on reality monitoring. Indeed, a significant detrimental reduction in performance was observed in the sham group following stress induction, whereas no such reduction was observed in the active group. These findings are in contrast with those of previous studies involving healthy participants, which reported enhanced performance following stress [40, 41]. The ambivalent effect of stress on reality monitoring in healthy and at-risk individuals may also be explained by the timing of stimulation to the task. This is evidenced by a previous study, which reported decreased memory when stress was induced before the encoding phase and improved memory when stress was induced between the encoding and the retrieval phases [55]. Furthermore, our results do not support the idea that stress specifically impairs recognition of a particular type of source; rather, they suggest a global deficit in reality monitoring. Notably, although not statistically significant, we observed that stress may impair recognition of imagined words more than heard words. These results are consistent with previous studies reporting that acute stress affects mental imagery [56] but not auditory perception [57]. Moreover, our results indicated that active bifrontal tDCS would prevent the detrimental effect of stress on reality monitoring. A recent review has highlighted the positive effects of prefrontal stimulation on reality monitoring performance in healthy individuals [37]. Indeed, the prefrontal cortex is considered a key region for reality monitoring [58], and a reduction in its activity has been associated with impaired reality monitoring performance in patients with schizophrenia [59]. Consequently, the preservation of reality monitoring observed after active bifrontal tDCS could be attributed to the prevention of stress-induced alterations in prefrontal cortex activity, thereby sustaining the neural activation of this region during the task. This perspective is of considerable interest, given that these cognitive alterations have been associated with symptoms of schizophrenia [60].

Improving the biological and cognitive stress response in unaffected siblings of patients with schizophrenia is crucial, as these individuals have elevated mean daily cortisol levels and an

exaggerated cortisol response to acute stress [18, 61, 62]. Altered cortisol levels have been repeatedly associated with an increased risk of psychosis. Indeed, individuals at clinical risk of schizophrenia exhibited increased cortisol levels at baseline and in response to stress [23, 63]. Furthermore, individuals who developed psychosis had higher initial baseline cortisol levels than those who remitted and controls [25]. By normalizing the stress response of at-risk populations, it might be possible to prevent the degenerative processes that are responsible for the onset of schizophrenia and the worsening of symptoms. The diathesis-stress model proposes that environmental stresses will alter the HPA axis, as well as brain regions involved in regulating the stress response [10]. The accumulation of these alterations to a breaking point would then be responsible for the onset of the first symptoms. Acting on the systems involved in the stress response in at-risk populations, such as siblings of patients, would therefore appear to be the key to curbing these pathological mechanisms. We chose to investigate these mechanisms in young adults, believing that they had not yet reached their peak risk for developing schizophrenia and could therefore still benefit from the effects of tDCS [64].

This study has some limitations that need to be emphasized. Firstly, we included only siblings of patients, which precluded comparison of stress response with a control group. Secondly, although the sex distribution was balanced between the groups (11 females and 3 males in the active group versus 9 females and 4 males in the sham group), it has been reported that sex may influence stress response [65]. Given the limited sample size, we did not conduct a subgroup analysis. However, the effects of this intervention should be explored separately in these populations. Finally, although the bifrontal model is thought to be able to reach areas of the brain close to the electrodes, we have not been able to verify which areas are actually affected by the stimulation. Further studies combining tDCS, stress induction, and neuroimaging are required to ascertain whether this region is indeed involved in regulating the stress response. Moreover, the specific effect of the bifrontal montage on stress response should be validated by comparison with other active control montages. Lastly, the timing between the stress situation and the tDCS session appears to be a critical factor. A recent review of the literature on this specific issue [31] indicates that, for beneficial effects on cortisol release, stimulation sessions must be delivered either before or during the stress situation. Delivering a brain stimulation session after stress exposure did not result in modulation of cortisol release. In our study, we chose to administer tDCS during stress exposure [42]. Further research exploring the effects of delivering tDCS before stress exposure is warranted to better understand its potential as a preventive tool in real-life situations.

In conclusion, this study highlights the potential of tDCS as an effective intervention to prevent exaggerated stress-induced cortisol release and protect against cognitive alterations induced by stress in first-degree relatives of patients with schizophrenia. These results offer new insights into the development of early intervention strategies for individuals at risk for psychosis, who display hyperreactivity to stress, but also in people at risk for other psychiatric conditions, where abnormal stress responses have been observed.

**Data availability statement.** Data are available upon request from the corresponding author [J.B.].

**Acknowledgements.** We thank the Fondation Pierre Deniker for their interest in this research and funding support for [O.A.]. We thank the Fondation de l'Avenir for their interest in this research and funding support for [C.D.]. We would like to thank the medical investigators from the Clinical Units of CH Le Vinatier for their assistance in participant recruitment and screening.

**Financial support.** This research was supported by the Brain and Behavior Research Foundation BBR-NARSAD YI grant 2013, (#20988) [J.B.] and by the scientific research council of Le Vinatier Hospital (#2016-CSRJ01; #2019-CSRL08) [J.B.].

**Competing interest.** The authors have nothing to disclose.

## References

[1] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137–50.

[2] McGue M, Gottesman II. The genetic epidemiology of schizophrenia and the design of linkage studies. Eur Arch Psychiatry Clin Neurosci. 1991; 240(3):174–81.

[3] Xu F, Xian Z. Study investigating executive function in schizophrenia patients and their unaffected siblings. PLoS One. 2023;18(4):e0285034.

[4] Velthorst E, Mollon J, Murray RM, de Haan L, Germeys IM, Glahn DC, et al. Cognitive functioning throughout adulthood and illness stages in individuals with psychotic disorders and their unaffected siblings. Mol Psychiatry. 2021;26(8):4529–43.

[5] Cella M, Hamid S, Butt K, Wykes T. Cognition and social cognition in non-psychotic siblings of patients with schizophrenia. Cogn Neuropsychiatry. 2015;20(3):232–42.

[6] Saoud M, d'Amato T, Gutknecht C, Triboulet P, Bertaud JP, Marie-Cardine M, et al. Neuropsychological deficit in siblings discordant for schizophrenia. Schizophr Bull. 2000;26(4):893–902.

[7] Brunelin J, d'Amato T, Brun P, Bediou B, Kallel L, Senn M, et al. Impaired verbal source monitoring in schizophrenia: an intermediate trait vulnerability marker? Schizophr Res. 2007;89(1):287–92.

[8] Lavallé L, Dondé C, Gawęda Ł, Brunelin J, Mondino M. Impaired self-recognition in individuals with no full-blown psychotic symptoms represented across the continuum of psychosis: a meta-analysis. Psychol Med. 2021;51(16):2864–74.

[9] Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, et al. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide danish twin register. Biol Psychiatry. 2018;83(6):492–8.

[10] Pruessner M, Cullen AE, Aas M, Walker EF. The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci Biobehav Rev. 2017;73:191–218.

[11] Oliver D, Reilly TJ, Baccaredda Boy O, Petros N, Davies C, Borgwardt S, et al. what causes the onset of psychosis in individuals at clinical high risk? A meta-analysis of risk and protective factors. Schizophr Bull. 2020;46(1): 110–20.

12] Gomes FV, Grace AA. Adolescent stress as a driving factor for schizophrenia development—a basic science perspective. Schizophr Bull. 2017;43(3): 486–9.

13] van Os J, Kenis G, Rutten BPF. The environment and schizophrenia. Nature. 2010;468(7321):203–12.

14] Castro MN, Bocaccio H, De Pino G, Sánchez SM, Wainsztein AE, Drucaroff L, et al. Abnormal brain network community structure related to psychological stress in schizophrenia. Schizophr Res. 2023;254:42–53.

[15] Schifani C, Tseng HH, Kenk M, Tagore A, Kiang M, Wilson AA, et al. Cortical stress regulation is disrupted in schizophrenia but not in clinical high risk for psychosis. Brain. 2018;141(7):2213–24.

[16] Mizrahi R, Addington J, Rusjan PM, Suridjan I, Ng A, Boileau I, et al. Increased Stress-Induced Dopamine Release in Psychosis. Biol Psychiatry. 2012;71(6):561–7.

[17] Lynall ME, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, et al. functional connectivity and brain networks in schizophrenia. J Neurosci. 2010;30(28):9477–87.

[18] Brunelin J, d'Amato T, van Os J, Cochet A, Suaud-Chagny MF, Saoud M. Effects of acute metabolic stress on the dopaminergic and pituitary–adrenal axis activity in patients with schizophrenia, their unaffected siblings and controls. Schizophr Res. 2008;100(1):206–11.
[19] Pariante CM. Pituitary volume in psychosis: the first review of the evidence. J Psychopharmacol. 2008;22(2_suppl):76–81.
[20] Joëls M. Corticosteroids and the brain. J Endocrinol. 2018;238(3):R121–30.
[21] Misiak B, Pruessner M, Samochowiec J, Wiśniewski M, Reginia A, Stańczykiewicz B. A meta-analysis of blood and salivary cortisol levels in first-episode psychosis and high-risk individuals. Front Neuroendocrinol 2021; 62:100930.
[22] Girshkin L, Matheson SL, Shepherd AM, Green MJ. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. Psychoneuroendocrinology. 2014;49:187–206.
[23] Chaumette B, Kebir O, Mam-Lam-Fook C, Morvan Y, Bourgin J, Godsil BP, et al. Salivary cortisol in early psychosis: new findings and meta-analysis. Psychoneuroendocrinology. 2016;63:262–70.
[24] Berger M, Kraeuter AK, Romanik D, Malouf P, Amminger GP, Sarnyai Z. Cortisol awakening response in patients with psychosis: systematic review and meta-analysis. Neurosci Biobehav Rev. 2016;68:157–66.
[25] Walker EF, Trotman H, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, et al. Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. Biol Psychiatry. 2013; 74(6):410–17.
[26] Sugranyes G, Thompson JL, Corcoran CM. HPA-axis function, symptoms, and medication exposure in youths at clinical high risk for psychosis. J Psychiatr Res. 2012;46(11):1389–93.
[27] Brunelin J, d'Amato T, Van Os J, Costes N, Suaud Chagny MF, Saoud M. Increased left striatal dopamine transmission in unaffected siblings of schizophrenia patients in response to acute metabolic stress. Psychiatry Res. 2010;181(2):130–5.
[28] van Leeuwen JMC, Vinkers CH, Vink M, Kahn RS, Joëls M, Hermans EJ. Disrupted upregulation of salience network connectivity during acute stress in siblings of schizophrenia patients. Psychol Med. 2020;51(6):1–11.
[29] Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397–409.
[30] Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18(10):1376–85.
[31] Vignaud P, Adam O, Palm U, Baeken C, Prieto N, Poulet E, et al. Can a single session of noninvasive brain stimulation applied over the prefrontal cortex prevent stress-induced cortisol release? Prog Neuropsychopharmacol Biol Psychiatry. 2023;121:110667.
[32] Kim S, Stephenson MC, Morris PG, Jackson SR. tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: a 7T magnetic resonance spectroscopy study. NeuroImage. 2014;99:237–43.
[33] Kwon YH, Jang SH. The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. Neurosci Lett. 2011;492(2):105–8.
[34] Baudewig J, Nitsche MA, Paulus W, Frahm J. Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med. 2001;45(2):196–201.
[35] Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, et al. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31(43):15284–93.
[36] Wischnewski M, Mantell KE, Opitz A. Identifying regions in prefrontal cortex related to working memory improvement: a novel meta-analytic method using electric field modeling. Neurosci Biobehav Rev. 2021;130: 147–61.
[37] Perret M, Neige C, Brunelin J, Mondino M. Unraveling the brain mechanisms of source monitoring with non-invasive brain stimulation: a systematic review. Int J Clin Health Psychol. 2024;24(2):100449.
[38] Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int J Neuropsychopharmacol. 2021;24(4):256–313.
[39] Brunelin J, Fecteau S. Can the effects of noninvasive brain stimulation alleviating neuropsychiatric symptoms result from a common beneficial regulation of the hypothalamic-pituitary-adrenal axis? Brain Stimul. 2015; 8(2):173–6.
[40] Smeets T, Jelicic M, Merckelbach H, Peters M, Fett A, Taverniers J, et al. Enhanced memory performance on an internal-internal source monitoring test following acute psychosocial stress. Behav Neurosci. 2006;120(6): 1204–10.
[41] Smeets T, Sijstermans K, Gijsen C, Peters M, Jelicic M, Merckelbach H. Acute consolidation stress enhances reality monitoring in healthy young adults. Stress. 2008;11(3):235–45.
[42] Brunelin J, Fecteau S. Impact of bifrontal transcranial direct current stimulation on decision-making and stress reactivity. A pilot study. J Psychiatr Res. 2021;135:15–19.
[43] Imbert L, Moirand R, Bediou B, Koenig O, Chesnoy G, Fakra E, Brunelin J. A single session of bifrontal tDCS can improve facial emotion recognition in major depressive disorder: an exploratory pilot study. Biomedicines. 2022;10(10):2397. doi:10.3390/biomedicines10102397.
[44] Moirand R, Imbert L, Haesebaert F, Chesnoy G, Bediou B, Poulet E, et al. Ten sessions of 30 min tDCS over 5 days to achieve remission in depression: a randomized pilot study. J Clin Med. 2022;11(3):782. doi:10.3390/jcm11030782.
[45] Smeets T, Cornelisse S, Quaedflieg CWEM, Meyer T, Jelicic M, Merckelbach H. Introducing the maastricht acute stress test (MAST): a quick and non-invasive approach to elicit robust autonomic and glucocorticoid stress responses. Psychoneuroendocrinology. 2012;37(12):1998–2008.
[46] Brunelin J, Poulet E, Marsella S, Bediou B, Kallel L, Cochet A, et al. Un déficit de mémoire de la source spécifique chez les patients schizophrènes comparés à des volontaires sains et des patients présentant un épisode dépressif majeur. Rev Eur Psychol Appl. 2008;58(2):105–10.
[47] Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009;34(2):163–71.
[48] Antonelli G, Ceccato F, Artusi C, Marinova M, Plebani M. Salivary cortisol and cortisone by LC–MS/MS: validation, reference intervals and diagnostic accuracy in Cushing's syndrome. Clin Chim Acta. 2015;451:247–51.
[49] Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17(4):555–64.
[50] Beck AT, Ward CH, Mendelson M, Mock J, Erhaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
[51] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9): 1774–809.
[52] Diorio D, Viau V, Meaney M. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. J Neurosci. 1993;13(9):3839–47.
[53] Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: a meta-analysis and comparison with cortisol. Neurosci Biobehav Rev. 2016;68:651–68.
[54] Qin S, Hermans EJ, van Marle HJF, Luo J, Fernández G. Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. Biol Psychiatry. 2009;66(1):25–32.
[55] Shields GS, Sazma MA, McCullough AM, Yonelinas AP. The effects of acute stress on episodic memory: a meta-analysis and integrative review. Psychol Bull. 2017;143(6):636–75.
[56] Schlatter S, Guillot A, Faes C, Saruco E, Collet C, Di Rienzo F, et al. Acute stress affects implicit but not explicit motor imagery: a pilot study. Int J Psychophysiol. 020;152:62–71.
[57] Hoskin R, Hunter MD, Woodruff PWR. The effect of psychological stress and expectation on auditory perception: a signal detection analysis. Br J Psychol. 2014;105(4):524–46.
[58] Simons JS, Garrison JR, Johnson MK. Brain mechanisms of reality monitoring. Trends Cogn Sci. 2017;21(6):462–73.
[59] Garrison JR, Fernandez-Egea E, Zaman R, Agius M, Simons JS. Reality monitoring impairment in schizophrenia reflects specific prefrontal cortex dysfunction. Neuroimage Clin. 2017;14:260–8.
[60] Waters F, Woodward T, Allen P, Aleman A, Sommer I. Self-recognition deficits in schizophrenia patients with auditory hallucinations: a meta-analysis of the Literature. Schizophr Bull. 2012;38(4):741–50.

[61] Habets P, Collip D, Myin-Germeys I, Gronenschild E, Van Bronswijk S, Hofman P, et al. Pituitary volume, stress reactivity and genetic risk for psychotic disorder. Psychol Med. 2012;42(7):1523–33.
[62] Collip D, Nicolson NA, Lardinois M, Lataster T, van Os J, Myin-Germeys I. Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. Psychol Med. 2011;41(11):2305–15.
[63] Nordholm D, Rostrup E, Mondelli V, Randers L, Nielsen MØ, Wulff S, et al. Multiple measures of HPA axis function in ultra high risk and first-episode schizophrenia patients. Psychoneuroendocrinology. 2018;92: 72–80.
[64] Dondé C, Pouchon A, Brunelin J, Polosan M. tDCS as a first-choice agent in individuals at high-risk for psychosis? Encephale. 2022;48(4):472–3. doi:10.1016/j.encep.2021.02.011.
[65] Heck AL, Handa RJ. Sex differences in the hypothalamic–pituitary–adrenal axis' response to stress: an important role for gonadal hormones. Neuropsychopharmacology. 2019;44(1):45–58.