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Review article

Mood moderates the effects of prefrontal tDCS on executive functions: A meta-analysis testing the affective state-dependency hypothesis

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ABSTRACT

Background: In recent decades, numerous studies have investigated the effects of transcranial direct current stimulation (tDCS) on cognitive functioning. However, results of these studies frequently display inconsistency and pose challenges regarding replicability. The present work aimed at testing the hypothesis of mood as potential moderator of prefrontal tDCS effects on executive functions (EF). This hypothesis refers to the relationship between mood and EF, as well as to the association of mood with the dorsolateral prefrontal cortex (dlPFC) activity.

Methods: We conducted a meta-analysis of 11 articles where the dlPFC was stimulated with anodal tDCS, EF were measured, and mood was assessed prior to the stimulation. We then conducted a meta-regression to examine whether mood moderated the tDCS effects on EF.

Results: While no significant effect of tDCS on EF emerged from the meta-analysis, the meta-regression indicated that mood plays a significant role as moderator, with greater tDCS effects on EF in individuals with higher depressive symptoms.

Limitations: The limited number of studies included, the heterogeneous samples considered, and the limited generalizability to other non-invasive brain stimulation techniques and affective states.

Conclusions: Findings suggest that evaluating mood prior to stimulation could increase the sensitivity and specificity of tDCS application, and provide the first meta-analytic evidence in favor of the affective state-dependency hypothesis.

1. Introduction

It's not uncommon to come across the sentence "Transcranial Direct Current Stimulation (tDCS) did not affect cognitive performance" in the field of Non-Invasive Brain Stimulation (NIBS). In fact, over the last few years, several scientific papers have been published that have reduced the initial excitement about the potential benefits of NIBS techniques on cognitive functions like attention, memory, perception, and language, as well as executive functions (EF) such inhibitory control and working memory (for a review, refer to de Boer et al., 2021; Hill et al., 2016; Hoy et al., 2013; Imburgio and Orr, 2018; Mancuso et al., 2016; Müller et al., 2022; Yu et al., 2020). These papers reported the results of studies aimed at investigating causal relationships between brain structures and cognitive functions, as well as of studies aimed at boosting cognitive performance in healthy individuals and those with neurological or psychiatric disorders. The majority of these studies focused on the dorsolateral prefrontal cortex (dlPFC). The dlPFC is considered to be critical hub for the kinds of high-level cognition (i.e. the EF), (Panikratova et al., 2020; Stuss, 2011) that undergo significant changes in many neurological and psychiatric disorders (Amanzio et al., 2020, as well as in healthy ageing (Reuter-Lorenz et al., 2016; Malloy-Diniz et al., 2017). The fact that these studies often obtained significant findings but were small in their effect size or not replicated by subsequent attempts, as well as null results, clearly indicated the need for systematic

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investigations employing meta-analytic approaches aimed at shedding light on this research field.

In a recent umbrella review of 11 meta-analysis, Farhat et al. (2022) examined the effects of prefrontal tDCS on various cognitive domains in both healthy and clinical conditions. The domains examined included working memory, set shifting, response inhibition, long term memory, impulsivity and risk taking, language, emotional and implicit bias. Out of the 55 comparisons made in these 11 studies, only 16 showed significant effects of prefrontal tDCS on the cognitive functions examined. The authors also noted that of these 16 comparisons, 13 provided low or very low quality of evidence. These results suggest what we need is to identify potential moderators, variables that may explain outcome variability across studies, using meta-analytic approaches.

Indeed, several authors have suggested that we should take into account various factors when it comes to NIBS, such as stimulation parameters, task features, experimental design characteristics, and, moreover, individual differences (Fertonani and Miniussi, 2017; Dedoncker et al., 2016; Silvanto and Pascual-Leone, 2008).

The study of individual differences, in particular, has contributed to the development of a new theoretical framework called *state-dependency*. This framework emphasizes the importance of taking into account the variability of physiological states across individuals as well as within each individual, with the objective of enhancing the reliability and optimisation of NIBS (Bradley et al., 2022; Masina et al., 2021, 2022).

The *state-dependency* framework is commonly used by studies that investigate changes in neural activity as an indicator of physiology (Bradley et al., 2022; Hartwigsen and Silvanto, 2022; Penton et al., 2022), although a small number of studies have also applied this framework to psychological measures, such as cognitive performance, to assess the potential baseline states that could influence tDCS outcomes. The results of these studies have shown significant influences of these baseline measures on the post-stimulation cognitive performance (Benwell et al., 2015; Di Rosa et al., 2019; Learmonth et al., 2015; Schwippel et al., 2018). Despite the relevance of these investigations, only few studies have explored the potential role of affective states in modulating the effects of NIBS.

Affective states are the conscious experience of feeling the underlying emotion or mood (Panksepp and Biven, 2012) and motivational dispositions like reward sensitivity (Schutter et al., 2023). Recent evidence suggests significant associations between baseline affective states, cortical activity, and cognitive functions in healthy and clinical conditions. This has been reviewed by Schutter et al. (2023), who suggested the hypothesis of an *affective-state dependency* in NIBS. This hypothesis suggests that affective states can have 'added value in explaining intra- and inter-individual study-outcome variability' (Schutter et al., 2023, page 7).

However, as far as the authors are aware, a comprehensive examination of the *affective-state dependency* hypothesis through a meta-analysis has never been conducted. To address this gap in knowledge, we conducted the present study, which investigates the potential role of affective states on tDCS and its effect on cognition. Specifically, we conducted a meta-analysis to assess the relationship between mood and the effects of prefrontal tDCS on EF.

Our meta-analysis focused on mood because of two primary pieces of evidence.

Firstly, the relationship between dlPFC and mood. Clinical studies have in fact shown that dlPFC, the brain region involved in EF, is also involved in mood and emotion regulation. Damage to the dlPFC, can result in emotional changes including abulia, apathy, and lack of initiative (Blumer, 1975; Szczepanski and Knight, 2014). Recent neuroimaging and NIBS studies have also indicated a significant relationship between dlPFC activity, mood, and EF in psychiatric conditions such as depression and schizophrenia, as well as healthy volunteers (Koenigs and Grafman, 2009; Lefaucheur et al., 2014; Marvel and Paradiso, 2004; Meron et al., 2015; Razza et al., 2020; Ursu et al., 2011; Tully et al., 2014). This set of evidence is highly relevant for the understanding the functions of dlPFC functions in neurotypical and psychiatric conditions, with several recent studies investigating the possibility of improving symptoms of mood disorders by targeting the dlPFC through NIBS (Razza et al., 2020; Perera et al., 2016).

Secondly, the relationship between mood and EF, reported in studies involving both healthy volunteers and clinical conditions (Bartolic et al., 1999; Carvalho and Ready, 2010; Gabel and McAuley, 2018; Phillips et al., 2002). These studies have shown that mood can modulate performance at executive tasks (Phillips et al., 2002, Carvalho and Ready, 2010), with several theories suggesting why mood has this effect. One theory is that mood can act as a cognitive load, meaning that both positive and negative mood can increase activation of networks involved in emotion-regulation thoughts. This can therefore be detrimental for EF as it uses up cognitive resources (Mackie and Worth, 1989; Seibert and Ellis, 1991). Another theory is that the motivational influence of mood on cognitive processing can affect performance, with positive mood leading to a more heuristic processing style (compared to neutral mood states), and consequently to an impaired performance (e.g. Bless et al., 1990; Bohner et al., 1994; Park and Banaji, 2000). On the other hand, negative mood can motivate an increase in analytic processing, and therefore improve performance on EF tasks (e.g. Park and Banaji, 2000). Mood can also act as a modulator of cognitive flexibility, with positive mood states promoting flexibility and improving performance in tasks demanding novel and strategic approaches (Isen, 1999; for a review of these theories, see Mitchell and Phillips, 2007). Lastly, emotional reactivity can also play a role in the relationship between mood and EF performance, with high-reactive individuals performing better on EF tasks when experiencing high levels of negative affect, whereas low-reactive individuals would show the opposite pattern (Gabel and McAuley, 2018).

Based on this set of evidence, our hypothesis is that mood can significantly influence the effects of tDCS over the dlPFC on EF.

As the dlPFC is associated with both EF and mood, it is possible that mood states can affect the performance of EF tasks and the effect of tDCS on EF.

To test this hypothesis, we conducted a meta-analysis of the effects of tDCS over the dlPFC on EF tasks, considering mood. Specifically, we evaluated the results of studies where tDCS was delivered over the dlPFC, the effects were assessed with EF tasks, and mood was evaluated before stimulation. This study is part of a pre-registered protocol (PROSPERO 2020 CRD42020189745).

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting meta-analysis and systematic reviews including literature review, article selection based on predefined criteria, data extraction, and quantitative synthesis (Liberati et al., 2009; Page et al., 2021).

2.1. Literature search

The search was conducted on articles published up to November 8th 2021, and present in the following database: PubMed, ScienceDirect, and PsychINFO.

The keywords that were used in the searches were: "transcranial direct current stimulation" or "direct current stimulation" or "tDCS", and "DLPFC" or "dorsolateral prefrontal cortex" or "LPFC" or "PFC" or "prefrontal cortex" or "lateral prefrontal cortex".

The included studies fulfilled the following criteria: (a) English language; (b) randomized and sham-controlled; (c) within-subject; (d) inclusion of healthy volunteers or neuropsychiatric patients aged 18 years or older; e) within subject design; (f) use of anodal tDCS on dlPFC; (g) single session tDCS (sham-controlled); (h) included a mood assessment before the stimulation; (i) include at least a measure of EF; (l) employing both offline and online protocol; (m) provide data (in the article or upon

request) of the mean and standard deviation (SD) of EF and mood.

To reduce intrapersonal variation and increase the homogeneity of results across studies in examining tDCS effects, only within-subject and single-session sham-controlled (sham vs anodal) studies were included (Dedoncker et al., 2016; Müller et al., 2022).

A total of 2186 articles were initially identified, and after removing duplicates, 1713 articles remained. After the title and abstract screening, 1251 articles were excluded, and the remaining 462 articles were assessed for eligibility.

Of these, 451 articles were subsequently excluded after the full-text screening, with the final number of articles included in the analysis being = 11.

The details about the reasons for exclusion are reported in the PRISMA flow chart (Fig. 1), while the details of the included articles are reported in Table 1.

The screening was conducted by at least two independent reviewers using the web app "Rayyan" (Ouzzani et al., 2016). The selection of the included articles was double-checked, as well as the process of data extraction. In the former, two judges (AP and EG) went through the entire sample of articles and selected the one to be included independently and blindly.

A third judge (EDR) evaluated the discrepancies (71 articles, around 3 %) and solved them by consensus.

2.2. Quality assessment

For quality assessment, each article was checked for blinding and counterbalancing. The included studies were evaluated for quality using the Appraisal tool for Cross-Sectional Studies (AXIS) (Downes et al., 2016). This scale examines several aspects of study quality, such as the

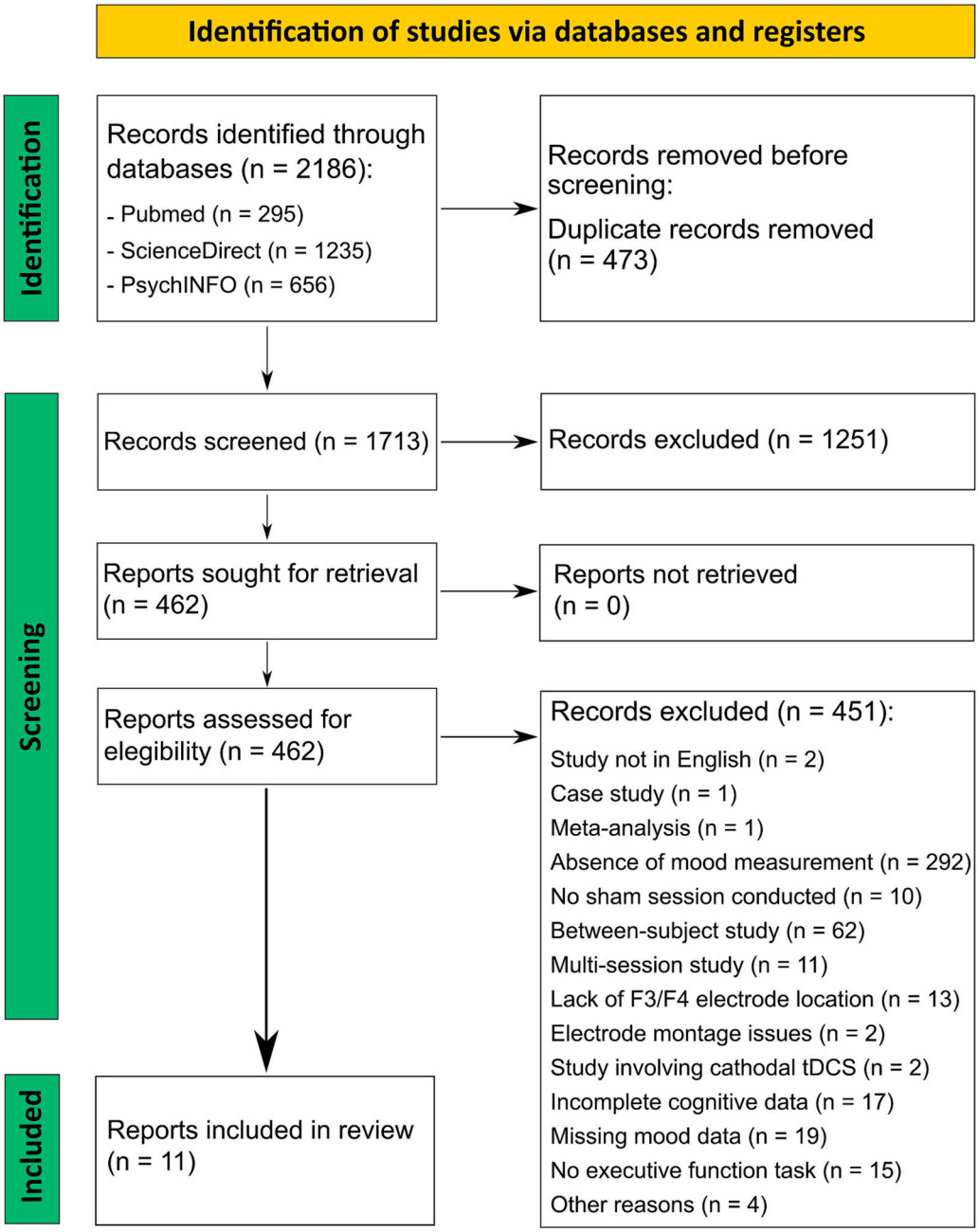

Fig. 1. The flowchart depicts the systematic literature search and study selection process following PRISMA guidelines. The figure illustrates the number of records identified, screened, and included at each stage, leading to the final selection of studies for meta-analysis.

Table 1
Overview of the studies included in this meta-analysis, highlighting key characteristics such as group and demographics, sample size, EF tasks and outcome, mood assessment, electrodes position and size, stimulation intensity, stimulation duration, and stimulation timing (i.e., online/offline), as well as Hedges' *g* and the relative variance.

ID study	Author	Year	Group	Sample size	Sex	Mean age	EF task	Outcome	Mood assessment	Mood score	Electrode size	Anode position	Cathode position	Current intensity (mA)	Stimulation duration (min)	Online/ offline	Hedges' *g*	Variance
1	Coussement et al.	2019	H	20	13F	24,5	PDT	Accuracy	BDI-II	9.8	35 cm^2 (7 × 5 cm)	F3	L arm	2	25	Online	−0.018	0.05
2	Eddy et al.	2017	HD	20	NA	55,4	N-back Stroop task	Response time	HADS-Depression	31.2	Anodal 25 mm, return 35 mm	F3	FP2	1.5	15	Offline	0.077	0.03
2	Eddy et al.	2017	HD	20	NA	55,4	N-back DOT-A	Accuracy	HADS-Depression	31.2	anodal 25 mm, return 35 m.	F3	FP2	1.5	15	Offline	0.158	0.03
3	Keeser et al.	2010	H	10	5F	28,9	N-back	Response time	PANAS	3.8	35 cm^2 (7 × 5 cm)	F3	R SupOr	2	20	Offline	0.585	0.08
3	Keeser et al.	2010	H	10	5F	28,9	N-back	Accuracy	PANAS	m	35 cm^2 (7 × 5 cm)	F3	R SupOr	2	20	Offline	0.176	0.07
4	Lema et al.	2021	H	24	19F	22,2	ANT (executive)	Response time	BDI	6.3	35 cm^2 (7 × 5 cm)	F3	FP2	2	20	Online	−0.042	0.04
4	Lema et al.	2021	H	24	19F	22,2	ANT (executive)	Accuracy	BDI	6.3	35 cm^2 (7 × 5 cm)	F3	FP2	2	20	Online	−0.275	0.04
5	Martin et al.	2015	BD	15	6F	36,9	3 N-back	Response time	DASS-21	16.8	35 cm^2 (7 × 5 cm)	F3	R arm	2	30	Online	0.005	0.07
5	Martin et al.	2015	BD	15	6F	36,9	3 N-back (d index)	Accuracy	DASS-21	16.8	35 cm^2 (7 × 5 cm)	F3	R arm	2	30	Online	0.157	0.07
6	Nejati et al.	2018	H	24	0F	26,8	Go/No-Go; TOH; BART	Response time	DASS-21	44	35 cm^2 (7 × 5 cm)	F3	FP2	1.5	20	Online	0.718	0.04
6	Nejati et al.	2018	H	24	0F	26,8	Go/No-Go; TOH; BART	Accuracy	DASS-21	44	35 cm^2 (7 × 5 cm)	F3	FP2	1.5	20	Online	0.778	0.04
7	Papazova et al.	2018 (exp.1)	SZ	20	5F	36,6	N-back	Response time	CDSS	12.2	35 cm^2	F3	R Delt	1	21	Online	−0.137	0.04
7	Papazova et al.	2018 (exp.1)	SZ	20	5F	36,6	N-back	Accuracy	CDSS	12.2	35 cm^2	F3	R Delt	1	21	Online	0.223	0.03
7	Papazova et al.	2018 (exp.2)	SZ	20	4F	37,7	N-back	Response time	CDSS	13.8	35 cm^2	F3	R Delt	2	21	Online	−0.057	0.03
7	Papazova et al.	2018 (exp.2)	SZ	20	4F	37,7	N-back	Accuracy	CDSS	13.8	35 cm^2	F3	R Delt	2	21	Online	0.027	0.03
8	Schwippel et al.	2018 (exp.1)	SZ	16	4F	32,0	Spatial N-back	Response time	CDSS	14.8	35 cm^2	F4	L Delt	1	21	Online	−0.127	0.05
8	Schwippel et al.	2018 (exp.1)	SZ	16	4F	32,0	Spatial N-back	Accuracy	CDSS	14.8	35 cm^2	F4	L Delt	1	21	Online	−0.888	0.06
8	Schwippel et al.	2018 (exp.2)	SZ	16	5F	37,3	Spatial N-back	Response time	CDSS	9.6	35 cm^2	F4	L Delt	2	21	Online	−0.534	0.05
8	Schwippel et al.	2018 (exp.2)	SZ	16	5F	37,3	Spatial N-back	Accuracy	CDSS	9.6	35 cm^2	F4	L Delt	2	21	Online	0.055	0.06
9	Sreeraj et al.	2019	SZ	11	4F	28,9	Sternberg's task	Response time	CDSS	4.4	NA	F3-FP1	T3-P3	2	20	Online	−0.05	0.09
9	Sreeraj et al.	2019	SZ	11	4F	28,9	Sternberg's task	Accuracy	CDSS	4.4	NA	F3-FP1	T3-P3	2	20	Online	−0.195	0.09
10	Vanderhasselt et al.	2020	hD	37	15F	21,2	Go/No-Go	Accuracy	VAS	30	35 cm^2	F4	F3	2	20	Offline	−0.051	0.02
11	Vanderhasselt et al.	2013	H	32	20F	22,3	IST	Response time	PANAS	11.2	35 cm^2	F3	R SupOr	2	20	Offline	−0.23	0.03

Notes: Abbreviations of "Group": H = healthy; SZ = patients with Schizophrenia; HD = patients with Huntington's Disease; BD = patients with Bipolar Disorder; hD = heavy drinkers.
Notes: Abbreviations of "EF Task": ANT = Attention Network Test; BART = Balloon analogue risk task; DOT-A = Digit Ordering Test-Adapted; IST = Internal shift task; PDT = probe discrimination task. TOH = Tower of Hanoi task;
Notes: Abbreviations of "Mood assessment": BDI = Beck Depression Inventory; DASS-21 = Depression Anxiety and Stress Scale; CDSS = Calgary Depression Scale for Schizophrenia; HADS = Hospital Anxiety and Depression Scale; PANAS = Positive and Negative Affect Schedule; VAS = Visual Analog Scale.
Notes: Abbreviations of "Cathode": L = left; R = right; SupOr = Supraorbital; delt = deltoid. NA = not available.

appropriateness of sample size justification, clarity of study objectives, suitability of study design and measurements, adequacy of result reporting, justification of significance, the logical connection between results and conclusions, and limitations. In the present meta-analysis, certain items (i.e., 5, 7, 13, 14, 19, and 20) were excluded from the assessment because they were not relevant to the specific goals of the current study or were already taken into account in the inclusion criteria (such as the presence of a sham condition). The complete scale consists of 16 items. Table S1 in Supplementary Material shows details on the quality assessment process.

2.3. Data extraction

From each article, we extracted the following information: sample characteristics (i.e., healthy volunteers vs. clinical conditions; age; education; sex; sample size); study design (i.e., online vs. offline stimulation; number of sessions; wash-out period); tDCS parameters (i.e., montage; stimulation duration; amplitude); mood measurements (test score); EF task parameters (accuracy and/or response times). For the EF outcomes, we extracted the following data: (a) mean response times (RTs) and the corresponding *SDs*, latencies, completion times, and differential latencies; (b) percentage of correct responses and the corresponding *SD*; (c) percentage of errors and the corresponding *SD*, hit rates, average scores, discriminability index, and error rates.

2.4. Statistical analysis

Data analysis was conducted using R (version 4.1.0, R Core Team, 2021) and the *metafor* package (version 3.0.2, Viechtbauer, 2010). We calculated the effect size as the standardised mean difference between the effect of anodal tDCS and sham tDCS on the EF outcomes both for RTs and accuracy. We used the standardised effect size measure for paired samples with the approach suggested by Borenstein et al. (2021), implemented in the *escalc* function from the *metafor* package. We used the raw-score standardisation (see Morris and DeShon, 2002) by dividing the difference between anodal tDCS and sham tDCS with the pooled standard deviations of the two conditions. We calculated the sampling variability of the effect size measure considering the correlation between repeated measures (Borenstein et al., 2021). Given that the correlation is rarely reported, we used a fixed value of 0.5 for each study. We assessed the impact of imputing the correlation with a sensitivity analysis. Finally, we computed the Hedges' *g* applying the small-samples correction to the calculated effect size and the sampling variability (Hedges, 1981). When studies reported multiple outcomes (e.g., multiple measures of accuracy), we computed an aggregated effect size. The aggregation approach requires averaging the effect sizes and computing an aggregated variance considering the correlation (Borenstein et al., 2021). Again, this correlation is rarely reported thus we assumed a fixed value of 0.5 assessing the impact with a sensitivity analysis.

Importantly, we reversed the sign of the effect sizes when necessary to maintain consistency in the interpretability of the effect sizes. This adjustment ensures that, regardless of the outcome, a positive effect size consistently indicates improved performance (when comparing real tDCS vs. sham tDCS). In contrast, negative effect sizes signify decreased performance.

For the statistical model, firstly we used a random-effects meta-analysis to estimate the average effect on RTs and accuracy. Furthermore, we estimated the between-studies heterogeneity (2) and the I2statistics representing the percentage of total variability due to real heterogeneity and not sampling variability.

Finally, we explore the presence of publication bias using the funnel plot (Sterne et al., 2005) and tested the funnel plot asymmetry with the rank correlation test (Begg and Mazumdar, 1994) and the Egger's regression test (Sterne et al., 2005). Crucially, in the presence of heterogeneity and with a limited number of studies the assessment of publication bias, results need to be interpreted with caution (e.g., Sterne et al., 2011).

We used a random-effects meta regression model to explore the impact of mood on RTs and accuracy effect sizes. Wald's tests (Viechtbauer, 2010) were used to examine the moderator effect.

In 7 studies, mood measurements were taken in more than one session (i.e., pre-anodal and pre-sham). Both measures were considered and averaged into one.

To standardise the mood measure across studies, we divided each mood score by the maximum score obtainable on that specific measure and multiplied by 100. For instance, in the Beck Depression Inventory-II (Beck et al., 1996) the maximum obtainable score is 63, hence if the sample has an overall score of 6.20, the final score that we use for the analysis is 9.8. Moreover, we transformed each mood measure to have the same direction (i.e., higher values represent a more negative mood). When the minimum score of a mood measure was not zero, we rescaled the variable subtracting the minimum value before transforming into a percentage. For example, in the Negative Affect Scale of PANAS (Watson et al., 1988), the minimum score is 10 thus we removed 10 before computing the mood percentage.

All relevant data and R scripts are available at https://osf.io/q962b/.

3. Results

3.1. Quality assessment

The 11 articles that were included in the study were of high quality. On average, they met 91.5 % (SD = 6) of the required criteria. However, the main limitation of these studies was the absence of a power analysis. Details about the quality assessment results for each study are reported in Table S1 of the Supplementary Material.

3.2. tDCS effects on response times

Eleven studies with a total sample of 199 participants were included to examine the effects of anodal tDCS on RTs. The observed effect sizes ranged from −0.53 to 0.72. The random-effects model (see Fig. 2) estimated an average effect of 0.03, not significantly different from zero (SE = 0.1021, 95 % CI [−0.17, 0.23], z = 0.32, $p = 0.747$). The estimated heterogeneity (2) is 0.07 ($Q_{10} = 23.96$, $p = 0.008$, $I^2 = 59$ %).

The funnel plot analysis revealed no evidence of publication bias, as neither the rank correlation ($p = 0.648$) nor the regression test ($p = 0.77$) indicated any significant asymmetry (see Fig. 3).

3.3. tDCS effects on accuracy

Twelve studies were included, with a total of 248 participants, to examine the effects of anodal tDCS on accuracy (one article had data on 2 studies). The observed effect size ranged from −0.89 to 0.78. The random-effects model (see Fig. 4) estimated an average effect of 0.003, not significantly different from zero (SE = 0.110, 95 % CI [−0.214, 0.219], $z = 0.023$, $p = 0.982$). The estimated heterogeneity (2) is 0.10 ($Q_{11} = 35.55$, $p < 0.001$, $I^2 = 59$ %). The analysis of the funnel plot suggested no evidence for publication bias where neither the rank correlation ($p = 1$) nor the regression test ($p = 0.657$) indicated any significant asymmetry (see Fig. 5).

3.4. The effect of mood on response times

The analysis found that a person's mood can significantly affect their RTs, with a positive association between effect size and mood ($\beta = 0.015$, SE = 0.007, 95 % CI [0.002, 0.029], $z = 2.251$, $p = 0.024$; see Fig. 6). After including the predictor, the Q-test indicated that residual heterogeneity was reduced resulting no longer different from zero ($Q_9 = 14.93$, $p = 0.092$, $\tau^2 = 0.026$, $I^2 = 36$ %).

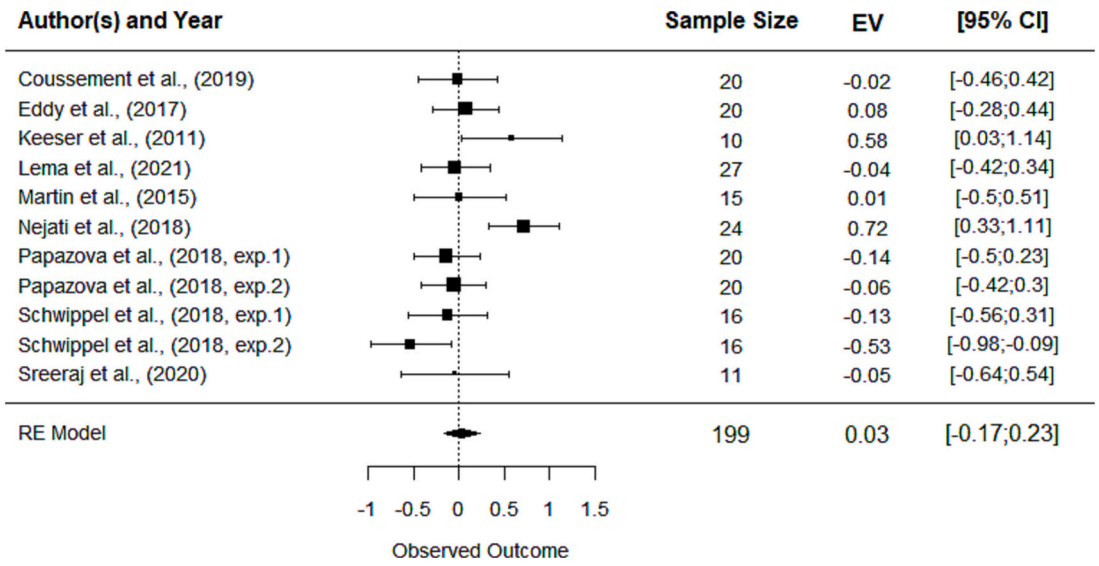

Fig. 2. Forest plot showing the effect sizes of response times (anodal vs. sham tDCS). Each square represents the effect size of the study along with a 95% confidence interval. Positive effect sizes indicate improved performance (when comparing real vs. sham tDCS), while negative effect sizes indicate decreased performance. The size of the symbol (the square) is proportional to the study's weight.

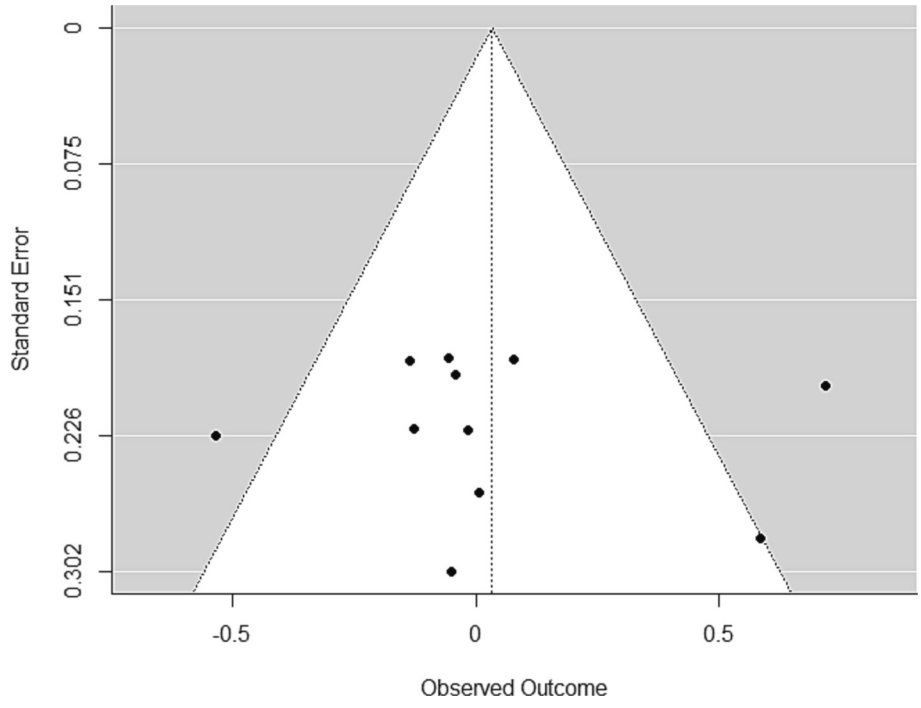

Fig. 3. Funnel plot (response times). Each black dot represents one study included in the meta-analysis.

3.5. The effect of mood on accuracy

Results showed that mood had a significant effect in modulating accuracy, with a positive association between effect size and mood (β = 0.016, SE = 0.008, 95 % CI [0.0004, 0.032], z = 2.006, p = 0.049; see Fig. 7). The Q-test suggested that the residual heterogeneity is different from zero (Q_{10} = 26.127, p = 0.004, τ^2 = 0.068, I^2 = 63 %).

3.6. Sensitivity analysis

The determination of sampling variance required the specification of correlation values between repeated observations. As these correlations are often missing in studies, we performed a sensitivity analysis using a range of reasonable correlation values to assess their influence on the estimated parameters. This allowed us to examine their potential impact on effect size calculations. Participants were subjected to both real and sham stimulation conditions in a within-subject design. To address the interdependence between these conditions, we explored three correlation values (*rstim*): 0.5, 0.7, and 0.9. For the main analysis in the manuscript, we used an *rstim* value of 0.5. In cases where studies involved multiple outcomes, we accounted for the correlation among these outcomes using the method described by Borenstein et al. (2021). Once again, we evaluated the effect of various correlation values (*routcomes*) on the results. Specifically, we considered three possible

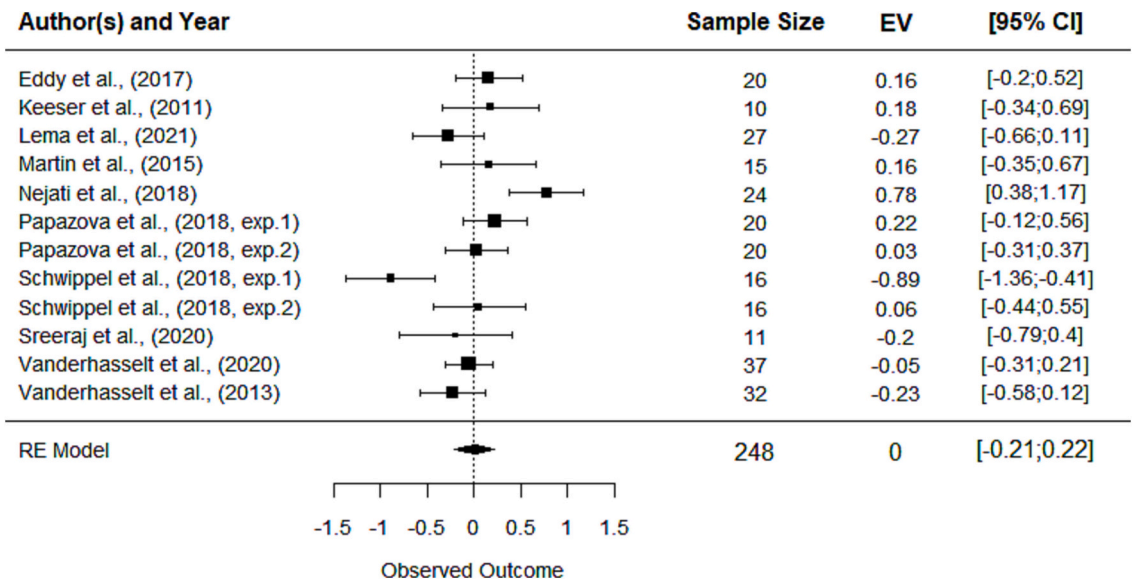

Fig. 4. Forest plot showing the effect sizes of accuracy (anodal vs. sham tDCS). Each square represents the effect size of the study along with 95% confidence level. Positive effect sizes indicate improved performance (when comparing real vs. sham tDCS), while negative effect sizes indicate decreased performance. The size of the symbol (the square) is proportional to the study's weight.

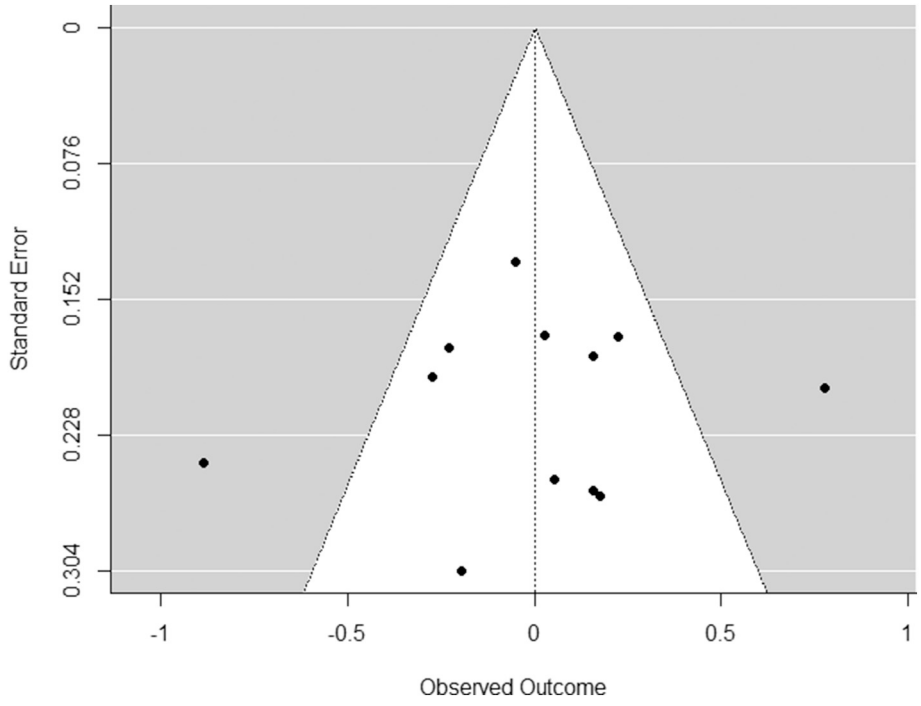

Fig. 5. Funnel plot (accuracy). Each black dot represents one study included in the meta-analysis.

correlations (*routcomes*) of 0.3, 0.5, and 0.7. The main manuscript's analysis was performed with a *routcomes* value of 0.5. To assess the impact of different correlation values, we ran all the 4 models using the 3 × 3 range of correlation values for the determination of sampling variance. We found that the effect sizes consistently ranged from 0.032 to 0.034 in the model testing tDCS effects on RTs, from −0.001 to 0.003 in the model examining tDCS effects on accuracy, from 0.014 to 0.016 in the model investigating the effect of mood on RTs, and from 0.016 to 0.017 in the model testing the effect of mood on accuracy. Thus, the effect sizes remained quite similar, regardless of the selected correlations.

4. Discussion

The overarching goal of this meta-analysis is to enhance our understanding of the impact of tDCS on EF and develop tailored and more effective stimulation protocols. We tested the novel hypothesis that the effect of tDCS on EF could be significantly influenced by mood, which serves as an indicator of affective state, when the stimulation is applied over the dlPC.

According to the results of the meta-analysis, depressive symptoms increase the influence of dlPFC-tDCS on EF tasks, as measured by both RTs and accuracy.

Importantly, we must acknowledge that the model examining the

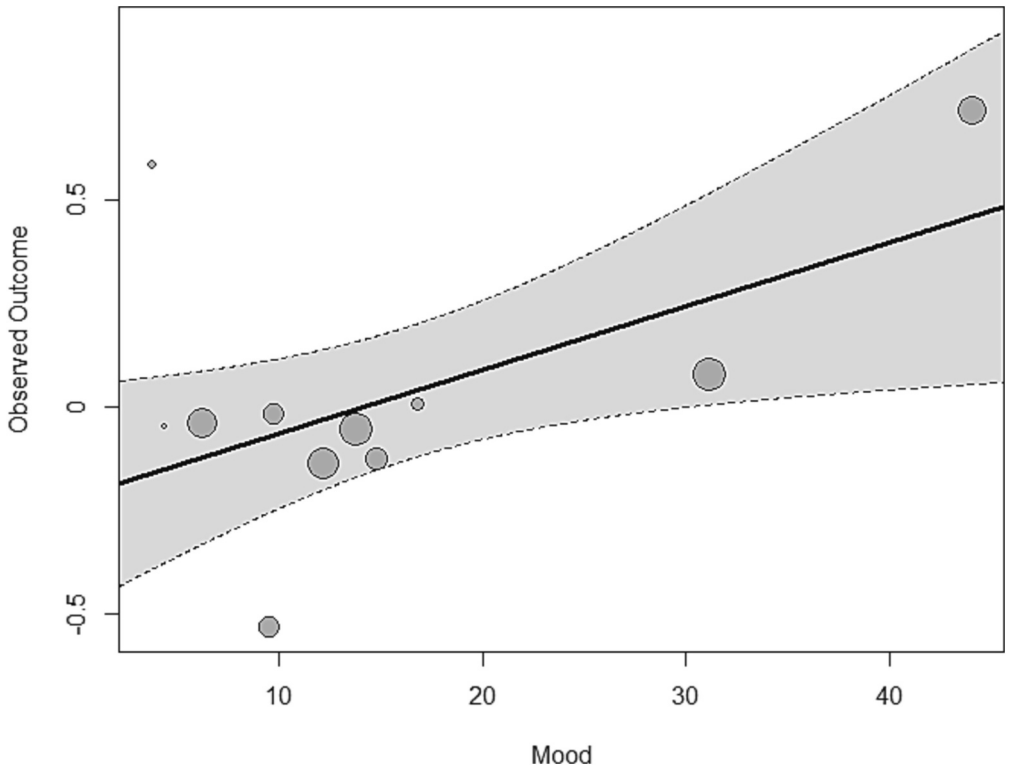

Fig. 6. The scatter plot shows the effect of mood on response times (Observed Outcome).

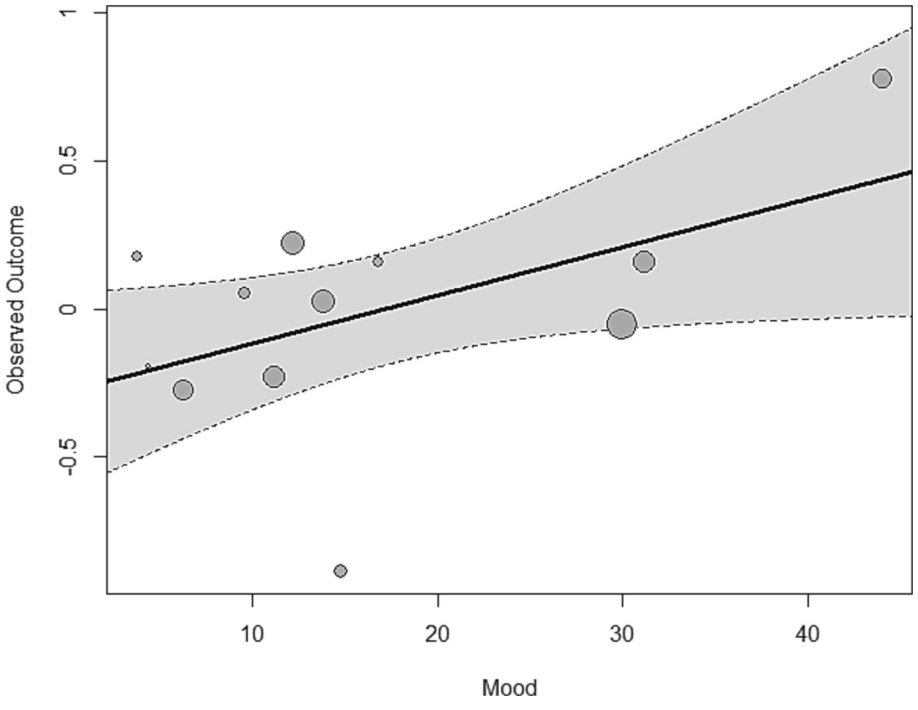

Fig. 7. The scatter plot shows the effect of mood on accuracy (Observed Outcome).

effect of mood in moderating tDCS effects on accuracy showed a small effect with considerable uncertainty, potentially linked to the limited number of studies included in the present meta-analysis.

However, regardless of the number of included studies, a further explanation for this result may relate to the fact that accuracy, as opposed to RTs, in some cases reaches ceiling effects in certain tasks, potentially limiting the possibility of observing a considerable effect when comparing real versus sham tDCS. Overall, this highlights the importance of future studies further investigating the role of mood on prefrontal tDCS effects on cognition, especially EF.

Our findings align with recent studies that suggest that mood can moderate the effects of prefrontal tDCS on EF. For instance, Riddle et al. (2022) found that patients with major depressive disorder showed significant changes in their electroencephalogram (EEG) resting state

activity and emotional response after receiving bifrontal tDCS. They observed that stimulation-induced reduction in EEG alpha power was correlated with depression scores and, with greater effects in individuals with lower mood levels (Riddle et al., 2022). Similarly, Abend et al. (2019) reported that levels of self-reported depression predicted the effects of supraorbital-occipital tDCS on behaviour and brain activity in the subgenual anterior cingulate cortex while healthy volunteers during an emotional induction task.

Other studies have also found that negative affective states influence the effects of prefrontal tDCS. For example, Esposito et al. (2022) found that higher levels of state anxiety were associated with slower RT in an auditory oddball task following prefrontal tDCS in healthy volunteers. Similarly, Sagliano et al. (2017) showed that trait anxiety was positively associated with attentional holding in healthy volunteers after prefrontal tDCS.

Studies have also found similar results using a technique called transcranial magnetic stimulation (TMS), which involves delivering a strong electrical current to the brain to generate a transient magnetic field that can depolarize neurons. For example, Vanderhasselt et al. (2011) found that healthy individuals with higher state anxiety showed increased attentional bias after receiving right dlPFC TMS. Similarly, Sagliano et al. (2016) reported that healthy individuals with higher trait anxiety had higher disengagement bias after receiving left dlPFC TMS.

The present meta-analysis, along with previous studies, suggests that the relationship between affective state and cortical excitability might explain the results. Recent research by Schutter et al. (2023) has shown that mood disorders are linked to changes in neural activity, particularly in frontal cortical regions. Cotovio et al. (2022) found evidence of motor cortical excitability asymmetry in major depressive disorder and bipolar depression, with lower excitability of the left and right sides, respectively. This could explain the increased response to tDCS in individuals with depressive symptoms, even in cognitive domains such as EF, and supports the hypothesis of increased susceptibility to NIBS. It is also noteworthy that three out of seven clinical studies included in the present meta-analysis involved patients with schizophrenia, a condition where imbalance between signals that stimulate the brain and those that inhibit it, as well as abnormal connections between the left and right dlPFC, have been reported (Kostova et al., 2020; Liu et al., 2021; Webler et al., 2020). As a result, further research is needed to gain a better understanding of the relationship mood, prefrontal tDCS and EF, and the underlying neural mechanisms, in individuals with schizophrenia.

In summary, our results suggests that mood assessment could improve the sensitivity and specificity of tDCS application over the dlPFC, and provide the first meta-analytic evidence supporting the *affective state-dependency hypothesis* (Schutter et al., 2023).

4.1. Limitations and future directions

It is important to keep in mind the following limitations while interpreting our results.

Firstly, we included a small number of studies in this meta-analysis. This is because mood is not commonly used as a baseline measure in experimental designs that focus on cognition, especially EF, as the primary prefrontal tDCS outcome. However, a larger sample size would likely have produced stronger findings.

Secondly, there is a lack of consistent information about blinding success, and the included studies show heterogeneity in terms of EF tasks, the number and type of pre-stimulation mood measures, sample size, and population tested. These factors could explain the reasons why we did not find any significant effects of tDCS on EF. Due to the small number of studies, we could not conduct separate analyses on healthy vs clinical groups (respectively 4 vs 7). Future meta-analyses with a larger number of studies should ideally do so, considering healthy individuals and persons with clinical conditions in two separate analyses.

Thirdly, our study's results have limited generalizability to other NIBS techniques and affective states, as well as to the clinical field, where multiple sessions are often employed. Our results are based on the use of a single-session anodal tDCS, and on the consideration of mood as a measure of affective state. Future research should include studies of multiple sessions design, other NIBS such as TMS, and different measures of affective state.

5. Conclusion

In conclusion, our meta-analysis suggests that mood plays a significant role in moderating the effects of prefrontal tDCS on EF. Specifically, our findings indicate that prefrontal anodal tDCS has stronger effects on EF in individuals with lower mood levels. These results are consistent with previous evidence that shows stronger NIBS effects on emotion and cognition in individuals with high levels of depressive symptoms. This could be due to the altered prefrontal cortex excitability reported in mood disorders. However, further research is needed to test this hypothesis and replicate our findings.

Therefore, we recommend that future experimental brain stimulation studies, especially those targeting dlPFC and assessing EF, should include affective state measures and test the *affective state-dependency hypothesis*. This will enable the scientific community to rely on more evidence, and conduct more robust meta-analyses. Additionally, it may be possible to compare different NIBS, different affective states, and study healthy and clinical conditions separately.

CRediT authorship contribution statement

Elisa Di Rosa: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing, Funding acquisition, Visualization. **Fabio Masina:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Annachiara Pastorino:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Eleonora Galletti:** Data curation, Formal analysis, Methodology, Software, Validation. **Filippo Gambarota:** Data curation, Formal analysis, Methodology, Software, Validation, Writing – review & editing, Writing – original draft. **Gianmarco Altoè:** Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nicky Edelstyn:** Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing, Methodology. **Daniela Mapelli:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing, Investigation, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.02.009.

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