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A meta-analysis of non-invasive brain stimulation (NIBS) effects on cerebellar-associated cognitive processes

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ABSTRACT

Non-invasive brain stimulation (NIBS) techniques, including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), have provided valuable insights into the role of the cerebellum in cognitive processes. However, replicating findings from studies involving cerebellar stimulation poses challenges. This meta-analysis investigates the impact of NIBS on cognitive processes associated with the cerebellum. We conducted a systematic search and analyzed 66 studies and 91 experiments involving healthy adults who underwent either TMS or transcranial direct current stimulation (tDCS) targeting the cerebellum. The results indicate that anodal tDCS applied to the medial cerebellum enhances cognitive performance. In contrast, high-frequency TMS disrupts cognitive performance when targeting the lateral cerebellar hemispheres or when employed in online protocols. Similarly, low-frequency TMS and continuous theta burst stimulation (cTBS) diminish performance in offline protocols. Moreover, high-frequency TMS impairs accuracy. By identifying consistent effects and moderators of modulation, this meta-analysis contributes to improving the replicability of studies using NIBS on the cerebellum and provides guidance for future research aimed at developing effective NIBS interventions targeting the cerebellum.

1. Introduction

Over the past few decades, our understanding of the cerebellum's role in cognition has undergone significant transformation (Devita et al., 2021; Koziol et al., 2014). While the cerebellum was previously believed to be exclusively relevant to the control of movement, it is now generally accepted that it plays a role in high-order functions (Schmahmann, 1997). This is anatomically plausible due to the cerebellum's connections with the cerebral hemispheres and brainstem through the cerebellarthalamocortical (Ishikawa et al., 2014; Kelly and Strick, 2003) and corticopontocerebellar (Kratochwil et al., 2017; Ramnani, 2012) tracts. The cerebellum's functional organization is characterized by a division between its anterior and posterior regions (Stoodley and Schmahmann, 2018), with the anterior region associated with sensorimotor processes, while the posterior region involved in cognitive and affective ones (Schmahmann, 2019). Specifically, the posterior cerebellar vermis, located medially, is referred to as the "limbic cerebellum" (Argyropoulos et al., 2020) because of its involvement in affective-emotional processes. In contrast, the posterior lateral region of the cerebellum is responsible for higher-level processes, such as memory (Clark et al., 2021), executive functions (Beuriat et al., 2022), and language (Mariën and Borgatti, 2018).

Non-invasive brain stimulation (NIBS) techniques, comprising transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), have provided causal evidence supporting the involvement of the cerebellum in cognitive processes (Cattaneo et al., 2022; Manto et al., 2022; Tremblay et al., 2016). However, similar to studies on the cerebral cortex, the results of cerebellar stimulation research are inconsistent and challenging to be replicated (Filmer et al., 2020; Guerra et al., 2020; Miterko et al., 2019; Woods et al., 2016). This

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can be partially attributed to inconsistent methodological aspects across studies, for example to different stimulation parameters (Guerra et al., 2020; Polanía et al., 2018). A further crucial aspect that can undermine the reliability of cerebellar stimulation is the assumption that the same conditions that apply to the cortex also apply to the cerebellum. This underlying assumption generates an anticipation of comparable effects to those observed in cortex stimulation, thereby introducing potential pitfalls in the choice of NIBS techniques or in the formulation of protocols for cerebellar stimulation. As a result, the reliability of NIBS in assessing cerebellar function in humans and its effectiveness in clinical interventions (Billeri and Naro, 2021; Manto et al., 2022) may be undermined.

Although there is considerable evidence demonstrating the possibility of modulating cerebellar-mediated cognitive processes through NIBS (Manto et al., 2022), what remains unclear is the best way to exploit NIBS to induce this modulation while reducing inconsistent effects. One relevant aspect concerns the selection of stimulation parameters. Currently, our understanding of the ideal stimulation parameters for effective cerebellar modulation remains limited (Billeri and Naro, 2021; Oldrati and Schutter, 2018). For example, in the case of TMS, it has been observed that keeping the same stimulation intensity, it produces a different modulation of motor-evoked potentials when stimulating the primary motor cortex or the cerebellum (Fernandez et al., 2020). The shape of the TMS coil also makes a difference as shown in a study demonstrating that only double-cone coils can reach the necessary depth to effectively target the cerebellum's anterior (i.e., motor) regions and consistently induce cerebellar-brain inhibition. In case figure-of-8 coils are employed, the stimulation intensity should be adjusted based on the distance of the cerebellar target from the scalp (Popa et al., 2010). Additionally, a recent study using electric field modeling techniques revealed that achieving stimulation of the cerebellar gray matter through figure-of-8 coils, particularly in lateral regions associated with cognition, requires very high intensities (Çan et al., 2018).

A further important aspect, often overlooked but with the potential to impact NIBS effects, concerns the spatial resolution of these techniques when targeting the cerebellum. Some authors have raised the issue of how the skin-cerebellum distance, which is higher than the skin-cortex distance (Del Olmo et al., 2007), may contribute to a different distribution of electrical field when stimulating the cerebellum in contrast to the cerebral cortex. For example, it has been suggested that the spatial resolution of transcranial direct current stimulation (tDCS) could be limited by the skin-cerebellum distance, resulting in significant variability in the efficacy of tDCS to modulate the cerebellum (Oldrati and Schutter, 2018). More recently, Maas and colleagues (2023) have shown that as much as 70% of the variability in electric field strength induced by cerebellar tDCS can be attributed to individual variations in the distance between the skin and the cerebellum, as well as the morphometry of the posterior fossa. In addition, when focusing on the midline cerebellum, the authors found that cephalic and extracephalic electrode montages can determine variations in the electric field strength and focality.

Taken together, these studies emphasize the importance of selecting the appropriate NIBS techniques, stimulation protocols, and stimulation parameters for cerebellar stimulation. Such a choice cannot be based on the same rationale that guides the stimulation of the cortex.

Two meta-analyses conducted so far have provided an initial understanding of the cerebellum's role in cognition. However, they have only examined one specific technique at a time, such as TMS (Gatti et al., 2021a) or tDCS (Oldrati and Schutter, 2018). While relevant, these studies do not allow for a comparison of the effects between different NIBS techniques. Furthermore, there are concerns about the methods used to estimate effects in these previous meta-analyses. For example, one study estimated effect sizes based on comparing the effect of real vs. control conditions after stimulation, without considering the baseline (Gatti et al., 2021a). This was done despite some of the experimental designs measuring the outcome both before (i.e., baseline) and after the stimulation. Although this practice is not unusual in meta-analyses (Dedoncker et al., 2016), it may introduce bias, reduce precision, and limit the robustness of the results due to heterogeneity of variance (Morris, 2008). Another potential confounding factor is the consideration of multiple experiments nested within a study as independent studies (Oldrati and Schutter, 2018), without accounting for their dependence.

This meta-analysis aims to overcome these limitations by providing a comprehensive and thorough examination of how NIBS affects cognitive processes associated with the cerebellum in healthy adults, as defined by response times and accuracy. The primary objective of this meta-analysis is to explore the impact of NIBS on cognitive functions while considering the specific site of stimulation, as previous literature consistently reports that the effects of NIBS on cognitive functions vary depending on the stimulation location. Second, this study aims to unveil the potential effects of NIBS on cognitive performance by examining the timing of NIBS administration - whether it is during the participant's engagement in a task (online protocol) or after the task (offline protocol). Lastly, the study aims to examine whether NIBS modulates cognitive performance by targeting specific outcomes such as response times or accuracy. The purpose of this meta-analysis is thus to guide researchers in the creation of adequate protocols for cerebellar stimulation, based on the evidence collected so far.

2. Material and Methods

The present study was conducted according to the most recently updated guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

2.1. Literature search

A systematic literature search was conducted on three databases: PubMed, PsycInfo, and Embase. Search terms indicating NIBS (e.g., TMS, tDCS) were combined with the terms "cerebellum" or "cerebellar". For a comprehensive search strategy for all databases, please refer to the Supplementary Materials. To minimize the risk of overlooking potentially relevant studies for inclusion, reference lists of previous studies were also screened. No restriction on the publication date range was applied (last search: March 31st, 2023).

The included studies fulfilled the following criteria: (i) use of TMS or theta-burst stimulation (TBS) or tDCS or transcranial alternating current stimulation (tACS) or transcranial random noise stimulation (tRNS) for cerebellar stimulation, (ii) inclusion of healthy adult participants aged 18 years or older, (iii) employment of sham-controlled or site-controlled designs, (iv) placement of at least one electrode over the cerebellum for tES studies; (v) measurement of cognitive outcomes in terms of response times and/or accuracy; (vi) provision of sufficient information to calculate effect size statistics or availability of these data from corresponding authors upon request; (vii) publication in a peer-reviewed English language journal; and (viii) approval by a medical ethical committee or review board.

A total of 812 articles were initially identified after deduplication. The title, abstract, and full text were screened by RP, VT, and FM through Rayyan (Ouzzani et al., 2016). Conflicts were resolved through pairwise discussions until a consensus was reached. After title and abstract screening, there were 157 articles left, of which another 91 were excluded. As only one tACS study was identified through the search (Giustiniani et al., 2021), it was excluded from the analyses. A final set of 66 articles were judged suitable to be included in the meta-analysis (Fig. 1).

2.2. Quality assessment and data extraction

The quality assessment of the included studies was carried out using the Appraisal tool for Cross-Sectional Studies (AXIS) (Downes et al.,

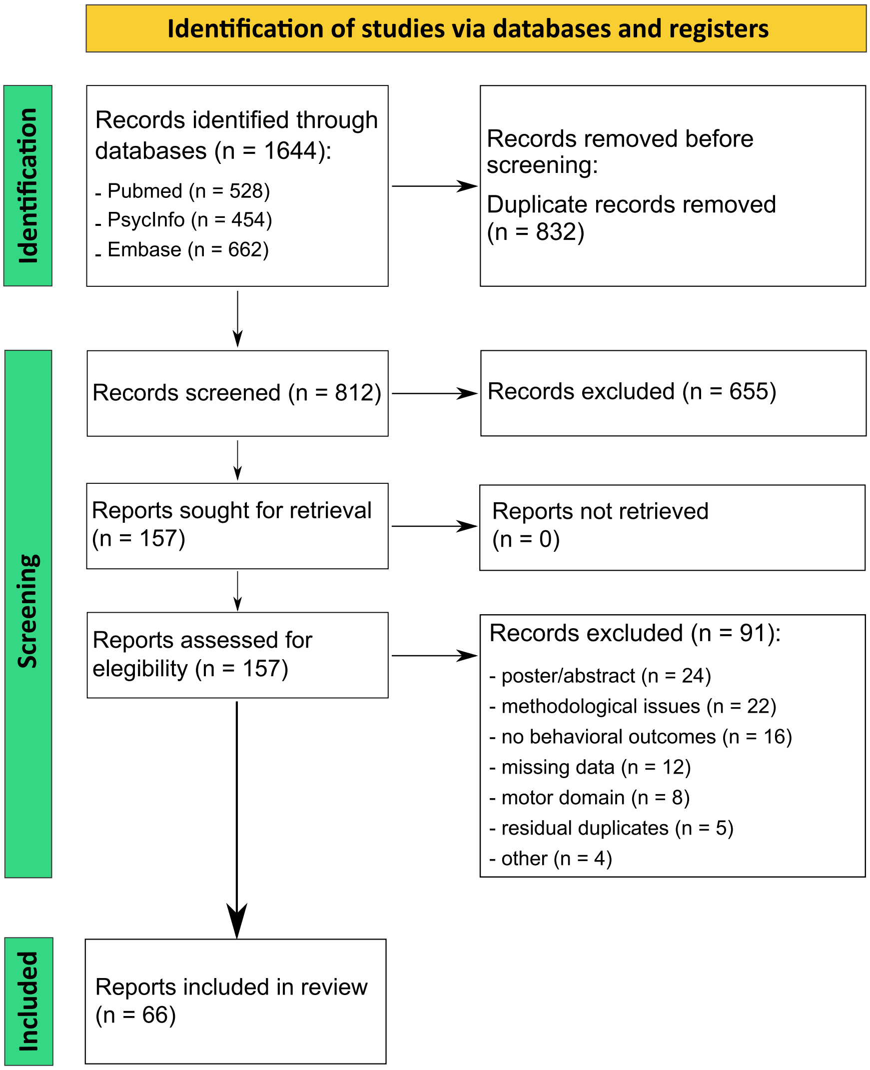

Fig. 1. The flowchart depicts the systematic literature search and study selection process following PRISMA guidelines. The figure illustrates the number of records identified, screened, and included at each stage, leading to the final selection of studies for meta-analysis.

2016). The overall scale contains 17 items (see Table S1 in the Supplementary Materials). The quality assessment was conducted by two reviewers (VT and MD).

The data that was encoded primarily included information necessary for calculating the effect size and its variance, along with any moderators that were analyzed in the meta-regression analyses. The principal outcomes of cognitive task performance were extracted: (1) mean response times and the corresponding standard deviation (*SD*); (2) mean accuracy and the corresponding *SD*. The analysis included those outcomes that the authors hypothesized to be modulated by NIBS. Additionally, other relevant study characteristics were also encoded (Table 1). When means and *SD*s for computing effect size and the variance were not available or provided, they were extracted from the figures using the WebPlotDigitizer software (version 4.6) (Rohatgi, 2022). Three authors (RP, VT, and FM) independently encoded each study.

There were 91 experiments from 66 studies included. Fig. 2 shows how the experiments were categorized based on four factors: NIBS, stimulation site, stimulation timing, and outcome. NIBS encompasses anodal or cathodal tDCS, low-frequency ($\leq$ 1 Hz) or high-frequency repetitive ($\geq$ 5 Hz) TMS, single-pulse TMS, or Continuous TBS (cTBS). Stimulation site refers to the targeted cerebellar location, including the right or left hemisphere or the medial cerebellum (vermis). As the aim of this meta-analysis was not to investigate the impact of NIBS on a specific cognitive domain, we opted to combine the stimulation of the right and left cerebellar hemispheres into a unified category referred to as the "lateral" cerebellum. In fact, as previously mentioned, the lateral part of the cerebellum controls high-level cognitive functions (Beuriat et al., 2022; Clark et al., 2021; Mariën and Borgatti, 2018). This distinction is made in contrast to the "medial" cerebellum, responsible for affective-emotional processes (Argyropoulos et al., 2020). Stimulation timing indicates whether NIBS was applied online (concurrently with a task) or offline (before a task). Lastly, outcome reflects the measure to quantify the impact of NIBS on cognitive performance, namely response times or accuracy. Notably, 38 experiments included both response times and accuracy (Table 1 and Fig. 2).

2.3. *Statistical analysis*

All quantitative analyses were conducted using R (R Development Core Team, 2021, version 4.0.1, 2020–06-06) with the *metafor* package (Viechtbauer, 2010).

2.4. *Effect size*

The effect sizes were estimated comparing the effects of real vs. sham/control stimulation on performance at a cognitive task, as defined by response times and accuracy. Four distinct experimental designs were identified among the studies included in the meta-analysis. To calculate

Table 1

Overview of the experiments included in this meta-analysis, highlighting key characteristics such as stimulation site, stimulation timing, outcome, stimulation intensity, stimulation duration, and the cognitive domain under investigation (studies in table are categorized according to the NIBS technique, and within the technique in alphabetical order).

Author & Year	Experiment	Experimental design	Time	Sample size	NIBS	Control condition	Stimulation site	Stimulation intensity	Stimulation duration	Stimulation frequency	Stimulation timing	Outcome	Cognitive domain	Task
Alsultan et al. (2020)	1	Between-subject	Pre Post	14	Anodal tDCS	Sham	Right	1.5 mA	20 mins		Offline	Response Times and Accuracy	Attention	Attention switching
Ballard et al. (2019)	2	Within-subject	Post	23	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Motor learning
Bongaerts et al. (2022)	1	Within-subject	During	36	Anodal tDCS	Sham	Right	2 mA			Online	Response Times and Accuracy	Language	Verbal fluency, sentence comprehension, lexical decision
Catoira et al. (2023)	1	Within-subject	Post	23	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Mentalizing	Picture sequencing
Clausi et al. (2022)	1	Between-subject	Pre Post	32	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times and Accuracy	Mentalizing	Reading the mind in the eyes test
D’Mello et al. (2017)	1	Between-subject	Pre Post	32	Anodal tDCS	Sham	Right	1.5 mA	20 mins		Offline	Response Times and Accuracy	Language	Predictive language
Ehsani et al. (2016)	1	Between-subject	Pre Post	39	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Ferrucci et al. (2012)	1	Within-subject	Pre Post	21	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times	Social Cognition	Facial emotion recognition
Ferrucci et al. (2013)	1	Within-subject	Pre Post	21	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Ferrucci et al. (2019)	1	Between-subject	Post	40	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times	Spatial Cognition	Virtual reality spatial navigation
Jackson et al. (2019)	1	Between-subject	Pre Post	42	Anodal tDCS	Sham	Right	2 mA	25 mins		Offline	Accuracy	Motor Learning	3D overhand throwing
Jongkees et al. (2019)	1	Between-subject	Post	48	Anodal tDCS	Sham	Medial	1 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Serial reaction time task (SRTT)
Lametti et al. (2016)	1	Between-subject	Pre Post	35	Anodal tDCS	Sham	Right	2 mA	15 mins		Offline	Response Times	Language	Speech perceptual learning
Liebrand et al. (2020)	1	Within-subject	During	24	Anodal tDCS	Sham	Right	1 mA	20 mins		Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Lindberg et al. (2022)	1	Between-subject	Post	20	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times	Motor Learning	Multi-finger tapping
Macher et al. (2014)	1	Within-subject	Post	16	Anodal tDCS	Sham	Right	2 mA	25 mins		Offline	Accuracy	Short-term Memory	Sternberg
Maldonado and Bernard (2021)	1	Between-subject	Post	52	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Sequence learning
Maldonado et al. (2023)	1	Between-subject	Post	47	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Sequence learning
Mannarelli et al. (2019)	1	Within-subject	Pre Post	25	Anodal tDCS	Sham	Left	2 mA	20 mins		Offline	Response Times and Accuracy	Attention	Attention network test (ANT)

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Table 1 (*continued*)

Author & Year	Experiment	Experimental design	Time	Sample size	NIBS	Control condition	Stimulation site	Stimulation intensity	Stimulation duration	Stimulation frequency	Stimulation timing	Outcome	Cognitive domain	Task
Miall et al. (2016)	1	Between-subject	During	46	Anodal tDCS	Sham	Right	2 mA	20 mins		Online	Response Times	Language	Visual word paradigm
Nankoo et al. (2021)	1	Within-subject	During	16	Anodal tDCS	Sham	Medial	2 mA	20 mins		Online	Accuracy	Motion Discrimination	Optic flow motion discrimination
Oldrati et al., (2021)	1	Within-subject	During	24	Anodal tDCS	Sham	Medial	1.5 mA	20 mins		Online	Accuracy	Social Cognition	Action and shape prediction
Pope and Miall (2012)	1	Between-subject	Pre Post	44	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Executive Functions	Working memory for paced arithmetic
Rufener et al. (2020)	1	Within-subject	During	20	Anodal tDCS	Sham	Right	2 mA	30 mins		Online	Accuracy	Attention	Oddball
Samaei et al. (2017)	1	Between-subject	Pre Post	30	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Serial reaction time task (SRTT)
Seyed Majidi et al. (2017)	1	Between-subject	During	20	Anodal tDCS	Sham	Right	2 mA	20 mins		Online	Response Times and Accuracy	Probabilistic Association	Weather prediction
Shimizu et al. (2017)	1	Between-subject	Post	34	Anodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Turkeltaub et al. (2016)	1	Between-subject	Pre Post	40	Anodal tDCS	Sham	Right	2 mA	20 mins		Offline	Accuracy	Language	Phonemic fluency, articulation task
van Wessel et al. (2016)	1	Within-subject	During	12	Anodal tDCS	Sham	Right	2 mA			Online	Response Times and Accuracy	Short-term Memory	n-back
Verhage et al. (2017)	1	Between-subject	Pre Post	39	Anodal tDCS	Sham	Right	1.5 mA	20 mins		Online	Response Times and Accuracy	Categorization	Implicit categorization learning
Voegtle et al. (2022)	1	Between-subject	During	40	Anodal tDCS	Sham	Right	2 mA	15 mins		Online	Response Times	Motor Learning	Serial reaction time task (SRTT)
Wessel et al. (2021)	1	Within-subject	Post	40	Anodal tDCS	Sham	Left	2 mA	20 mins		Offline	Accuracy	Motor Learning	sequential finger tapping task (SRTT)
Yuan et al., (2022)	1	Between-subject	Pre Post	44	Anodal tDCS	Sham	Right	2 mA	14 mins		Offline	Response Times and Accuracy	Language	Digit naming
Yuan et al., (2022)	2	Between-subject	Pre Post	45	Anodal tDCS	Sham	Left	2 mA	14 mins		Offline	Response Times and Accuracy	Language	Digit naming
Ballard et al. (2019)	1	Within-subject	Post	21	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Motor learning
Boehringer et al. (2013)	1	Within-subject	Pre Post	39	Cathodal tDCS	Sham	Right	2 mA	25 mins		Offline	Accuracy	Short-term Memory	Digit span
Clausi et al. (2022)	2	Between-subject	Pre Post	32	Cathodal tDCS	Sham	Medial	2 mA	20 mins		Offline	Response Times and Accuracy	Mentalizing	Reading the mind in the eyes test
Jongkees et al. (2019)	2	Between-subject	Post	48	Cathodal tDCS	Sham	Medial	1 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Serial reaction time task (SRTT)
Maldonado et al. (2019)	1	Within-subject	Post	24	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Executive Functions	Stroop and stenberg

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Table 1 (*continued*)

Author & Year	Experiment	Experimental design	Time	Sample size	NIBS	Control condition	Stimulation site	Stimulation intensity	Stimulation duration	Stimulation frequency	Stimulation timing	Outcome	Cognitive domain	Task
Maldonado and Bernard (2021)	2	Between-subject	Post	52	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Sequence learning
Maldonado et al. (2023)	2	Between-subject	Post	46	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Motor Learning	Sequence learning
Mannarelli et al. (2020)	1	Within-subject	Pre Post	16	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Accuracy	Executive Functions	Go/no-go
Miall et al. (2016)	2	Between-subject	During	46	Cathodal tDCS	Sham	Right	2 mA	20 mins		Online	Response Times	Language	Visual world paradigm
Panico et al. (2016)	1	Between-subject	During	26	Cathodal tDCS	Sham	Right	2 mA	21 mins		Online	Accuracy	Motor Learning	Prism adatpation
Panico et al. (2018)	1	Between-subject	Post	26	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Accuracy	Motor Learning	Pointing, prism adaptation
Pope and Miall (2012)	2	Between-subject	Pre Post	44	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times and Accuracy	Executive Functions	Working memory for paced arithmetic processing
Spielmann et al. (2017)	1	Within-subject	Pre Post	24	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Response Times	Language	Verb generation
Turkeltaub et al. (2016)	2	Between-subject	Pre Post	39	Cathodal tDCS	Sham	Right	2 mA	20 mins		Offline	Accuracy	Language	Phonemic fluency, articulation
Wynn et al. (2019)	1	Within-subject	During	26	Cathodal tDCS	Sham	Medial	2 mA	30 mins		Online	Response Times and Accuracy	Executive Functions	Go/no-go
Ferrari et al., (2018)	1	Within-subject	During	18	High-frequency TMS	Control Site	Right	100% MT		20	Online	Response Times and Accuracy	Short-term Memory	Visual sequences
Ferrari et al., 2018	2	Within-subject	During	18	High-frequency TMS	Control Site	Right	100% MT		20	Online	Response Times and Accuracy	Short-term Memory	Visual sequences
Ferrari et al., 2018	1	Within-subject	During	36	High-frequency TMS	Control Site	Left	100% MT		20	Online	Response Times and Accuracy	Social Cognition	Emotion discrimination
Ferrari et al., 2018	2	Within-subject	During	20	High-frequency TMS	Control Site	Left	100% MT		20	Online	Response Times and Accuracy	Social Cognition	Emotion discrimination
Ferrari et al. (2022)	1	Within-subject	During	32	High-frequency TMS	Control Site	Medial	100% MT		20	Online	Response Times and Accuracy	Visual Processing	Body motion discrimination
Ferrari et al. (2022)	3	Within-subject	During	32	High-frequency TMS	Control Site	Left	100% MT		20	Online	Response Times and Accuracy	Visual Processing	Body motion discrimination
Ferrari et al. (2019)	1	Within-subject	During	20	High-frequency TMS	Control Site	Left	100% MT		20	Online	Response Times and Accuracy	Social Cognition	Emotion discrimination
Ferrari et al. (2019)	2	Within-subject	During	40	High-frequency TMS	Control Site	Left	100% MT		20	Online	Response Times and Accuracy	Social Cognition	Emotion discrimination
Gamond et al. (2017)	1	Within-subject	During	20	High-frequency TMS	Control Site	Right	100% MT		20	Online	Response Times and Accuracy	Social Cognition	Standard attitude priming task

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Table 1 (*continued*)

Author & Year	Experiment	Experimental design	Time	Sample size	NIBS	Control condition	Stimulation site	Stimulation intensity	Stimulation duration	Stimulation frequency	Stimulation timing	Outcome	Cognitive domain	Task
Gatti et al. (2020)	1	Within-subject	During	24	High-frequency TMS	Control Site	Right	100% MT		20	Online	Accuracy	Semantic Memory	Word-pair paradigm
Gatti et al. (2020)	2	Within-subject	During	20	High-frequency TMS	Control Site	Right	100% MT		20	Online	Accuracy	Semantic Memory	Word-pair paradigm
Gatti et al., (2021b)	1	Within-subject	During	24	High-frequency TMS	Control Site	Right	100% MT		20	Online	Accuracy	Semantic Memory	False memory paradigm
Gatti et al., (2021b)	2	Within-subject	During	22	High-frequency TMS	Control Site	Right	100% MT		20	Online	Accuracy	Semantic Memory	False memory paradigm
Koch et al. (2007)	1	Within-subject	During	8	High-frequency TMS	Control Site	Right	90% MT		20	Online	Response Times	Time Perception	Time reproduction
Koch et al. (2007)	2	Within-subject	During	8	High-frequency TMS	Control Site	Left	90% MT		20	Online	Response Times	Time Perception	Time reproduction
Schutter et al. (2009)	1	Within-subject	Post	15	High-frequency TMS	Sham	Medial	80% MT	15 mins	20	Offline	Response Times	Social Cognition	Implicit emotional processing
Sheu et al. (2019)	1	Within-subject	During	23	High-frequency TMS	Control Site	Right	110% MT		20	Online	Accuracy	Short-term Memory	Verbal working memory
Avanzino et al. (2015),	1	Between-subject	Post	26	Low-frequency TMS	Sham	Right	90% MT	10 mins	1	Offline	Response Times	Time Perception	Temporal expectation
Fierro et al. (2007)	1	Within-subject	Pre Post	10	Low-frequency TMS	Control Site	Right	90% MT	15 mins	1	Offline	Accuracy	Time Perception	Temporal discrimination
Heleven et al. (2021)	1	Between-subject	Pre Post	46	Low-frequency TMS	Sham	Medial	80% MT	17 mins	1	Offline	Response Times and Accuracy	Social Cognition	Picture and story sequencing
Lee et al. (2007)	1	Within-subject	Post	11	Low-frequency TMS	Sham	Medial	90% MT	8 mins	1	Offline	Response Times	Time Perception	Subsecond bisection
Lee et al. (2007)	2	Within-subject	Post	11	Low-frequency TMS	Sham	Medial	90% MT	8 mins	1	Offline	Response Times	Time Perception	Suprasecond bisection
Lee et al. (2007)	3	Within-subject	Post	18	Low-frequency TMS	Sham	Medial	90% MT	8 mins	1	Offline	Response Times	Time Perception	Subsecond and suprasecond bisection
Lega et al. (2016)	1	Within-subject	Pre Post	14	Low-frequency TMS	Sham	Right	45% MT	15 mins	1	Offline	Response Times	Music Perception	Pitch and a timbre discrimination
Runnqvist et al. (2016)	1	Within-subject	Post	16	Low-frequency TMS	Control Site	Right	60% MT	15 mins	1	Offline	Response Times and Accuracy	Language	Speech production
Théoret et al. (2001)	1	Within-subject	Post	7	Low-frequency TMS	Sham	Medial	90% MT	5 mins	1	Offline	Response Times	Motor Learning	Finger tapping
Torriero et al. (2004)	1	Between-subject	Post	13	Low-frequency TMS	no TMS	Left	90% MT	10 mins	1	Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)

(*continued on next page*)

Table 1 (*continued*)

Author & Year	Experiment	Experimental design	Time	Sample size	NIBS	Control condition	Stimulation site	Stimulation intensity	Stimulation duration	Stimulation frequency	Stimulation timing	Outcome	Cognitive domain	Task
Torriero et al. (2004)	2	Between-subject	Post	13	Low-frequency TMS	no TMS	Left	90% MT	10 mins	1	Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Torriero et al. (2004)	3	Between-subject	Post	12	Low-frequency TMS	no TMS	Right	90% MT	10 mins	1	Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Torriero et al. (2004)	4	Between-subject	Post	11	Low-frequency TMS	no TMS	Right	90% MT	10 mins	1	Offline	Response Times	Motor Learning	Serial reaction time task (SRTT)
Viñas-Guasch et al., (2023)	1	Within-subject	During	31	Low-frequency TMS	Sham	Left	120% MT		1	Online	Response Times and Accuracy	Working Memory	Visual working memory
Gilligan and Rafal (2019)	1	Within-subject	Pre Post	21	Continuous TBS	Control Site	Right	80% MT	40 s	50	Offline	Response Times	Language	Lexical decision
Gilligan and Rafal (2019)	2	Within-subject	Pre Post	20	Continuous TBS	Control Site	Left	80% MT	40 s	50	Offline	Response Times	Language	Lexical decision
Grube et al. (2010)	1	Between-subject	Post	24	Continuous TBS	Sham	Medial	80% MT	40 s	50	Offline	Response Times	Perceptual Timing	Perceptual timing
Picazio et al. (2020)	1	Within-subject	During	12	Continuous TBS	Sham	Right	80% MT		50	Online	Response Times	Executive Functions	Verbal and spatial task switching
Tomlinson et al. (2014)	1	Within-subject	Pre Post	10	Continuous TBS	Control Site	Left	80% MT	40 s	50	Offline	Response Times and Accuracy	Short-term Memory	Spatial working memory
Tomlinson et al. (2014)	2	Within-subject	Pre Post	13	Continuous TBS	Control Site	Left	80% MT	40 s	50	Offline	Response Times and Accuracy	Short-term Memory	Spatial working memory
Ciricugno et al. (2020)	1	Within-subject	During	30	Single-pulse TMS	Control Site	Medial	100% MT			Online	Response Times	Attention	Spatial attention
Ciricugno et al. (2020)	2	Within-subject	During	24	Single-pulse TMS	Control Site	Left	100% MT			Online	Response Times	Attention	Spatial attention
Desmond et al. (2005)	1	Within-subject	During	17	Single-pulse TMS	Control Site	Right	120% MT			Online	Response Times and Accuracy	Short-term Memory	Verbal working memory
Ferrari et al. (2022)	2	Within-subject	During	48	Single-pulse TMS	Control Site	Medial	100% MT			Online	Response Times and Accuracy	Visual Processing	Body motion discrimination
Lo et al. (2009)	1	Within-subject	During	6	Single-pulse TMS	Sham	Right	90% MT	8 mins		Online	Response Times	Motor Learning	Motor cancellation

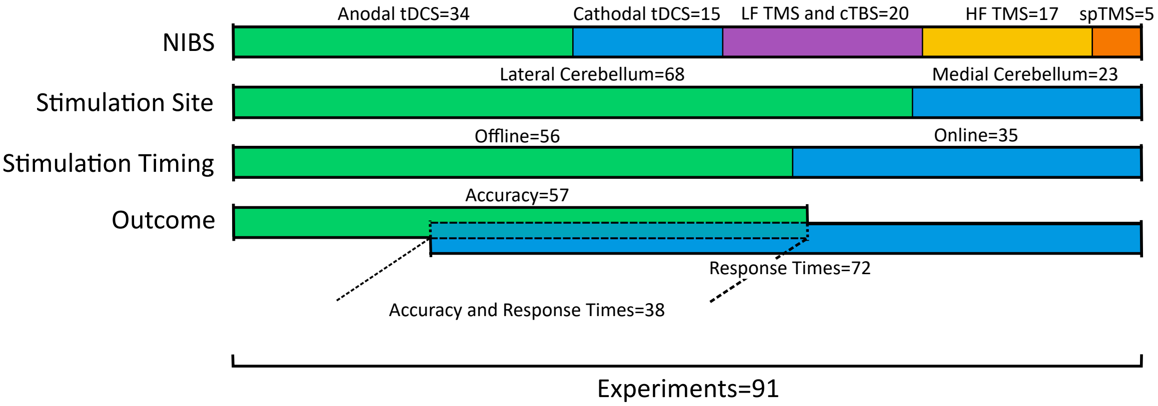

Fig. 2. The figure illustrates the categorization of experiments based on four factors (i.e., NIBS, Stimulation Site, Stimulation Timing, and Outcome) and the number of experiments for a specific factor. Each color represents a level of the factor. For example, the 5-level NIBS factor is depicted as follows: green for anodal tDCS, blue for cathodal tDCS, purple for low-frequency TMS and cTBS, yellow for high-frequency TMS, and orange for single-pulse TMS. The Outcome factor includes 2 levels that partially overlap, representing those experiments that included both response times and accuracy as outcomes.

the effect size, we used a specific approach for each of them (further details in the Supplementary Materials).

2.5. Meta-analysis models

In several studies, multiple experiments were conducted on independent samples, resulting in a total of 91 experiments nested within 66 studies. To account for this nested data structure, we conducted a series of multilevel random-effects meta-analysis, also including moderators (i.e., subgroup analysis) (Konstantopoulos, 2011). Additional information on the meta-analysis models can be found in the Supplementary Materials.

Random effects models were employed to address the research question concerning the effectiveness of NIBS in inducing behavioral effects. In order to consider the impact of *Stimulation Site, Stimulation Timing,* and *Outcome* for each specific NIBS technique, subgroup analyses were conducted. In these analyses, each NIBS technique was examined separately by running models that could include one of the moderators *Stimulation Site, Stimulation Timing,* or *Outcome*. The Supplementary Materials contain the code and formulas for the effect sizes and variance computation. All relevant data and R scripts are available at https://osf.io/a5tur/.

3. Results

3.1. Quality assessment

The 66 included studies were of moderate to high quality (Table S1, Supplementary Materials). On average, they reached 80% ($SD = 7$) of all the required criteria. The main limitations were the absence of power analysis, the poor reporting of inclusion and exclusion criteria for participation, and a lack of acknowledgment of the study's limitations.

3.2. Main results

There were 129 effect sizes (72 for response times and 57 for accuracy) from 66 studies included (Fig. 3). Considerable heterogeneity was observed in the results obtained across studies [QE($df = 128$) = 530.65, $p < 0.0001$]. Without considering moderators, the overall mean weighted effect size was not significant [Hedges' *g*: − 0.04 (95% CI −0.15 to 0.08, $p = 0.5552$)].

3.3. NIBS technique and stimulation site

Subgroup analyses were performed to examine the effects of each NIBS technique based on the stimulation site. The main results of subgroup analyses are reported in Table 2 and Fig. 4. For anodal tDCS, a significant role of the moderator *Stimulation Site* was found [QM(df = 2) = 19.28, $p < 0.0001$]. Anodal tDCS over the medial cerebellum enhanced performance [Hedges' *g*: 0.63 (95% CI 0.34 to 0.91, $p < 0.0001$)]. In addition, the model considering high-frequency TMS and the moderator *Stimulation Site* appeared to explain a significant amount of variance [QM(df = 2) = 8.44, $p = 0.0147$]. Unlike anodal tDCS, high-frequency TMS over the lateral cerebellum significantly reduced performance [Hedges' *g*: − 0.23 (95% CI −0.39 to −0.07, $p = 0.0048$)]. No significant effects were observed for cathodal tDCS, low-frequency TMS and cTBS, and single-pulse TMS.

3.4. NIBS technique and Stimulation Timing

Subgroup analyses were carried out to examine the effect of each NIBS technique with respect to the stimulation timing (Table 2 and Fig. 4). Significant results were found for high-frequency TMS, showing the role of the moderator *Stimulation Timing* [QM(df = 2) = 8.25, $p = 0.0162$]. Online high-frequency TMS protocols were found to significantly reduce performance [Hedges' *g*: − 0.22 (95% CI −0.38 to −0.06, $p = 0.0071$)]. The model considering low-frequency TMS and cTBS showed that the moderator *Stimulation Timing* contributed to explaining a significant amount of variance [QM(df = 2) = 6.95, $p = 0.031$]. Contrary to high-frequency TMS, low-frequency TMS and cTBS significantly reduced performance when used in offline protocols [Hedges' *g*: − 0.29 (95% CI −0.51 to −0.07, $p = 0.0104$)]. No significant effects were observed for anodal tDCS, cathodal tDCS, and single-pulse TMS.

3.5. NIBS technique and Outcome

Subgroup analyses were conducted to investigate whether each NIBS technique selectively affected response times and accuracy. Consequently, the outcome (i.e., response times or accuracy) was included into the models as a moderator (Table 2 and Fig. 4). Results indicated that, in the model examining high-frequency TMS, the moderator *Outcome* yielded significant results [QM(df = 2) = 127.34, $p < 0.0001$]. Specifically, high-frequency TMS was found to significantly decrease accuracy [Hedges' *g*: − 0.41 (95% CI −0.54 to −0.29, $p < 0.0001$)]. Conversely, no significant effects were observed for anodal and cathodal tDCS, low-frequency TMS and cTBS, and single-pulse TMS.

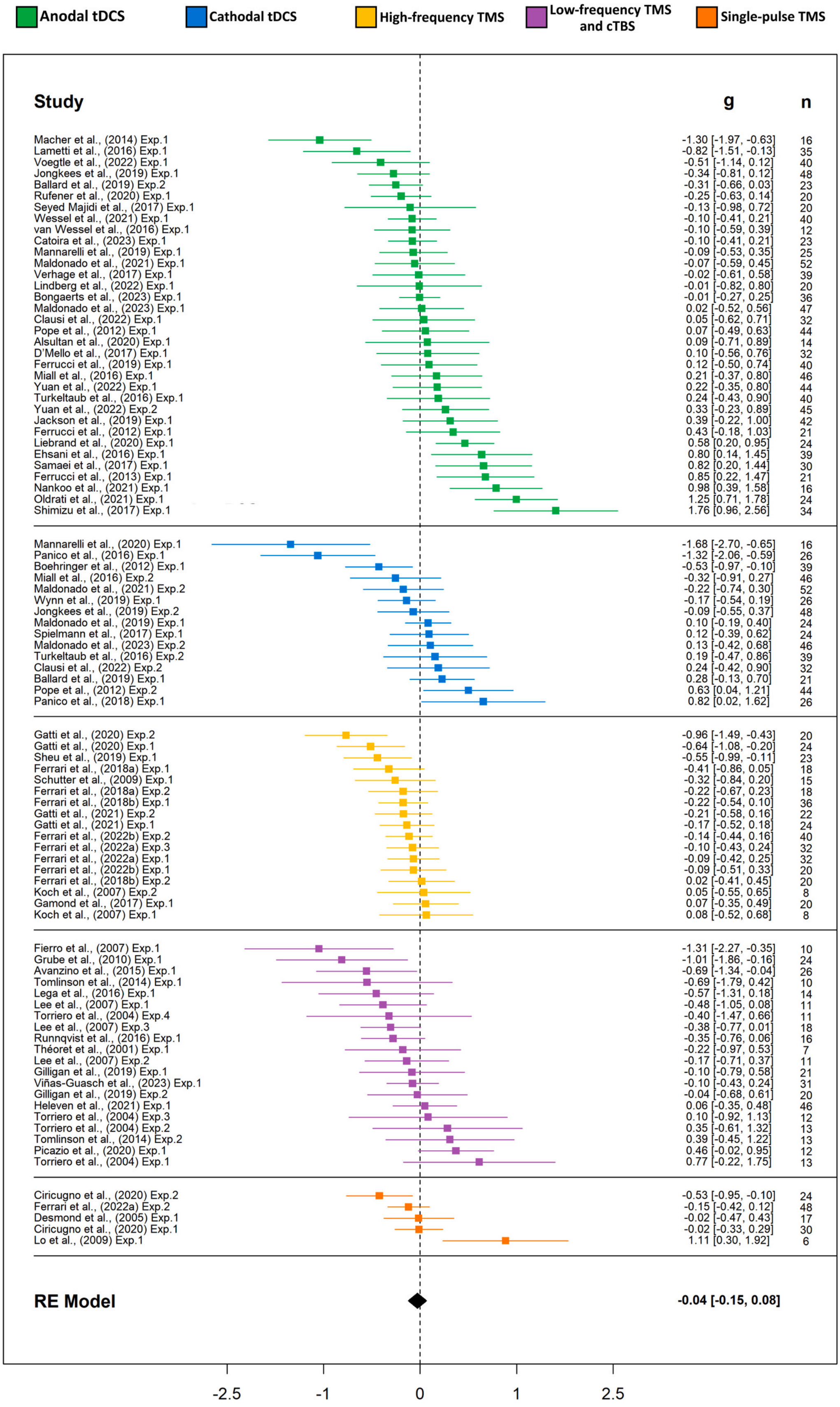

Fig. 3. The forest plot shows the effect sizes estimated from the comparison between real vs. sham/control stimulation for cognitive performance, using the Hedges' *g* random effects model. Positive values indicate an increase in performance following real stimulation vs. sham/control, while negative values indicate a decrease in performance. The error bars represent the 95% confidence interval.

Table 2
Text in bold font indicates that the test of moderator achieved statistical significance ($p < 0.05$) and specifies the particular moderator conditions in which Hedges' g demonstrated a statistically significant deviation from 0. Abbreviations: HF TMS = High-frequency TMS; LF TMS = Low-frequency TMS; cTBS = Continuous theta burst stimulation; spTMS = Single-pulse TMS.

NIBS technique (moderator: Stimulation Site)

NIBS technique	*Moderator*	*Test of Moderator (p-value)*	*Moderator Level*	*estimate*	*CI (lower bound)*	*CI (upper bound)*	*Model Results (p-value; value is different from 0)*
Anodal tDCS	Stimulation Site	< .0001	Lateral Cerebellum	-0.0649	-0.2414	0.1117	0.4714
Anodal tDCS	**Stimulation Site**	**< .0001**	**Medial Cerebellum**	**0.6298**	**0.3448**	**0.9147**	**< .0001**
Cathodal tDCS	Stimulation Site	0.8299	Lateral Cerebellum	-0.0961	-0.4081	0.2159	0.5461
Cathodal tDCS	Stimulation Site	0.8299	Medial Cerebellum	-0.028	-0.6256	0.5696	0.9268
HF TMS	**Stimulation Site**	**0.0147**	**Lateral Cerebellum**	**-0.2294**	**-0.3887**	**-0.07**	**0.0048**
HF TMS	Stimulation Site	0.0147	Medial Cerebellum	-0.2066	-0.5552	0.1421	0.2456
LF TMS and cTBS	Stimulation Site	0.1463	Lateral Cerebellum	-0.1736	-0.4415	0.0943	0.2042
LF TMS and cTBS	Stimulation Site	0.1463	Medial Cerebellum	-0.3005	-0.6946	0.0937	0.1352
spTMS	Stimulation Site	0.9412	Lateral Cerebellum	0.0961	-0.5897	0.7819	0.7836
spTMS	Stimulation Site	0.9412	Medial Cerebellum	-0.0837	-0.8509	0.6835	0.8306

NIBS technique (moderator: Stimulation Timing)

NIBS technique	*Moderator*	*Test of Moderator (p-value)*	*Moderator Level*	*estimate*	*CI (lower bound)*	*CI (upper bound)*	*Model Results (p-value; value is different from 0)*
Anodal tDCS	Stimulation Timing	0.3624	Offline	0.126	-0.0939	0.3459	0.2613
Anodal tDCS	Stimulation Timing	0.3624	Online	0.1586	-0.1961	0.5133	0.3807
Cathodal tDCS	Stimulation Timing	0.1476	Offline	0.0388	-0.225	0.3026	0.7732
Cathodal tDCS	Stimulation Timing	0.1476	Online	-0.5191	-1.045	0.0068	0.053
HF TMS	Stimulation Timing	0.0162	Offline	-0.3223	-0.9549	0.3104	0.3181
HF TMS	**Stimulation Timing**	**0.0162**	**Online**	**-0.2208**	**-0.3814**	**-0.0601**	**0.0071**
LF TMS and cTBS	**Stimulation Timing**	**0.031**	**Offline**	**-0.2897**	**-0.5113**	**-0.068**	**0.0104**
LF TMS and cTBS	Stimulation Timing	0.031	Online	0.14	-0.2999	0.5799	0.5329
spTMS	Stimulation Timing	0.8715	Online	0.0376	-0.4178	0.493	0.8715

NIBS technique (moderator: Outcome)

NIBS technique	*Moderator*	*Test of Moderator (p-value)*	*Moderator Level*	*estimate*	*CI (lower bound)*	*CI (upper bound)*	*Model Results (p-value; value is different from 0)*
Anodal tDCS	Outcome	0.0528	Accuracy	0.0346	-0.171	0.2402	0.7415
Anodal tDCS	Outcome	0.0528	Response Times	0.238	0.0448	0.4312	0.0158
Cathodal tDCS	Outcome	0.4898	Accuracy	-0.008	-0.2966	0.2805	0.9565
Cathodal tDCS	Outcome	0.4898	Response Times	-0.1338	-0.432	0.1644	0.3791
HF TMS	**Outcome**	**< 0.0001**	**Accuracy**	**-0.4164**	**-0.5385**	**-0.2943**	**0.0001**
HF TMS	Outcome	< 0.0001	Response Times	0.0227	-0.102	0.1474	0.7214
LF TMS and cTBS	Outcome	0.1242	Accuracy	-0.2538	-0.5157	0.0081	0.0576
LF TMS and cTBS	Outcome	0.1242	Response Times	-0.1901	-0.4	0.0198	0.0758
spTMS	Outcome	0.9699	Accuracy	-0.0525	-0.6164	0.5114	0.8552
spTMS	Outcome	0.9699	Response Times	0.0192	-0.3996	0.4381	0.9283

4. Discussion

This meta-analysis aimed to assess the effectiveness of NIBS in modulating cerebellar-associated cognitive processes in healthy adults. Sixty-six studies were included in which either TMS or tES could be used to stimulate the cerebellum. As expected, when considering the overall effects of NIBS, we did not observe significant modulation of the cognitive functions associated with the cerebellum. As a matter of fact, this model overlooked the influence of possible significant aspects, such as the different kinds of NIBS techniques that have demonstrated potentially divergent effects on cortical-associated cognitive processes (Beynel et al., 2019; Chen et al., 2022; Koo et al., 2023). Following this evidence, subgroup analyses were conducted in which the moderators considered relevant in the context of non-invasive cerebellar stimulation (i.e., *Stimulation Site*, *Stimulation Timing*, *Outcome*) were included.

The first subgroup analysis investigated NIBS effects by stimulation site, assuming cognitive impact depends on where NIBS is applied. The findings reveal that the application of anodal tDCS to the medial cerebellum induces modulation of cognitive processes, resulting in improved performance. This result is consistent with previous meta-analyses that showed that anodal tDCS can enhance cognitive processes when administered over the cortex (Chen et al., 2022). In the context of non-invasive cerebellar stimulation, the only meta-analysis conducted on tDCS found a general modulatory effect but did not differentiate between anodal or cathodal stimulation, nor specified whether cognitive performance improved or worsened (Oldrati and Schutter, 2018). The

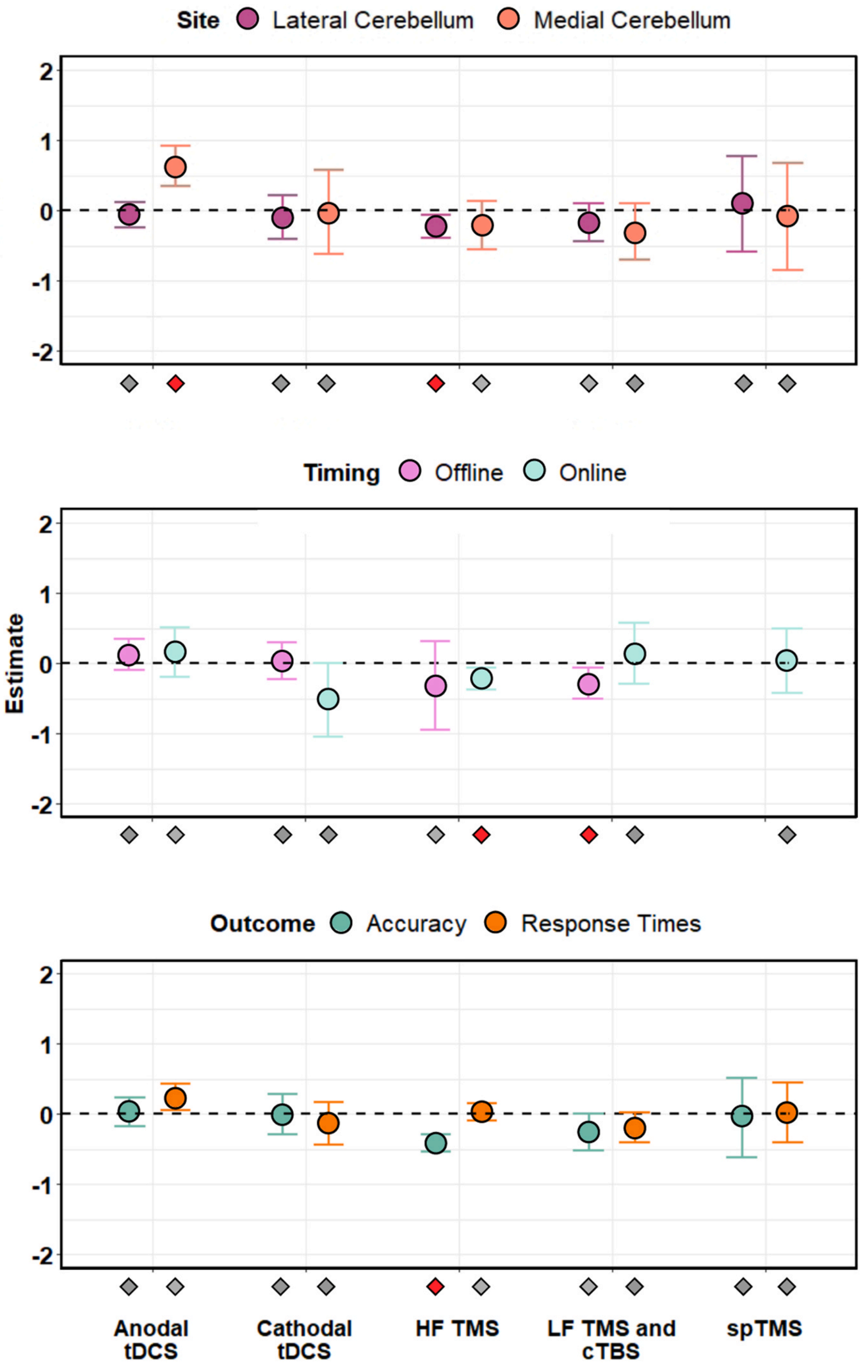

Fig. 4. Results of subgroup analyses based on three moderators: *Stimulation Site* (top), *Stimulation Timing* (middle), and *Outcome* (bottom). The red diamonds at the base of each graph represent conditions significantly different from zero ($p < 0.05$). Abbreviations: HF TMS = High-frequency TMS; LF TMS = Low-frequency TMS; cTBS = Continuous theta burst stimulation; spTMS = Single-pulse TMS.

result of the present study is also important because it suggests that the medial cerebellum may be potentially involved not only in affective-emotional processes (Argyropoulos et al., 2020) but it might also contribute to motor learning, social cognition, motion discrimination, and spatial cognition. Nonetheless, it is crucial to recognize that the tDCS studies included in this meta-analysis frequently positioned a sizable electrode (e.g., 5 ×7 cm) over the medial cerebellum, introducing the possibility of simultaneous stimulation of the lateral cerebellar hemisphere. In future studies, the use of high-definition tDCS montages, which enhance the spatial resolution of tDCS (Datta et al., 2009; Masina et al., 2021), will be crucial to disambiguate this question.

Unlike the facilitatory effects of anodal tDCS, high-frequency TMS has been found to impair cognitive performance when applied to the lateral cerebellum. This finding is consistent with previous studies highlighting the involvement of the lateral cerebellum in higher-order cognitive processes (Beuriat et al., 2022; Clark et al., 2021; Mariën and Borgatti, 2018).

Regarding the other NIBS techniques and their potential modulatory effect based on the stimulation site, our findings do not find evidence that cathodal tDCS, low-frequency TMS and cTBS, and single-pulse TMS can modulate cerebellar-related cognitive functions.

Null cathodal tDCS effects align with previous meta-analyses focusing on the cortex that found an anodal-excitation but not a cathodal-inhibition effect (Dedoncker et al., 2016; Jacobson et al., 2012;

Schroeder et al., 2020). However, cathodal tDCS impact varies; some meta-analyses show positive cognitive effects (Chu et al., 2021; Yuan et al., 2022). These inconsistencies may arise from diverse stimulation protocols: montages, timing, and parameters. For example, an important aspect to consider is the intensity of cathodal stimulation, which should be carefully tuned to modulate cognitive processes associated with the cerebellum. In this regard, it is essential to emphasize that this choice cannot follow a simple "cumulative" rationale, where an increase in intensity leads to an increase in effects. Indeed, as suggested by Batsikaze and colleagues (2013), studies often apply high current intensities (e.g., 2 mA) which may turn inhibitory-reducing effects of cathodal tDCS into excitability-enhancing effects (Batsikadze et al., 2013). Thus, it seems that cathodal tDCS induces non-linear brain effects tied to intensity, as shown in several studies (Batsikadze et al., 2013; Ghasemian-Shirvan et al., 2022; Vimolratana et al., 2023). Future cathodal tDCS studies should investigate the optimal dose-response balance to induce modulation of cerebellar processes. To shed light on the variability of effects due to cathodal tDCS, also the co-registration with neuroimaging tools may provide additional information on the modulation induced by this technique.

Regarding low-frequency TMS and cTBS, it is noteworthy that no effect on cognitive performance was found, despite these stimulation techniques having shown modulatory effects on cortical processes (Brückner et al., 2013; Chung et al., 2016; Fitzgerald et al., 2006; Lowe et al., 2018). It may be that these techniques are not able to produce modifications at the cerebellar level, unless other stimulation parameters are taken into account. Further studies are needed to confirm this claim. The lack of effect of single-pulse TMS should be taken with caution given the small number of studies included in the present meta-analysis.

In the second subgroup analyses, the effect of NIBS with respect to the stimulation timing was investigated to account for the evidence based on the different neurobiological mechanisms known to occur during online or offline stimulation. The online effects of tDCS are thought to be caused by alterations in the resting membrane potential, which can alter neuronal excitability (Liu et al., 2018). In addition, the online application of TMS generates brief bursts of action potentials that can interfere with ongoing neuronal processes or facilitate brain oscillations corresponding to specific frequencies of TMS pulses (Polanía et al., 2018). Differently, the offline effects of both tDCS and TMS appear to result from long-term potentiation (LTP)- or long-term depression (LTD)-like effects (Polanía et al., 2018).

Our findings highlight that high-frequency TMS disrupts cognitive performance during online protocols, emphasizing the critical role of TMS pulse timing in modulating cerebellar-associated cognitive processes (Gatti et al., 2021a). The timing of TMS pulses within experimental designs is particularly crucial, especially in online TMS protocols that can be used to uncover precise temporal information about a specific cognitive process by transiently affecting the function within different time windows. Consequently, variations in TMS pulse timing can yield distinct effects (Miniussi and Ruzzoli, 2013).

In contrast, we found that low-frequency TMS and cTBS disrupt performance only in offline protocols, with no corresponding effects during online protocols. While the former aligns with existing literature on TMS applied to the cortex (Beynel et al., 2019), interpreting the absence of online effects for low-frequency TMS and cTBS is challenging due to the limited number of experiments analyzed in the present meta-analysis. Studies on the cortex seldom use low-frequency TMS protocols online, possibly due to the slow pace of pulses that may not align well with the rapid temporal dynamics of most cognitive tasks, consequently failing to induce online modulation (Beynel et al., 2019). As a result, studies often choose for short bursts or trains at higher frequencies to interfere with ongoing cognitive processes. This assumption appears to extend to cerebellar studies, where the experimental design using online low-frequency TMS protocols are limited. However, given the paucity of evidence regarding the effects of these protocols on the cerebellum, future studies should be conducted to validate possible limitations (or benefits) of online low-frequency TMS protocols in inducing modulation of cerebellar-associated cognitive processes.

Overall, it is crucial to emphasize that our findings do not necessarily imply that TMS exclusively influences cognition when the cerebellum is stimulated online with high-frequency TMS protocols or offline with low-frequency TMS and cTBS protocols. As previously mentioned, it is essential to consider a potential bias introduced by the distribution of studies included in our meta-analysis that used both online and offline protocols. In fact, the majority of included experiments using high-frequency TMS employed online protocols (16 out of 17 experiments), which limits the observation of potential effects stemming from high-frequency TMS offline protocols. Similarly, most of the included experiments involving low-frequency TMS and cTBS were applied offline (18 out of 20 experiments), thereby hindering the exploration of the potential online effects of these two techniques.

The third subgroup analyses explored NIBS effects on response times and accuracy. High-frequency TMS significantly impacted cognitive performance, specifically reducing accuracy, with no evidence of effects on response times. This result must be interpreted with caution. We believe that the literature on cerebellar stimulation is still insufficient to hypothesize that high-frequency TMS protocols exclusively modulate accuracy. This result may also be attributed to the fact that our meta-analysis considered a broad range of cognitive functions. It is likely that the selective effect on the outcome depends on the cognitive domain and, consequently, on the type of task used to investigate that domain. In designing future studies on NIBS and the cerebellum, this finding emphasizes the importance of carefully considering the outcome that the investigator expects to be affected by NIBS. This is crucial because each technique may have a selective impact on a specific outcome. Regarding the question of task (outcome) selection, we believe it is also important to highlight that, in this meta-analysis, only a few studies included a control task to assess unintentional motor effects unrelated to the primary cognitive modulation of interest. We recommend for future studies, according to the main hypothesis of each study, incorporating a control task specifically designed to address unintentional motor effects resulting from cerebellar stimulation.

This study significantly contributes by using a novel statistical approach to assess the impact of various NIBS techniques on cognitive processes in the cerebellum, considering specific experimental designs. Here, we investigated how factors like the stimulation site and stimulation timing might influence cognitive processes, and specifically we examined the direction of the effects of these techniques. Applying anodal tDCS to the medial cerebellum can improve cognitive performance across a wide range of functions. This suggests that there may be similarities between the effects of cerebellar and cortical electrical stimulation (Huo et al., 2021; Indahlastari et al., 2021). On the other hand, when applied laterally to the cerebellar hemispheres, high-frequency TMS disrupts cognitive performance. This latter result requires careful interpretation, taking into account the specific stimulation protocol employed. In fact, within the high-frequency TMS cluster, the majority of experiments used triple-pulse 20 Hz TMS protocols (15 out of 17 experiments), which have been proven to transiently disrupt the stimulated cortical and cerebellar areas (Ferrari et al., 2018, 2022; Koch et al., 2007; Schwarzkopf et al., 2011).

It is important to recognize that while anodal tDCS and triple-pulse 20 Hz TMS over the cerebellum may have similar effects as when stimulating the cortex (i.e., improving and disrupting cognitive performance, respectively), it would be incorrect to generalize these findings by claiming that NIBS over the cortex has an identical impact on the cerebellum. The specific stimulation protocol and other stimulation parameters employed can influence these effects, and therefore, caution should be taken in drawing broad conclusions.

A common aspect affecting meta-analyses is that the results are influenced by how the original studies conducted their analyses. A concept that is often overlooked, but holds great importance, is state-dependency. State-dependency has a substantial impact on the effects of NIBS when applied to the cortex (Silvanto and Cattaneo, 2017; Silvanto and Pascual-Leone, 2008), and unfortunately, it has been neglected in the majority of the studies included in this meta-analysis. State-dependency refers to the notion that the effects of NIBS can vary based on the initial neural state or functional context of the brain. Studies have shown that state-dependency can be statistically modeled to account for its effects (Masina et al., 2022, 2021). In the case of the cerebellum, factors such as baseline cerebellar activity, task engagement, or specific cognitive states may interact with NIBS interventions and influence the observed effects. Accounting for state-dependency can help identify potential moderators or factors that influence the efficacy of NIBS on the cerebellum, leading to a better understanding of the overall effects and potentially guiding future research and clinical applications. These factors have likely not been considered, but the outcome of a meta-analysis could change drastically if they were taken into account.

The current study has limitations in terms of providing a comprehensive understanding of the underlying mechanisms of cerebellar functioning. It suggests the necessity of future meta-analyses that combine neuroimaging techniques with cerebellar stimulation to address this gap in knowledge. In particular, the influence of tES on brain activity is still not fully understood (Chan et al., 2021; Sale et al., 2015; Vöröslakos et al., 2018). Co-registering tES with EEG, for example, can provide a high-temporal resolution understanding of the modulations of cerebellar activity in local regions and distributed networks (Vöröslakos et al., 2018). Additionally, the observed high heterogeneity in our results may be attributed to the inclusion of studies investigating various cognitive domains. However, it is worth mentioning that the aim of this meta-analysis was not to provide conclusive evidence on the effects of NIBS in a specific cognitive process. Rather, the objective was to offer guidance to researchers in developing appropriate protocols for cerebellar stimulation based on the existing evidence gathered thus far.

In the present study, a considerable variability of the stimulation intensity was found across NIBS. Although the question of intensity was not addressed in our study, it is crucial to discuss its potential implications in the field of cerebellar modulation with NIBS techniques. TMS protocols offer a degree of personalization by adjusting the intensity relative to an individual's motor threshold - the minimum magnetic stimulus intensity required for a measurable muscle response, often quantified through motor-evoked potentials. Unlike TMS, tES does not induce action potentials and does not elicit motor-evoked potentials, even when targeting motor regions. This lack of measurable response makes customizing tES approaches challenging, leading many studies to select for a fixed intensity across participants. An emerging strategy to customize NIBS involves adopting computational electric field modeling as the standard (Numssen et al., 2023; Weise et al., 2023), particularly in studies involving the cerebellum (Grimaldi et al., 2016). In this field, where the question of proper stimulation intensity remains debated, employing this practice may contribute to minimizing variability of effects.

Additionally, a further aspect that this study does not address concerns all the secondary effects induced by NIBS and their potential impact on results. When planning cerebellar stimulation with NIBS, it is important to also consider the possible unpleasant effects that may occur during or after stimulation. Regarding tES techniques, studies on the cortex have shown that electrode size and intensity play a role in the sensations induced by tDCS, with larger electrodes causing stronger sensations compared to smaller ones, and higher intensities being more strongly perceived by the individual (Fertonani et al., 2015). When applying TMS on the cortex, mild effects are commonly reported, such as headaches, changes in hearing, local pain at the site of stimulation, muscle contractions, non-specific tingling, and discomfort (Rossi et al., 2021). In the field of non-invasive cerebellar stimulation, it has been observed that TMS has the potential to trigger muscle contractions and discomfort by activating the neck muscles (Demirtas-Tatlidede et al., 2011). Regarding these secondary induced effects, ad hoc questionnaires should be included in future studies to monitor the subjective feelings associated with NIBS applied to the cerebellum (for tES stimulation, see Fertonani et al., 2015; for TMS stimulation, see Giustiniani et al., 2022).

Overall, this study holds significant implications that counter criticisms concerning the use of NIBS techniques on the cerebellum. One common concern raised was the cerebellum's deeper placement in the brain, which could make it challenging to access from the scalp. Nevertheless, our findings indicate that despite the greater skin-cerebellum distance compared to the skin-cortex distance, cognitive functions can still be influenced by techniques like anodal tDCS and TMS. This means these methods can effectively modulate cerebellar processes, despite the cerebellum's tricky location.

5. Conclusions and recommendations for future studies

The results of this meta-analysis offer several recommendations for future NIBS studies probing cognitive processes associated with the cerebellum.

Regarding tES, anodal tDCS applied to the medial cerebellum induces modulation of cognitive processes, resulting in improved performance. Most of the studies use a sizable electrode (i.e., 5 ×7 cm) over the medial cerebellum. Although this montage is effective to induce modulation, it can also introduce the possibility of simultaneous stimulation of the lateral cerebellar hemisphere. Thus, it is vital to introduce approaches to enhance the spatial resolution of tDCS protocols, such as high-definition tDCS montages and electric field modeling.

In the context of TMS, it has been observed that high-frequency TMS can impair cognitive performance when applied to the lateral cerebellum. Moreover, high-frequency TMS disrupts cognitive performance during online protocols. This evidence underscores the critical role of TMS pulse timing in modulating cerebellar-associated cognitive processes, making high-frequency TMS suitable for investigating the time course of cerebellar functions. While high-frequency TMS appears to induce online and timing-dependent effects, low-frequency TMS and cTBS protocols seem appropriate for inducing offline and long-lasting effects on cerebellar processes. Lastly, the evidence that high-frequency TMS reduces accuracy but not response times highlights how this technique may exert selective effects on outcomes.

To conclude, this meta-analysis provides compelling evidence that both anodal tDCS and TMS can effectively modulate cognitive processes associated with the cerebellum, thereby highlighting the substantial potential of NIBS techniques to influence this crucial area of the brain. Overall, these remarkable results pave the way for additional investigations and hold promise for future therapeutic applications, ultimately expanding our understanding of the cerebellum's pivotal role in cognition and establishing its potential as a prime target for NIBS interventions.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105509.

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