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Review

# Transcranial direct current stimulation decreased cognition-related reaction time in older adults: A systematic review and meta-analysis

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ABSTRACT

*Background:* This systematic review and meta-analysis investigated the effects of transcranial direct current stimulation (tDCS) on the cognitive functions of healthy older adults by focusing on the changes in reaction time during cognitive tasks.

*Method:* A total of 31 studies qualified for this meta-analysis, and we acquired 36 comparisons from the included studies for data synthesis. The individual effect sizes were calculated by comparing the altered reaction time during the performance of a specific cognitive task between the active tDCS and sham groups. In two moderator variable analyses, we examined the potentially different effects of the tDCS protocols on the cognition-related reaction time based on the tDCS protocol used (i.e., online vs. offline tDCS) and the five cognitive domains: (a) perceptual-motor function, (b) learning and memory, (c) executive function / complex attention, (d) language, and (e) social cognition. Meta-regression analyses were conducted to estimate the relationship between demographic and tDCS parameter characteristics and the changes in reaction time.

*Results:* The random-effects model meta-analysis revealed significant small effects of tDCS on cognition-related reaction time. Specifically, providing online tDCS significantly reduced the reaction time, and these patterns were observed during learning and memory and executive function / complex attention tasks. However, applying offline tDCS failed to find any significant reduction of reaction time across various cognitive tasks. The meta-regression analysis revealed that the effects of tDCS on the reaction time during the performance of cognitive tasks increased for the older people.

*Conclusions:* These findings suggest that providing online tDCS may effectively improve the ageing-induced reaction time related to specific cognitive functions of elderly people.

## 1. Introduction

Ageing is a degenerative biological process that causes various diseases, such as cancer, stroke, and dementia, frequently accompanied by progressive cognitive impairment (Harada et al., 2013; Niccoli and Partridge, 2012). With increasing age, potential neurophysiological alterations in the brain, such as atrophy of the grey and white matter, loss of neural cells, and impaired synaptic connections, may cause various types of cognitive dysfunction (Bernard and Seidler, 2013; Burke and Barnes, 2006; Harada et al., 2013; Ramanoël et al., 2018). For example, in previous studies, although some cognitive domains (e.g., decision making, speech, and language) were relatively intact in the older adults, attention, perception, and memory were significantly affected (Glisky, 2007; Mokhber et al., 2019). Importantly, these ageing-induced cognitive deficits interfere with essential movement executions in daily living, leading to dreadful events, as evidenced by the increased occurrence rates of car accidents and falls among those aged 65 and over (Glisky, 2007; Murman, 2015; Society et al., 2001; Tefft, 2017). Thus, identifying optimal rehabilitation protocols that effectively arrest or reverse cognitive impairment is a critical goal for advancing the quality of life and independent living of older adults.

Quantifying the reaction time during the performance of a cognitive task is one of the useful approaches for estimating the specific cognitive functions mainly involved in successfully achieving task goals (Deary

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and Der, 2005; Jordan et al., 1992; Kosinski, 2012; Madden, 2001). For instance, the two-back task can be used for assessing a person's working memory and updating capability because the person needs to use a series of cognitive processes while carrying out such task, such as encoding and storing the sequential presentations and continuously absorbing incoming stimuli (Best and Miller, 2010; Gajewski et al., 2018). Thus, people with more advanced working memory and updating may quickly recognise and focus on a new stimulus that matches the prior stimulus presented to them two steps before in the sequence, resulting in a lower reaction time (Mokhber et al., 2019). Interestingly, a prior study showed that healthy young individuals demonstrated a decreased reaction time during their performance of a cognitive task (i.e., two-choice reaction time task) while showing greater neural activations in the prefrontal–parietal regions (Ramchurn et al., 2014). Further, the cortical activities in the prefrontal–parietal regions were more facilitated during the performance of tasks requiring higher cognitive loads (Braver et al., 1997; Fishburn et al., 2014; Jansma et al., 2000; Veltman et al., 2003). However, older adults and patients with neurological disorders accompanied by cognitive deficits tended to reveal a higher reaction time during the performance of cognitive tasks (Bloxham et al., 1987; Chen et al., 2017; Firbank et al., 2018; Richards et al., 2019) because of the potential structural and functional changes in the prefrontal cortex (Glisky, 2007; Samson and Barnes, 2013). Taken together, estimating the changes in the reaction time may effectively provide altered cognitive functions in older adults.

Many researchers have examined the effects of transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, on the reduction of age-associated cognitive impairment (Fiori et al., 2017; Madden et al., 2019; Samaei et al., 2017; Summers et al., 2016). For the potential mechanism of tDCS, delivering a constant weak electrical current (0.5–2 mA) to the scalp for up to 20 min may either increase or decrease the cortical excitability in the targeted cortical regions under the non-metallic and conductive electrodes (Nitsche et al., 2002). Previous studies have indicated that anodal tDCS over a region of the dorsolateral prefrontal cortex (DLPFC) or the inferior frontal gyrus improved the working memory, decision making, and verbal fluency of older adults (Berryhill and Jones, 2012; Leach et al., 2016; Nissim et al., 2017). Despite the fact that some meta-analysis studies have suggested the potential effects of tDCS on cognitive improvement in elderly people, the methods of estimating the cognitive functions that were used in such studies were inconsistent (Hsu et al., 2015; Indahlastari et al., 2021; Perceval et al., 2016; Summers et al., 2016). Thus, quantifying the overall effects of tDCS on the changes in the reaction time during the performance of various cognitive tasks may provide more information regarding cognitive function improvement in older adults with minimal methodological heterogeneity issues.

The purpose of this systematic review and meta-analysis was to investigate the effects of tDCS on the cognitive functions of healthy older adults by focusing on their reaction time. Previous studies have suggested that the timing of tDCS (e.g., online stimulation vs. offline stimulation) may affect the magnitude of cognitive improvement (Fertonani et al., 2014; Friehs and Frings, 2019). Furthermore, the cognitive impairment patterns in the ageing population may be shown to be different in the following five domains: (a) perceptual-motor function, (b) learning and memory, (c) executive function / complex attention, (d) language, and (e) social cognition (Sachdev et al., 2014). Based on these prior findings, we additionally asked two sub-leading questions: (1) Do the effects of tDCS on the reaction time differ depending on the timing of the stimulation (i.e., stimulation during the performance of a cognitive task vs. stimulation before the performance of a cognitive task)? and (2) Are the effects of tDCS protocols on the cognition-related reaction time different across the five key domains of cognitive function?

## 2. Materials and methods

### 2.1. Literature search and study inclusion

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). The computerised literature search that was performed on May 1, 2020–Mar 24, 2021 identified potential studies via PubMed and Web of Science. The keywords were: (tDCS or transcranial direct current stimulation) and (reaction time or response time or RT or cognitive or cognition) and (older adults or elderly or aging). The inclusion criteria in this meta-analysis were (a) studies that recruited cognitively healthy older adults with a sample mean age of 60 years or older (Chou et al., 2020; Gavelin et al., 2021), (b) studies that estimated the quantitative changes in the reaction time as an indicator of cognitive function, (c) studies that used either a randomised controlled trial or a crossover design, and (d) studies that compared the reaction time in the active tDCS group with that in the sham control group. We excluded the studies that focused on elderly people with critical cognitive impairments (e.g., dementia and major or mild cognitive impairment), the review papers, case studies, animal studies, and articles that were irrelevant to our main topic (e.g., people with specific diseases, young population, and no use of tDCS).

After identifying 926 potential studies through the initial literature search from two search engines (i.e., PubMed, 627 articles; Web of Science, 299 articles) and one article from another source, we excluded 172 duplicated studies. In addition, we removed 724 studies that were not related to our main topic (78 review studies, six animal studies, 11 case studies, and 629 studies). Finally, the remaining 31 studies qualified for this meta-analysis (Adenzato et al., 2019; Antonenko et al., 2019; Cespón et al., 2017; Conley et al., 2016; Deldar et al., 2019; Di Rosa et al., 2019; Dumel et al., 2018, 2016; Fertonani et al., 2014; Fiori et al., 2017; Gbadeyan et al., 2019; Habich et al., 2020b; Hanley et al., 2020; Heise et al., 2014; Holland et al., 2011; Horne et al., 2020; Huo et al., 2018; Jones et al., 2015; Learmonth et al., 2015; Ljubisavljevic et al., 2019; Madden et al., 2019; Manenti et al., 2013; Marquez et al., 2015; Meinzer et al., 2013; Nilsson et al., 2015; Nissim et al., 2019a; Nissim et al., 2019b; Park et al., 2014; Ross et al., 2011; Saldanha et al., 2020; Samaei et al., 2017). Fig. 1 shows the PRISMA flowchart illustrating our study identification procedure.

### 2.2. Outcome measures: reaction time during the performance of cognitive tasks

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Sachdev et al., 2014), neurocognitive disorders typically accompany with degeneration in one or more of the key six cognitive domains. Further, prior cognitive researchers suggested that complex attention such as selective attention and divided attention may be highly involved in inhibition and shifting of executive function (Diamond, 2013; Peterson et al., 2016). Thus, we finally categorized cognitive functions into five domains: (a) perceptual-motor function (e.g., visual perception and perceptual-motor coordination), (b) learning and memory (e.g., cued recall and implicit learning), (c) executive function / complex attention (e.g., working memory, inhibition, decision-making, and selective attention), (d) language (e.g., object naming and verbal fluency), and (e) social cognition (e.g., recognition of emotions and theory of mind).

Given that 26 out of the 31 qualified studies reported one comparison and five studies reported two comparisons due to the different timings of tDCS (i.e., online and offline stimulations), we included 36 total comparisons of the changes in the reaction time during the performance of cognitive tasks. Specifically, we categorized the 36 comparisons into following cognitive domains: (a) perceptual-motor function including lateralised visual detection tasks (two comparisons from one study) and simple reaction time tasks (two comparisons from one study), (b)

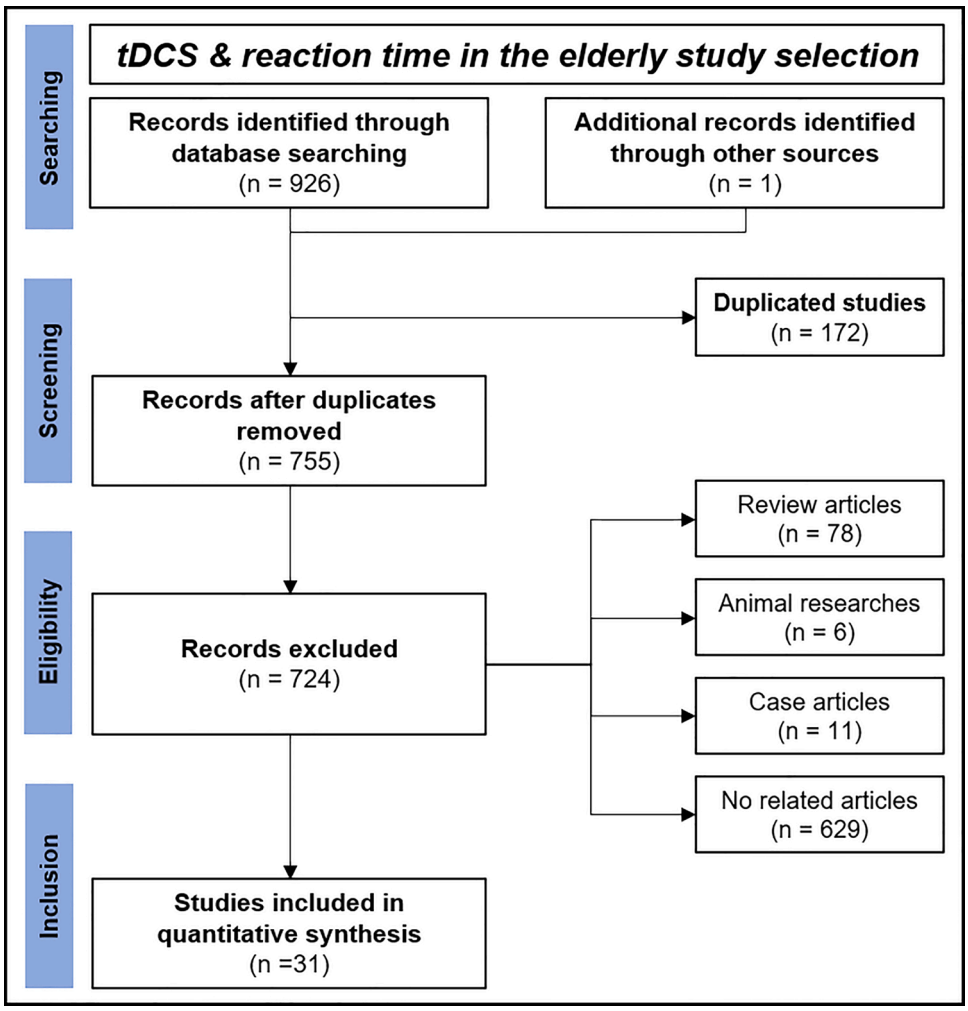



**Fig. 1.** PRISMA flowchart for the study identification procedure.

learning and memory including episodic memory tasks (three comparisons from three studies) and serial reaction time tasks (three comparisons from three studies), (c) executive function / complex attention including N-back tasks (10 comparisons from eight studies), go/nogo tasks (two comparisons from two studies), stop signal task (one comparison from one study), visuospatial working memory task (one comparison from one study), flanker task (one comparison from one study), Swansea Test of Attentional Control (one comparison from one study), decision-making task (one comparison from one study), and stroop task (one comparison from one study), (d) language including picture naming tasks (five comparisons from four studies), selection and generation task (one comparison from one study), and semantic word generation task (one comparison from one study), and (e) social cognition from one study (one comparison from one study). Specific information on cognitive task procedures and outcome measures used for the qualified studies were shown in Supplementary Table 1.

### 2.3. Meta-analytic approaches

Using the Comprehensive Meta-Analysis software (ver. 3.2, Englewood, NJ, USA), we performed meta-analytic procedures. For the parallel group studies, effect sizes were based on the differences in reaction time between the active tDCS and sham groups (e.g., values of sample size, mean, and standard deviation for two groups) at the post-test using standardised mean difference (*SMD*) with a 95 % confidence interval (CI) (Borenstein et al., 2009). For the crossover studies, we calculated *SMD* via a paired analysis (e.g., sample size and mean difference with *P*-value or sample size and mean difference with standard error) consistent with the prior suggestions (Borenstein et al., 2009; Miller et al., 2019; Nasser, 2020; Stedman et al., 2011). This procedure may reduce the possibility of disguising clinical important heterogeneity in the meta-analysis while incorporating crossover trials into a meta-analysis (Nasser, 2020). More positive *SMD* values indicated greater reduction in reaction time after active tDCS than after the sham control stimulation. Finally, we used random-effects meta-analysis models consistent with the traditional assumption that individual studies have heterogeneous experiment characteristics (Borenstein et al., 2010).

To measure the heterogeneity levels across the comparisons, we used the Higgins and Green $I^2$ test, which reported the percentage of heterogeneity from 0 to 100 % (Higgins and Thompson, 2002). Typically, the 25, 50, and 75 % values of $I^2$ indicate low, moderate, and high heterogeneity levels, respectively (Higgins et al., 2003). Moreover, Cochran's Q and *P*-value were used for the heterogeneity significance test based on the chi square distribution. A *P*-value less than 0.05 for the Q-statistic means significant heterogeneity levels across comparisons (Borenstein et al., 2009). The two publication bias assessments that were conducted in this study were (a) visual estimation of the changes in the overall effect size, with imputed values between an original funnel plot and a revised funnel plot after the use of the trim-and-fill technique (Duval and Tweedie, 2000) and (b) the Egger regression test, where a *P*-value for intercept ($\beta 0$) that is less than 0.05 indicates high publication bias (Egger et al., 1997).

To specify the effects of tDCS on the reaction time changes related to

cognitive function, we conducted two moderator variable analyses. The first focused on the effect sizes between two different timings of the following tDCS protocols: (a) online stimulation (i.e., applying tDCS during the performance of a cognitive task or task-related training) and (b) offline stimulation (i.e., applying tDCS before the performance of a cognitive task or task-related training). The second moderator variable analysis determined whether the effect sizes of the following five cognitive domains were different: (a) perceptual-motor function, (b) learning and memory, (c) executive function / complex attention, (d) language, and (e) social cognition (Sachdev et al., 2014). Finally, based on the prior findings (Dedoncker et al., 2016), we conducted meta-regression analyses to confirm if the effects of tDCS on reaction time during the performance of cognitive tasks were significantly associated with different demographic (i.e., mean age, gender proportion, and cognitive function level at baseline) and tDCS protocol parameters (e.g., stimulation intensity, electrode area, current density, session duration, and density charge) characteristics, respectively.

### 2.4. Methodological-quality assessment

Three authors (JHL, NK, and TLL) independently assessed the methodological quality of the individual studies included in this meta-analysis using the Physiotherapy Evidence Database (PEDro) scale (de Morton, 2009; Maher et al., 2003). Such assessment tool consists of 11 questionnaire domains (yes = 1 point; no = 0 point): (a) eligibility criteria specified, (b) random allocation, (c) concealed allocation, (d) group similarity at baseline, (e) subject blinding, (f) blinding of therapists who administered tDCS, (g) blinding of assessors who measured at least one key outcome, (h) less than 15 % dropouts, (i) intention-to-treat analysis, (j) between-group statistical comparisons, and (k) point measures and data variability for the outcome measures. The methodological quality of the included studies could be classified into four different levels: (a) excellent quality (9–10 points), (b) good quality (6–8 points), (c) fair quality (4–5 points), and (d) poor quality (less than 4 points) (Cashin and McAuley, 2020; Foley et al., 2003; Hariohm et al., 2015; Maher, 2000).

## 3. Results

### 3.1. Participants' characteristics

A total of 31 studies included 934 healthy older adults [range of mean age = 61.0–73.7 years; range of gender proportion (a ratio of females to total participants) = 27.3–100 %] without additional neurological diseases. In addition, we confirmed that 23 out of 31 total qualified studies conducted cognitive function tests at baseline. The remaining eight studies mentioned that they recruited healthy older adults. Specifically, the ranges of the mean cognitive function scores in the Mini-Mental State Examination (MMSE) from 13 studies and Montreal Cognitive Assessment (MoCA) from nine studies at baseline were 24.9–29.4 and 26.0–29.2, respectively. Given that the MMSE scores above 24 points (Folstein et al., 1975) and MoCA scores above 26 were considered as normal cognitive functions (Nasreddine et al., 2005), the cognitive function of the participants included in this meta-analysis were relatively intact. The detailed characteristics of the participants are shown in Table 1.

### 3.2. tDCS protocols

Thirty-one qualified studies applied tDCS over the cognition-related brain regions, such as the prefrontal cortex, primary motor cortex, inferior frontal cortex, and temporal cortex. Twenty-eight studies used tDCS alone whereas three applied tDCS with additional cognitive training. Regarding the tDCS timing, 15 studies used tDCS during the performance of a cognitive task or during cognitive training (online stimulation) and 11 applied tDCS before the performance of a cognitive

**Table 1**
Demographic and clinical information for participants.

| Study | Study Design | Total *N* | Age (years) | Gender (a ratio of females) | Pretreatment Cognitive Function Levels |
|---|---|---|---|---|---|
| Adenzato et al. (2019) | Crossover | 30 | 67.9 ± 6.0 | 15 F 15 M (50.0 %) | MMSE: 28.9 ± 1.0 |
| Antonenko et al. (2019) | Crossover | 34 | 63.1 ± 7.7 | 16 F 18 M (47.1 %) | MMSE: 29.4 ± 0.8 |
| Cespón et al. (2017) | Crossover | 14 | 70.2 ± 5.1 | 9 F 5 M (64.3 %) | NR |
| Conley et al. (2016) | Crossover | 16 | 61.2 ± 12.2 | 9 F 7 M (56.3 %) | MoCA: 27.3 ± 0.3 |
| Deldar et al. (2019) | Crossover | 15 | 64.0 ± 4.4 | 7 F 8 M (46.7 %) | MoCA: 29.2 ± 1.5 (range = 25–30) |
| Di Rosa et al. (2019) | Crossover | 21 | 69.7 ± 5.1 | 12 F 9 M (57.1 %) | MMSE: 28.4 ± 1.3 |
| Dumel et al. (2016) | RCT | 23 | 61.0 ± 4.6 | 12 F 11 M (52.2 %) | MMSE: 29.4 ± 0.9 |
| Dumel et al. (2018) | RCT | 37 | 61.6 ± 6.0 | 18 F 19 M (48.6 %) | MMSE: 29.2 ± 1.1 |
| Fertonani et al. (2014) | Crossover | 20 | 66.5 ± 5.5 | 10 F 10 M (50.0 %) | MMSE: 29.0 |
| Fiori et al. (2017) | Crossover | 15 | 72.0 ± 6.0 | NR | NR |
| Gbadeyan et al. (2019) | Crossover | 36 | 66.0 ± 6.9 | 18 F 18 M (50.0 %) | NR |
| Habich et al. (2020b) | Crossover | 22 | 67.3 ± 4.4 | 11 F 11 M (50.0 %) | MoCA: 26.2 ± 2.2 |
| Hanley et al. (2020) | Crossover | 40 | 67.1 ± 5.2 | 20 F 20 M (50.0 %) | MoCA: 27.8 ± 1.2 |
| Heise et al. (2014) | Crossover | 16 | 73.4 ± 6.3 | 7 F 9 M (43.8 %) | MMSE ≥ 29.0 |
| Holland et al. (2011) | Crossover | 10 | 69.0 | 7 F 3 M (70.0 %) | NR |
| Horne et al. (2020) | RCT | 129 | 67.6 ± 4.2 | 75 F 54 M (58.1 %) | MoCA: 28.3 ± 1.3 |
| Huo et al. (2018) | RCT | 64 | 66.1 ± 4.9 | 36 F 28 M (56.3 %) | MoCA: 26.0 ± 2.2 |
| Jones et al. (2015) | RCT | 72 | 64.4 ± 5.1 | 49 F 23 M (68.1 %) | MMSE: 28.5 ± 1.5 |
| Learmonth et al. (2015) | Crossover | 20 | 66.6 ± 5.1 | 10 F 10 M (50.0 %) | NR |
| Ljubisavljevic et al. (2019) | Crossover | 22 | 62.6 ± 3.2 | 6 F 16 M (27.3 %) | MMSE: 29.1 ± 1.0 |
| Madden et al. (2019) | RCT | 24 | 70.4 ± 6.6 | 10 F 14 M (41.7 %) | NR |
| Manenti et al. (2013) | Crossover | 32 | 67.9 ± 4.7 | 17 F 15 M (53.1 %) | MMSE: 28.6 ± 1.2 |
| Marquez et al. (2015) | Crossover | 34 | 61.4 ± 12.2 | 15 F 19 M (44.1 %) | MoCA: 27.9 ± 2.0 (range = 24–30) |
| Meinzer et al. (2013) | Crossover | 20 | 68.0 ± 5.7 | 10 F 10 M (50.0 %) | MMSE: 28.9 ± 0.9 |
| Nilsson et al. (2015) | Crossover | 30 | 69.0 ± 7.0 | 14 F 16 M (46.7 %) | NR |
| Nissim et al. (2019a) | RCT | 28 | 73.7 ± 7.3 | 15 F 13 M (53.6 %) | MoCA: 27.4 ± 2.0 |
| Nissim et al. (2019b) | Crossover | 16 | 71.8 ± 7.3 | 6 F 10 M (37.5 %) | MoCA: 26.6 ± 2.9 |
| Park et al. (2014) | RCT | 40 | 69.7 ± 3.3 | 27 F 13 M (67.5 %) | MMSE: 29.1 ± 1.5 |
| Ross et al. (2011) | Crossover | 14 | 64.4 ± 3.5 | 7 F 7 M (50.0 %) | MMSE: 28.6 ± 1.8 (range = 25–30) |
| Saldanha et al. (2020) | Crossover | 10 | 63.8 ± 2.6 | 10 F 0 M (100.0 %) | NR |
| Samaei et al. (2017) | RCT | 30 | 68.7 ± 5.3 | 23 F 7 M (76.7 %) | MMSE: 24.9 ± 1.6 |

Abbreviations. F: female; M: male; MMSE: mini-mental state exam; MoCA: montreal cognitive assessment; NR: not reported; RCT: randomised controlled trial.
Note. Data for age and pretreatment cognitive function levels are mean-±standard deviation; The MMSE and MoCA scores range from 0 to 30.

task or before cognitive training (offline stimulation). The remaining five studies administered both online and offline stimulation. For the number of tDCS sessions, 24 studies used a single session and seven studies used multiple tDCS sessions (i.e., 5–10 sessions). The ranges of specific parameters for tDCS protocols were: (a) stimulation intensity = 1.0–2.0 mA, (b) electrode area = 6–45 $cm^2$, (c) current density = 0.03–0.17 $mA/cm^2$, (d) session duration = 6–30 min, and (e) density charge = 0.24–3.40 $C/cm^2$. The specific parameters for tDCS and cognitive domain information are shown in Table 2.

### 3.3. Methodological-quality assessments

For the 31 qualified studies, the PEDro scores for the 11 items, with the mean and standard deviation (SD), were 7.7 ± 1.8. Given that the PEDro scores above six points were considered indicative of a higher methodological quality (Cashin and McAuley, 2020), the calculated means of PEDro scores revealed good overall quality across the included 31 studies. Importantly, six out of 31 qualified studies reported blinding of all therapists while providing tDCS intervention, and 15 studies exactly stated that they acquired data from more than 85 % of the participants initially allocated to groups. Table 3 shows the PEDro scores for specific assessment domains.

### 3.4. Meta-analytic findings

#### 3.4.1. Overall meta-analysis findings

The random-effects model meta-analysis of the 36 total comparisons from 31 studies revealed a significant low overall effect of tDCS on the reaction time during the performance of cognitive tasks ($SMD$ = 0.171; $SE$ = 0.077; 95 % CI = 0.020–0.321; $Z$ = 2.227; $P$ = 0.026). The heterogeneity tests reported a moderate level of variability across individual effect sizes ($Q$-statistics = 118.175 and $P < 0.001$; $I^2$ = 70.4 %), and the publication bias assessments showed a relatively asymmetrical distribution of individual effect sizes: (1) a revised funnel plot with eight imputed values (Supplementary Fig. 1) and (2) Egger's regression intercept ($\beta_0$) = 3.00 with $P$ = 0.01. Given that two comparisons (Dumel et al., 2016; Marquez et al., 2015) exceeded two SDs of the standardised mean effect size, we performed an additional sensitivity analysis after removing two potential outliers. The analysis of the 34 comparisons from 29 studies revealed a similar overall effect size ($SMD$ = 0.172; $SE$ = 0.063; 95 % CI = 0.049–0.295; $Z$ = 2.748; $P$ = 0.006) with slightly less heterogeneity levels ($Q$-statistics = 71.265 and $P < 0.001$; $I^2$ = 53.7 %) and significant publication bias (Egger's regression intercept: $\beta_0$ = 2.27 and $P$ = 0.03; Supplementary Fig. 2).

#### 3.4.2. Moderator variable analyses findings

The first moderator variable analysis that examined different effects of tDCS timing (i.e., online vs. offline stimulation) showed a significant reaction time reduction during the performance of cognitive tasks on the 20 online-stimulation comparisons from 20 studies ($SMD$ = 0.387; $SE$ = 0.112; 95 % CI = 0.167–0.606; Z = 3.452; $P$ = 0.001; $Q$-statistics = 64.405 and $P$ = 0.000; $I^2$ = 70.5 %; Fig. 2). However, the analysis on the 16 offline-stimulation comparisons from 16 studies revealed no significant effects ($SMD$ = -0.062; $SE$ = 0.086; 95 % CI = -0.231–0.106; Z = -0.725; $P$ = 0.468; $Q$-statistics = 33.609 and $P$ = 0.004; $I^2$ = 55.4 %; Fig. 2). The sensitivity analyses without two potential outliers (Dumel et al., 2016; Marquez et al., 2015) reported similar findings: (1) significant effects on the 19 online-stimulation comparisons from 19 studies ($SMD$ = 0.330; $SE$ = 0.104; 95 % CI = 0.127–0.533; Z = 3.180; $P$ = 0.001; $Q$-statistics = 52.121 and $P$ = 0.000; $I^2$ = 65.5 %) and (2) no significant effects on the 15 offline-stimulation comparisons from 15 studies ($SMD$ = 0.011; $SE$ = 0.058; 95 % CI = -0.103–0.124; Z = 0.187; $P$ = 0.852; $Q$-statistics = 8.500 and $P$ = 0.862; $I^2$ = 0.0 %).

Given that the effects of tDCS on the reaction time during the performance of cognitive tasks were different based on the tDCS timing, we conducted the second moderator variable analysis on the five cognitive function domains (i.e., perceptual-motor function, learning and memory, executive function / complex attention, language, and social cognition) between online and offline stimulation. For the online stimulation, the moderator variable analysis showed significant positive effects in two cognitive domains: (1) four learning and memory comparisons from four studies ($SMD$ = 0.990; $SE$ = 0.335; 95 % CI = 0.332–1.647; Z = 2.951; $P$ = 0.003; $Q$-statistics = 11.231 and $P$ = 0.011; $I^2$ = 73.3 %) and (2) seven executive function / complex attention comparisons from seven studies ($SMD$ = 0.314; $SE$ = 0.130; 95 % CI = 0.059–0.570; Z = 2.412; $P$ = 0.016; $Q$-statistics = 11.240 and $P$ = 0.081; $I^2$ = 46.6 %; Fig. 3). However, the analyses on the perceptual-motor function, language, and social cognition domains showed no significant effects: (1) two perceptual-motor function comparisons from two studies ($SMD$ = -0.042; $SE$ = 0.155; 95 % CI = -0.346–0.262; Z = -0.269; $P$ = 0.788; $Q$-statistics = 0.638 and $P$ = 0.424; $I^2$ = 0.0 %), (2) six language comparisons from six studies ($SMD$ = 0.402; $SE$ = 0.209; 95 % CI = -0.008–0.811; Z = 1.922; $P$ = 0.055; $Q$-statistics = 15.091 and $P$ = 0.010; $I^2$ = 66.9 %), and (3) one social cognition comparison from one study ($SMD$ = -0.272; $SE$ = 0.266; 95 % CI = -0.793–0.249; Z = -1.023; $P$ = 0.306; $Q$-statistics = 0.000 and $P$ = 1.000; $I^2$ = 0.0 %; Fig. 3). After removing one potential outlier (Dumel et al., 2016), the sensitivity analysis on the three learning and memory comparisons from three studies showed a significant effect size: $SMD$ = 0.738; $SE$ = 0.301; 95 % CI = 0.148–1.327; Z = 2.454; $P$ = 0.014; $Q$-statistics = 5.711 and $P$ = 0.058; $I^2$ = 65.0 %.

For the offline stimulation, the moderator variable analyses reported no significant effects across four cognitive domains: (1) two perceptual-motor function comparisons from two studies ($SMD$ = -0.139; $SE$ = 0.155; 95 % CI = -0.443–0.165; Z = -0.894; $P$ = 0.371; $Q$-statistics = 0.008 and $P$ = 0.929; $I^2$ = 0.0 %), (2) two learning and memory comparisons from two studies ($SMD$ = 0.114; $SE$ = 0.134; 95 % CI = -0.150–0.377; Z = 0.845; $P$ = 0.398; $Q$-statistics = 0.667 and $P$ = 0.414; $I^2$ = 0.0 %), (3) 11 executive function / complex attention comparisons from 11 studies ($SMD$ = -0.095; $SE$ = 0.127; 95 % CI = -0.344–0.154; Z = -0.747; $P$ = 0.455; $Q$-statistics = 30.545 and $P$ = 0.001; $I^2$ = 67.3 %), and (4) one language comparison from one study ($SMD$ = 0.021; $SE$ = 0.224; 95 % CI = -0.417–0.460; Z = 0.096; $P$ = 0.923; $Q$-statistics = 0.000 and $P$ = 1.000; $I^2$ = 0.0 %). Without one potential outlier (Marquez et al., 2015), the sensitivity analysis on the 10 executive function / complex attention comparisons from 10 studies revealed a comparable effect size ($SMD$ = 0.013; $SE$ = 0.074; 95 % CI = -0.133–0.158; Z = 0.169; $P$ = 0.866; $Q$-statistics = 6.308 and $P$ = 0.709; $I^2$ = 0.0 %).

#### 3.4.3. Meta-regression analyses findings

For the demographic characteristics, the random-effects meta-regression analyses revealed a significant relationship between age and reaction time reduction during the performance of cognitive tasks after tDCS (36 comparisons from 31 studies; $Y$ = -3.0893 + 0.0486$X$; $P$ = 0.03; $R^2$ = 0.13; Fig. 4). Without two potential outliers (Dumel et al., 2016; Marquez et al., 2015), the sensitivity analysis on the 34 comparisons from 29 studies reported a comparable significant relationship ($Y$ = -2.8414 + 0.0448$X$; $P$ = 0.02; $R^2$ = 0.13; Supplementary Fig. 3). However, the amount of reduction in cognition-related reaction time after tDCS protocols was not significantly associated with other demographic information: (a) gender proportion (35 comparisons from 30 studies; $Y$ = 0.0031 + 0.0028$X$; $P$ = 0.65; $R^2$ = 0.00), (b) cognitive function using MMSE at baseline (15 comparisons from 13 studies; $Y$ = 2.1949-0.0687$X$; $P$ = 0.61; $R^2$ = 0.00), and (c) cognitive function using MoCA at baseline (10 comparisons from nine studies; $Y$ = -0.2528 + 0.0119$X$; $P$ = 0.95; $R^2$ = 0.00).

Moreover, the meta-regression analyses found no significant relationship between tDCS protocol parameters and reduction of cognition-related reaction time on the 36 comparisons from 31 studies: (a) stimulation intensity ($Y$ = -0.2605 + 0.2743$X$; $P$ = 0.13; $R^2$ = 0.00), (b) electrode area ($Y$ = 0.0881 + 0.0027$X$; $P$ = 0.80; $R^2$ = 0.00), (c) current density ($Y$ = 0.0170 + 2.7749$X$; $P$ = 0.32; $R^2$ = 0.01), (d) session

**Table 2**
Specific parameters for tDCS protocols and cognitive domains.

| Study | Timing of tDCS | Anodal tDCS | Cathodal tDCS | Session (s) | Intensity, Area, Density, Duration, Density Charge | Cognitive Task (cognitive domains) |
|---|---|---|---|---|---|---|
| Adenzato et al. (2019) | Online | MPFC | Inion | $1^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 6 min, 0.24 $C/cm^2$ | Attribution of intentions task (Social cognition) |
| Antonenko et al. (2019) | Offline | L-TJ | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 20 min, 0.60 $C/cm^2$ | Episodic memory task (Learning and memory) |
| Cespón et al., 2017 | Offline | L-DLPFC | R-Shoulder | $1^{\#task}$ | 1.5 mA, 16 $cm^2$, 0.09 $mA/cm^2$, 13 min, 1.17 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Conley et al. (2016) | Offline | R-M1 | L-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 20 min, 0.60 $C/cm^2$ | Go/Nogo task (Executive function / Complex attention) |
| Deldar et al. (2019) | Online | L-DLPFC | R-Deltoid | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 22 min, 1.32 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Di Rosa et al. (2019) | Offline | L-PFC | R-Shoulder | $1^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 26 min, 1.04 $C/cm^2$ | Visuospatial working memory (Executive function / Complex attention) |
| Dumel et al. (2016) | Online | L-M1 | R-Supraorbital A | $5^{\#task}$ | 2.0 mA, 45 $cm^2$, 0.04 $mA/cm^2$, 20 min, 0.80 $C/cm^2$ | Serial reaction time task (Learning and memory) |
| Dumel et al. (2018) | Online | L-M1 | R-Supraorbital A | $5^{\#task}$ | 2.0 mA, 45 $cm^2$, 0.04 $mA/cm^2$, 20 min, 0.80 $C/cm^2$ | Serial reaction time task (Learning and memory) |
| Fertonani et al. (2014) | Online Offline | L-DLPFC | R-Shoulder | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 5 min, 0.30 $C/cm^2$ | Picture naming task (Language) |
| Fiori et al. (2017) | Online | L-TC L-TC | R-TC R-OFC | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 20 min, 1.20 $C/cm^2$ | Picture naming task (Language) |
| Gbadeyan et al. (2019) | Online | R-DLPFC | – | $1^{\#task}$ | 1.0 mA, 6 $cm^2$, 0.17 $mA/cm^2$, 20 min, 3.40 $C/cm^2$ | Flanker task (Executive function / Complex attention) |
| Habich et al. (2020b) | Offline | L-DLPFC | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 20 min, 0.60 $C/cm^2$ | Episodic memory task (Learning and memory) |
| Hanley et al. (2020) | Offline | L- or R-DLPFC | – | $1^{\#task}$ | 1.5 mA, 25 $cm^2$, 0.06 $mA/cm^2$, 20 min, 1.20 $C/cm^2$ | Swansea test of attentional control task (Executive function / Complex attention) |
| Heise et al. (2014) | Offline | L-M1 | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 25 $cm^2$, 0.04 $mA/cm^2$, 20 min, 0.80 $C/cm^2$ | Stop signal task (Executive function / Complex attention) |
| Holland et al. (2011) | Online | L-IFC | R-Frontopolar C | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 20 min, 1.20 $C/cm^2$ | Picture naming task (Language) |
| Horne et al. (2020) | Online | L-PFC L-SC | R-Supraorbital A R-Supraorbital A | $5^{\#training}$ | 2.0 mA, 25 $cm^2$, 0.08 $mA/cm^2$, 20 min, 1.60 $C/cm^2$ | Decision-making task (Executive function / Complex attention) |
| Huo et al. (2018) | Offline | L-DLPFC | R-Deltoid | $10^{\#task}$ | 2.0 mA, 25 $cm^2$, 0.08 $mA/cm^2$, 30 min, 2.40 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Jones et al. (2015) | Offline | R-PFC R-PPC R-PFC + PPC | L-Cheek | $10^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 10 min, 0.40 $C/cm^2$ | Stroop task (Executive function / Complex attention) |
| Learmonth et al. (2015) | Online Offline | L-PPC | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 25 $cm^2$, 0.04 $mA/cm^2$, 15 min, 0.60 $C/cm^2$ | Lateralised visual detection task (Perceptual-motor function) |
| Ljubisavljevic et al. (2019) | Online Offline | L-DLPFC L-DLPFC | R-DLPFC R-Supraorbital A | $1^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 30 min, 1.20 $C/cm^2$ | Simple reaction time task (Perceptual-motor function) |
| Madden et al. (2019) | Online | L-IFC | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 15 min, 0.45 $C/cm^2$ | Selection and generation task (Language) |
| Manenti et al. (2013) | Online | L-DLPFC L-PARC | R-Supraorbital A R-Supraorbital A | $1^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 6 min, 0.24 $C/cm^2$ | Episodic memory task (Learning and memory) |
| Marquez et al. (2015) | Offline | L-M1 | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 20 min, 0.60 $C/cm^2$ | Go/Nogo task (Executive function / Complex attention) |
| Meinzer et al. (2013) | Online | L-IFC | R-Supraorbital A | $1^{\#task}$ | 1.0 mA, 35 $cm^2$, 0.03 $mA/cm^2$, 20 min, 0.60 $C/cm^2$ | Semantic word generation task (Language) |
| Nilsson et al. (2015) | Online Offline | L-DLPFC | R-Supraorbital A | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 25 min, 1.50 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Nissim et al. (2019a) | Online | R-DLPFC | L-DLPFC | $10^{\#training}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 20 min, 1.20 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Nissim et al. (2019b) | Online Offline | R-DLPFC | L-DLPFC | $1^{\#task}$ | 2.0 mA, 35 $cm^2$, 0.06 $mA/cm^2$, 12 min, 0.72 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Park et al. (2014) | Online | Bi-PFC | Non-dominant arm | $10^{\#training}$ | 2.0 mA, 25 $cm^2$, 0.08 $mA/cm^2$, 30 min, 2.40 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Ross et al. (2011) | Online | L-ATL | R-Cheek | $1^{\#task}$ | 1.5 mA, 35 $cm^2$, 0.04 $mA/cm^2$, 15 min, 0.60 $C/cm^2$ | Picture naming task (Language) |
| Saldanha et al. (2020) | Offline | L-DLPFC L-M1 | R-Supraorbital A R-Supraorbital A | $1^{\#task}$ | 2.0 mA, 25 $cm^2$, 0.08 $mA/cm^2$, 30 min, 2.40 $C/cm^2$ | N-back task (Executive function / Complex attention) |
| Samaei et al. (2017) | Online | L-Cr | R-Shoulder | $1^{\#task}$ | 2.0 mA, 25 $cm^2$, 0.08 $mA/cm^2$, 20 min, 1.60 $C/cm^2$ | Serial reaction time task (Learning and memory) |

Abbreviations. A: area; atDCS: anodal-transcranial direct current stimulation; ATL: anterior temporal lobes; Bi: bilateral hemispheres; C: cortex; Cr: cerebellum; DLPFC: dorsolateral prefrontal cortex; HD: high-density; IFC: inferior frontal cortex; L: left; M: medial; M1: primary motor cortex; OFC: orbito-frontal cortex; PARC: parietal

cortex; PFC: prefrontal cortex; PPC: posterior parietal cortex; R: right; SC: striate cortex; TC: temporal cortex; TJ: temporoparietal junction; Number sign (#) indicates tDCS application with either cognitive task or training.

duration ($Y = 0.3042\text{-}0.0071X$; $P = 0.51$; $R^2 = 0.00$), and (e) density charge ($Y = 0.1159 + 0.0528X$; $P = 0.63$; $R^2 = 0.00$). Taken together, the effects of tDCS on the reaction time during the performance of cognitive tasks increased for the older people in this study.

## 4. Discussions

The current systematic review and meta-analysis investigated the effects of tDCS on the reaction time during the performance of various cognitive tasks in healthy older adults. The overall meta-analytic findings revealed a significant low overall effect size indicating reduction in the cognition-related reaction time after tDCS. Specific moderator variable analyses showed that online tDCS significantly reduced the reaction time of elderly people, whereas the analysis failed to find significant changes in cognition-related reaction time after offline tDCS protocols. Moreover, administering online tDCS during the performance of cognitive tasks significantly decreased the reaction time during cognitive tasks that estimated learning and memory and executive function. However, these patterns were not observed in cognitive function domains such as perceptual-motor function, language, and social cognition. Finally, the meta-regression analysis showed that the positive effects of tDCS on reaction time reduction during the performance of cognitive tasks were greater as the age of the older adults increased.

In this meta-analysis, we found that tDCS facilitated reaction time reduction during the performance of various cognitive tasks although the level of overall positive effects was relatively small. The study findings additionally support the previous meta-analytic findings that tDCS attenuated ageing-induced cognitive dysfunction, including short- and long-term memory, working memory, problem solving, decision making, and language processing (Hsu et al., 2015; Indahlastari et al., 2021; Summers et al., 2016). However, these prior findings were relatively limited due to inconsistent outcome measures such as task accuracy and response time during the performance of cognitive tasks and the completion of the clinical questionnaires (e.g., MMSE and MoCA). Measuring the reaction time during the performance of cognitive tasks may be an effective way of estimating ageing-induced cognitive deterioration (Woods et al., 2015) because of the altered reaction time related to the changes in the neural networks (Chou et al., 2013; Gimbel and Brewer, 2011; Kansaku et al., 2004) and the fact that there were less retest effects (Christ et al., 2018). In fact, slowing reaction time during cognition-related tasks was highly associated with greater severity of cognitive dysfunctions for elderly people (Chen et al., 2017). By focusing on the reaction time, we additionally provided the possibility of tDCS protocols contributing to improving age-related cognitive impairments.

The first moderator variable analysis revealed that providing online tDCS might effectively reduce older adults' reaction time during the performance of cognitive tasks. These results are consistent with previous meta-analytic findings that applying online timing of non-invasive brain stimulation (NIBS) protocols such as tDCS or repetitive transcranial magnetic stimulation (rTMS) during the task significantly improved overall cognitive functions in various populations including healthy older adults (Summers et al., 2016), patients with Alzheimer's disease (Hsu et al., 2015), and neuropsychiatric patients (Dedoncker et al., 2016). Presumably, the positive effects of online tDCS protocols on cognitive functions may be related to the facilitation of endogenous voltage-dependent Hebbian mechanisms (Kronberg et al., 2020). Kronberg and colleagues suggested that simultaneously applying tDCS protocols during tasks may reveal similar neuronal characteristics to the Hebbian plasticity contributing to improvements in task-related functions (Hebb, 1949; Kronberg et al., 2020). In the hippocampal brain slices experiments in vitro, the authors provided direct current stimulation under a state of long-term potentiation (LTP) by applying theta burst stimulation, similar to a learning process during a training task. Interestingly, they found that anodal direct current stimulation potentially boosted neural plasticity during ongoing endogenous synaptic activity, as indicated by two Hebbian properties: (a) enhanced LTP only at task-dependent synaptic pathway (i.e., pathway specificity) and (b) more cooperated connections from separate synaptic pathways (i.e., associativity) (Bliss and Collingridge, 1993; Kronberg et al., 2020). These findings support a proposition that administration of online tDCS protocols during specific cognitive tasks that presumably induce a state of endogenous synaptic activity may facilitate additional neural plasticity in the key regions of brain resulting in the reduction of cognition-related reaction time in older adults.

For the effects of offline tDCS protocols, we identified no significant reduction of cognition-related reaction time in older adults. Some prior ageing studies reported that applying anodal tDCS protocols before cognitive tasks such as explicit sequence learning and picture naming tasks did not significantly improve task performances (Fertonani et al., 2014; Stagg et al., 2011). The authors posited that a lack of offline tDCS-induced effects on cognitive functions may be responsible for potential ageing process such as dysregulation of calcium homeostasis, loss of synaptic spines, and impaired susceptibility of N-methyl-D-aspartic receptors presumably interfering with the synaptic efficacy and neural plasticity (Dickstein et al., 2013; Habich et al., 2020a; Magnusson, 2012; Morrison and Baxter, 2012; Nikoletopoulou and Tavernarakis, 2012). However, other meta-analysis and individual studies found treatment effects of offline NIBS protocols (e.g., tDCS and rTMS) on various cognitive functions in older adults and patients with Alzheimer's disease (Hsu et al., 2015; Summers et al., 2016). Perhaps, advancing stimulation intensity, frequency, and focality may facilitate after-effects of tDCS protocols on cognition-related reaction time because several neuroimaging studies suggested that tDCS-induced neural excitability in brain lasted longer with greater intensity and repetition of tDCS interventions and applying high-density tDCS (HD-tDCS) (Ammann et al., 2017; Jamil et al., 2020; Nitsche and Paulus, 2000). In fact, the 16 included studies that used offline tDCS protocols in this meta-analysis administered a relatively weak density charge (i.e., mean density charge = 1.0 C/cm$^2$), few stimulation sessions (i.e., 15 studies used a single session of tDCS protocols) using traditional tDCS electrodes. Investigating potential effects of offline tDCS protocols is crucial because the sustained treatment benefits are necessary in certain situations (e.g., after receiving home-based clinical tDCS interventions enhanced cognitive functions are required for conducting successful activities of daily living) (Carvalho et al., 2018; Gough et al., 2020; Park et al., 2019). Thus, future studies should examine potential effects of offline tDCS protocols with increased stimulation dose within safety criteria or a focalized stimulation protocol (e.g., HD-tDCS or rTMS) on reaction time during cognitive tasks.

Our second moderator variable analysis revealed that providing online tDCS during the performance of cognitive tasks requiring learning and memory and executive function / complex attention significantly reduced the reaction time. During language processing tasks, we found a tendency of reduced cognition-related reaction time (i.e., effect size = 0.402; $P = 0.055$). These findings are in line with the prior meta-analysis studies that evidenced tDCS protocols-induced cognitive improvements in healthy older adults (Indahlastari et al., 2021; Summers et al., 2016). Specifically, Summer and colleagues reported significant positive effects of online tDCS protocols on memory, working memory, and language production, as indicated by heterogenous outcome measures (e.g., the percentage of correct response and word recall, number of errors and ball rotation, error awareness, and reaction time) (Summers et al., 2016). Similarly, a recent ageing meta-analysis revealed functional improvements in specific cognitive domains including attention, working memory, episodic memory, and error awareness after tDCS protocols (Indahlastari et al., 2021).

**Table 3**
Methodological quality assessment using PEDro score.

| Items | Adenzato et al. (2019) | Antonenko et al. (2019) | Cespón et al. (2017) | Conley et al. (2016) | Deldar et al. (2019) | Di Rosa et al. (2019) | Dumel et al. (2016) | Dumel et al. (2018) | Fertonani et al. (2014) | Fiori et al. (2017) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Specific eligibility criteria | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. Subjects random allocation | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 |
| 3. Allocation concealment | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| 4. Similar groups at baseline | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 5. Blinding of all subjects | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 6. Blinding of all therapists | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 7. Blinding of all assessors (at least one key outcome) | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 |
| 8. Data measurement from more than 85 % of the subjects initially allocated to groups (at least one key outcome) | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| 9. All subjects received the treatment or control condition as allocated (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10. Between-group comparisons (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 11. Point measures and measures of variability (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | **10** | **6** | **4** | **10** | **9** | **6** | **9** | **8** | **6** | **9** |

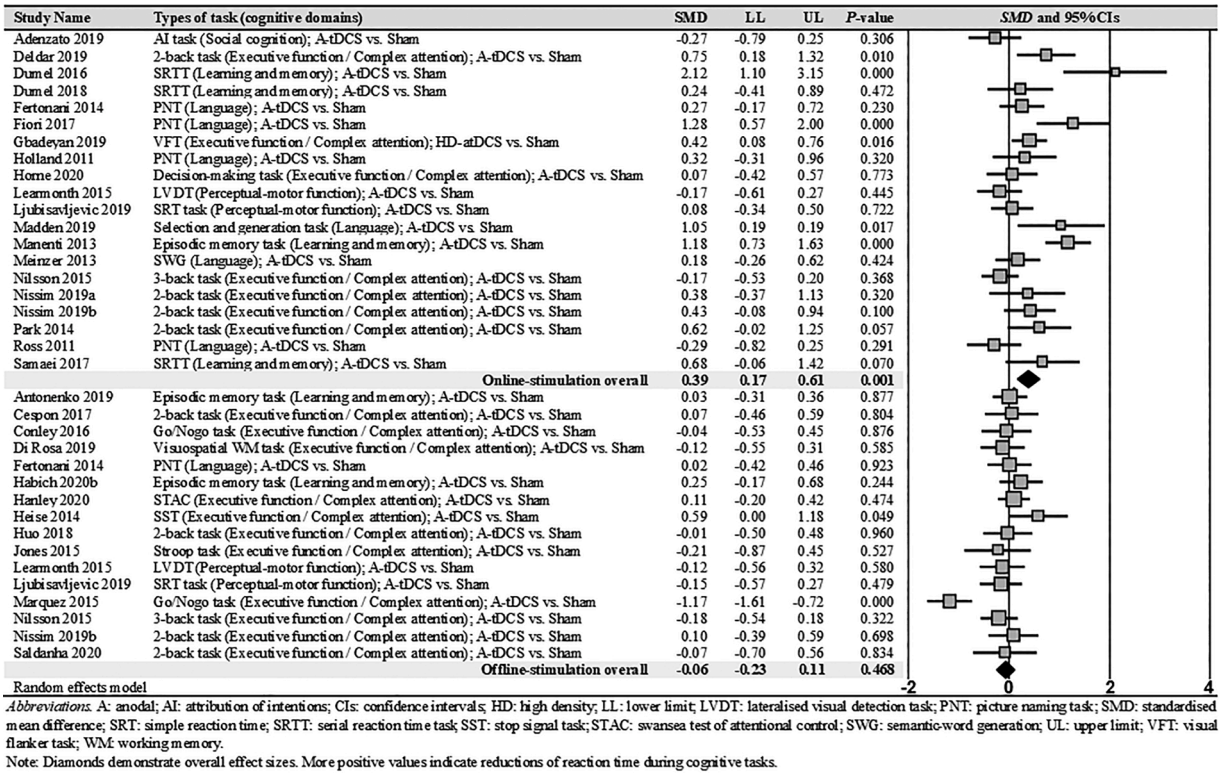
| Items | Gbadeyan et al. (2019) | Habich et al. (2020b) | Hanley et al. (2020) | Heise et al. (2014) | Holland et al. (2011) | Horne et al. (2020) | Huo et al. (2018) | Jones et al. (2015) | Learmonth et al. (2015) | Ljubisavljevic et al. (2019) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Specific eligibility criteria | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. Subjects random allocation | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 |
| 3. Allocation concealment | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 4. Similar groups at baseline | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| 5. Blinding of all subjects | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| 6. Blinding of all therapists | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7. Blinding of all assessors (at least one key outcome) | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 8. Data measurement from more than 85 % of the subjects initially allocated to groups (at least one key outcome) | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 0 |
| 9. All subjects received the treatment or control condition as allocated (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10. Between-group comparisons (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| 11. Point measures and measures of variability (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | **7** | **9** | **8** | **9** | **5** | **6** | **9** | **6** | **6** | **8** |

| Items | Madden et al. (2019) | Manenti et al. (2013) | Marquez et al. (2015) | Meinzer et al. (2013) | Nilsson et al. (2015) | Nissim et al. (2019a) | Nissim et al. (2019b) | Park et al. (2014) | Ross et al. (2011) | Saldanha et al. (2020) | Samaei et al. (2017) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Specific eligibility criteria | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. Subjects random allocation | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3. Allocation concealment | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 |
| 4. Similar groups at baseline | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| 5. Blinding of all subjects | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| 6. Blinding of all therapists | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 7. Blinding of all assessors (at least one key outcome) | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 |
| 8. Data measurement from more than 85 % of the subjects initially allocated to groups (at least one key outcome) | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 |
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

(*continued on next page*)

**Table 3** (*continued*)

| Items | Madden et al. (2019) | Manenti et al. (2013) | Marquez et al. (2015) | Meinzer et al. (2013) | Nilsson et al. (2015) | Nissim et al. (2019a) | Nissim et al. (2019b) | Park et al. (2014) | Ross et al. (2011) | Saldanha et al. (2020) | Samaei et al. (2017) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 9. All subjects received the treatment or control condition as allocated (at least one key outcome) | | | | | | | | | | | |
| 10. Between-group comparisons (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 11. Point measures and measures of variability (at least one key outcome) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | **5** | **7** | **10** | **8** | **6** | **10** | **10** | **8** | **6** | **9** | **9** |




*Abbreviations.* A: anodal; AI: attribution of intentions; CIs: confidence intervals; HD: high density; LL: lower limit; LVDT: lateralised visual detection task; PNT: picture naming task; SMD: standardised mean difference; SRT: simple reaction time; SRTT: serial reaction time task; SST: stop signal task; STAC: swansea test of attentional control; SWG: semantic-word generation; UL: upper limit; VFT: visual flanker task; WM: working memory.

Note: Diamonds demonstrate overall effect sizes. More positive values indicate reductions of reaction time during cognitive tasks.

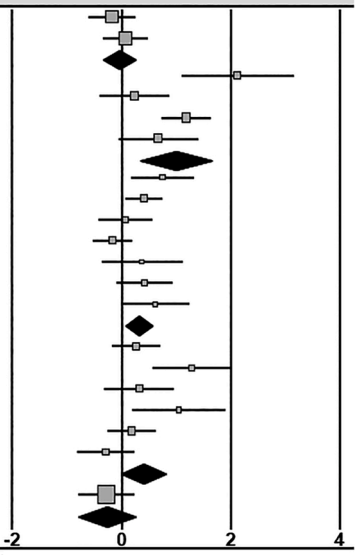
**Fig. 2.** Overall meta-analytic findings and forest plot for the cognition-related reaction time. A comparison between the different effects of tDCS timing.

Considering the ageing-induced cognitive impairments compromising cognition-related performances and slowing response time, our meta-analytic findings may be helpful to facilitating cognitive functions essentially requiring the rapid cognitive processing of extrinsic information from various activities. Importantly, the non-significant effects of online tDCS on reaction time during perceptual-motor function and social cognition tasks should be cautiously interpreted because the subgroups for the moderator variable analysis included the limited number of studies (i.e., two studies on perceptual-motor function and one study on social cognition) that used a single session of tDCS protocols. Given that perceptual-motor function and social cognition contribute to advancing independent living as well as interpersonal communication of elderly people (Arioli et al., 2018; Yan and Zhou, 2009), additional meta-analysis approaches with increased sample size are necessary to confirm the effects of tDCS protocols on reaction time during these cognitive domains.

The meta-regression analysis revealed that older adults had a greater reaction time reduction during the performance of cognitive tasks after tDCS. This finding is in line with the prior tDCS finding that the older adult groups showed more positive effects of tDCS on cognitive function than the young adult groups did (Ross et al., 2011; Zimerman et al., 2013) and the recent meta-regression finding that reported greater overall cognition improvements for the older people (above 65 years old) (Indahlastari et al., 2021). Presumably, tDCS is less effective for individuals with relatively better baseline cognitive function performance due to the ceiling effect (Hsu et al., 2015) or the counteraction of the brain to preserve the optimal activity of neurons (Habich et al., 2020a). On the other hand, progressive biological deteriorations in the human brain such as loss of neurons, synaptic connections, and grey and white matters, and impaired pre- and post-synaptic communication typically appear with ageing (Ghasemian-Shirvan et al., 2020). Thus, the application of tDCS may more effectively modulate abnormal brain activation patterns in older adults than in young adults with relatively intact brain functions (Habich et al., 2017; Hsu et al., 2015). Further, the reduction of the cognition-related reaction time after tDCS increased in the older adults, who could have had more types of neural dysfunction leading to greater cognitive deficits at baseline.

Although this meta-analysis showed the positive effects of tDCS on

| Study Name | Types of task | SMD | LL | UL | *P*-value |
|---|---|---|---|---|---|
| Learmonth 2015 | Lateralised visual detection task | -0.17 | -0.61 | 0.27 | 0.445 |
| Ljubisavljevic 2019 | Simple reaction time task | 0.08 | -0.34 | 0.50 | 0.722 |
| | **Perceptual-motor function overall** | **-0.04** | **-0.35** | **0.26** | **0.788** |
| Dumel 2016 | Serial reaction time task | 2.12 | 1.10 | 3.15 | 0.000 |
| Dumel 2018 | Serial reaction time task | 0.24 | -0.41 | 0.89 | 0.472 |
| Manenti 2013 | Episodic memory task | 1.18 | 0.73 | 1.63 | 0.000 |
| Samaei 2017 | Serial reaction time task | 0.68 | -0.06 | 1.42 | 0.070 |
| | **Learning and memory overall** | **0.99** | **0.33** | **1.65** | **0.003** |
| Deldar 2019 | 2-back task | 0.75 | 0.18 | 1.32 | 0.010 |
| Gbadeyan 2019 | Visual flanker task | 0.42 | 0.08 | 0.76 | 0.016 |
| Horne 2020 | Decision-making task | 0.07 | -0.42 | 0.57 | 0.773 |
| Nilsson 2015 | 3-back task | -0.17 | -0.53 | 0.20 | 0.368 |
| Nissim 2019a | 2-back task | 0.38 | -0.37 | 1.13 | 0.320 |
| Nissim 2019b | 2-back task | 0.43 | -0.08 | 0.94 | 0.100 |
| Park 2014 | 2-back task | 0.62 | -0.02 | 1.25 | 0.057 |
| | **Executive function / Complex attention overall** | **0.31** | **0.06** | **0.57** | **0.016** |
| Fertonani 2014 | Picture naming task | 0.27 | -0.17 | 0.72 | 0.230 |
| Fiori 2017 | Picture naming task | 1.28 | 0.57 | 2.00 | 0.000 |
| Holland 2011 | Picture naming task | 0.32 | -0.31 | 0.96 | 0.320 |
| Madden 2019 | Selection and generation task | 1.05 | 0.19 | 1.91 | 0.017 |
| Meinzer 2013 | Semantic-word generation task | 0.18 | -0.26 | 0.62 | 0.424 |
| Ross 2011 | Picture naming task | -0.29 | -0.82 | 0.25 | 0.291 |
| | **Language overall** | **0.40** | **-0.01** | **0.81** | **0.055** |
| Adenzato 2019 | Attribution of intentions task | -0.27 | -0.79 | 0.25 | 0.306 |
| | **Social cognition overall** | **-0.27** | **-0.79** | **0.25** | **0.306** |
| Random effects model | | | | | |




*Abbreviations.* CIs: confidence intervals; LL: lower limit; SMD: standardised mean difference; UL: upper limit.
Note. Each size of individual effects was proportional to their weight. Diamonds demonstrate overall effect sizes. More positive values indicate reductions of reaction time during cognitive tasks.

**Fig. 3.** Meta-analytic findings and forest plot for cognition-related reaction time. A comparison across five cognitive function domains after online tDCS.

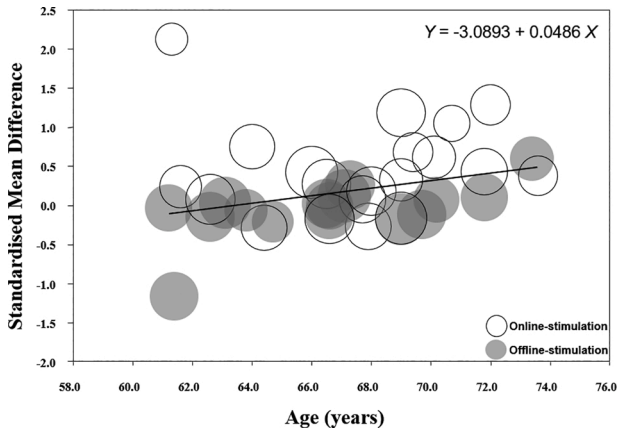



**Fig. 4.** Meta-regression findings. The relationship between the age of the elderly people and the changes in their reaction time after online and offline tDCS.

reaction time reduction during the performance of various cognitive tasks in healthy older adults, there are some limitations. First, some participants in the qualified studies may have mild or moderate cognitive impairments as shown in either SD or ranges of cognitive function test scores, and the different levels of cognitive impairments in older adults at the baseline test potentially mediates the effects of NIBS protocols (Cheng et al., 2018). Although our meta-regression analyses failed to identify any significant relationship between the levels of cognitive functions in older adults (e.g., MMSE and MoCA scores) and individual effect sizes, these results may be influenced by a limited number of the included studies that used an identical cognitive test. Thus, investigating how tDCS protocols differently influence cognition-related reaction time in older adults based on their pre-treatment cognitive function level should be necessary in future studies.

In addition, although overall findings of PEDro scores revealed a relatively moderate methodological quality in this meta-analysis, some potential methodological quality issues across the qualified studies still remain. For example, despite considering the nature of tDCS administration, only 20 % of the total included studies reported blinding of all therapists that may induce possibility of the observer bias (Hrobjartsson et al., 2013). Further, three studies reported that the data were acquired from 75 to 84% of the participants initially allocated to groups, and 13 studies missed reporting the exact numbers of participants before and after tDCS protocols. Granted, few dropout rates of participants in clinical trials can increase the validity of study findings. Taken together, these observations highlight the need for more tDCS studies with better methodological quality to support the positive effects on age-related cognitive impairments.

## 5. Conclusions

This systematic review and meta-analysis revealed that providing tDCS protocols during the performance of various cognitive tasks significantly reduced the reaction time in healthy older adults. Moreover, the positive effects on cognition-related reaction time were evident after applying online tDCS protocols, and specifically a significant reduction of reaction time was observed during learning and memory and executive function / complex attention tasks. Finally, the meta-regression analysis revealed that the greater reaction time reduction during the performance of various cognitive tasks after tDCS was associated with higher age in elderly people. These meta-analytic findings suggested that administering online tDCS protocol may be beneficial for reducing ageing-induced delayed reaction time during specific cognitive tasks. However, the qualified studies mainly focused on the transient effects of tDCS protocols, and only six studies performed sustained follow-up tests to examine potential long-term effects of tDCS protocols on cognition-related reaction time (Heise et al., 2014; Horne et al., 2020; Huo et al., 2018; Jones et al., 2015; Park et al., 2014; Samaei et al., 2017). Moreover, most of the studies that were included in this meta-analysis (24 out of 31 total studies) used a single session of tDCS and heterogeneous tDCS parameter setups (e.g., 0.03–0.17 mA/cm$^2$ of stimulation density and different targeted and reference brain areas). These methodological differences among the studies that were included in this meta-analysis can perhaps influence the effects of tDCS. Thus, future studies on tDCS should investigate the long-term effects of tDCS on cognition-related reaction time with more sessions of stimulation and homogeneous tDCS parameter setups.

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## Declaration of Competing Interest

The authors report no declarations of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101377.

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