# Does Transcranial Direct Current Stimulation Enhance Cognitive and Motor Functions in the Ageing Brain? A Systematic Review and Meta-Analysis

Jeffery J. Summers[1,2], Nyeonju Kang[3], and James H. Cauraugh[3]

[1]Human Motor Control Laboratory
University of Tasmania, Hobart, Tasmania, Australia

[2]Research Institute for Sport and Exercise Sciences
Liverpool John Moores University, Liverpool, UK

[3]Motor Behavior Laboratory
Applied Physiology and Kinesiology Dept.
University of Florida
Gainesville, Florida, USA

Corresponding Author: Jeffery J. Summers
Human Motor Control Laboratory
School of Medicine
University of Tasmania
Hobart, TAS, Australia
E-mail: Jeff.Summers@utas.edu.au
Phone: +61 3 6324 3266
Fax: +61 3 6324 3168

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**Abstract**

The use of transcranial direct current stimulation (tDCS) to enhance cognitive and motor functions has enjoyed a massive increase in popularity. Modifying neuroplasticity via non-invasive cortical stimulation has enormous potential to slow or even reverse declines in functions associated with ageing. The current meta-analysis evaluated the effects of tDCS on cognitive and motor performance in healthy older adults. Of the 81 studies identified, 25 qualified for inclusion. A random effects model meta-analysis revealed a significant overall standardized mean difference equal to 0.53 ($SE$ = 0.09; medium heterogeneity: $I^2$ = 57.08%; and high fail-safe: $N$ = 448). Five analyses on moderator variables indicated significant tDCS beneficial effects: (a) on both cognitive and motor task performances, (b) across a wide-range of cognitive tasks, (c) on specific brain areas, (d) stimulation offline (before) or online (during) the cognitive and motor tasks. Although the meta-analysis revealed robust support for enhancing both cognitive and motor performance, we outline a number of caveats on the use of tDCS.

**Keywords:** Meta-analysis; Transcranial direct current stimulation (tDCS); Anodal tDCS; Cognitive function; Motor function; Ageing

## 1. Introduction

Population ageing is a global phenomenon with the total number of people aged 60 or older worldwide is predicted to more than double from 841 million in 2013 to over 2 billion in 2050 (21.1% of the world population). Importantly, the number of people aged 80 years or more within the older population is expected to grow in the same time period from 14% to 19% (392 million persons) and the number of people with dementia is forecast to increase from 44.4 million to 135.5 million (Alzheimers Disease International, 2013; United Nations, Department of Economic and Social Affairs, Population Division, 2013).

Normal ageing is associated with progressive decline in cognitive and motor functions especially in basic information processing components, such as processing speed, working memory, and episodic memory. At the neurophysiological level, there is progressive shrinkage with age of gray matter volume in several brain regions and white matter loss, particularly in the prefrontal cortex. Even modest declines in cognitive and motor function can negatively impact on quality of life and the ability to live independently in older adults. Furthermore, signs of cognitive decline, particularly memory loss, are of considerable concern to older individuals because of the possible progression to Alzheimer's disease. Neurologists estimate that delaying onset of Alzheimer's disease by 5 years would reduce the overall prevalence rate by 50%, significantly reducing caregiver burden, institutional care, and enhancing quality of life (Brookmeyer et al., 1998).

Not surprisingly, there has been much recent research interest in discovering non-pharmacological ways in which cognitive and motor decline associated with ageing can be slowed or even reversed. Importantly, neuroscientists agree that the brain, rather than being static after childhood, is constantly adapting to changing conditions throughout adulthood and during physiological ageing. This process, known as neuroplasticity, is the basis for (a) cognitive/motor functions, (b) cognitive/motor learning, and (c) the brain's responses to

disease and injury (Berlucchi, 2011). Impaired neuroplasticity mechanisms are frequently linked to cognitive and motor deficits accompanying a variety of disorders including stroke, Parkinson's disease, and Alzheimer's disease. Therefore, the possibility of enhancing neuroplasticity with external stimuli has far-reaching clinical implications including slowing age-related cognitive or motor decline.

One possible way to boost and sustain cognitive and motor performance in older adults is through the provision of specific motor and cognitive skills training programs. While there have been a few positive studies of brain training in older adults (Bamidis et al., 2014; Klingberg, 2010; Rebok et al., 2014), recent meta-analyses indicate that there is a lack of robust findings regarding the long-term efficacy and generalizability of such programs (George and Whitehouse, 2011; Martin et al., 2011; Papp et al., 2009). Moreover, there is renewed interest in the use of non-invasive brain stimulation (NIBS) techniques to modify cortical plasticity by means of extrinsic transient magnetic fields (i.e., passive modification rather than use-dependent modification). One technique in particular, transcranial direct current stimulation (tDCS), has enjoyed an extraordinary increase in popularity despite limited understanding of the neural mechanisms underlying the reported behavioural effects (de Berker et al., 2013).

tDCS involves the application of a weak electrical current (0.5-2mA) continuously to the scalp via two surface electrodes (anode and cathode) for 10-20 min. Depending on the direction of current flow, tDCS can induce cortical excitability changes lasting for over 60 min following 15 min of stimulation (Nitsche and Fregni, 2007). Although there are a number of factors that may influence the response to tDCS (see sections 4.3 - 4.6), anodal stimulation typically increases cortical excitability while cathodal stimulation decreases excitability. The neurobiological mechanisms underlying tDCS effects, however, are complex involving changes at multiple levels of description from the cellular level to modulation of

the intrinsic network dynamics in the brain (Medeiros et al., 2012). Much of the knowledge regarding the physiological effects of tDCS has come from in vitro animal studies and pharmacological interventions in humans. Furthermore, somewhat different mechanisms appear to be involved in the cortical excitability changes evident during the period of stimulation and persistence of those changes following cessation of stimulation (Stagg and Nitsche, 2011).

*During stimulation*

The application of weak direct current stimulation (DCS) to the brain shifts the resting membrane potential of superficial horizontal intracortical interneurons resulting in changes to spontaneous neuronal excitability. Anodal stimulation increases neuronal firing rate through depolarization of resting membrane potentials whereas cathodal stimulation decreases firing rate and neuronal excitability through membrane hyperpolarization. Although the weak currents applied during stimulation do not evoke action potentials in a resting cell, recent in vitro research suggests that concurrent membrane potential changes in both the somata and axon terminals may underlie DCS-induced modulation of neuronal excitability (Rahman et al., 2013).

*Stimulation After-effects*

The transfer of the initial membrane potential shifts to longer-term modification of synaptic plasticity seem to involve processes similar to long-term potentiation (LTP) and long-term depression (LTD) through the modulation of NMDA receptors (Stagg and Nitsche, 2011). Pharmacological evidence indicates that tDCS elicits modifications in NMDA receptors via changes in post synaptic intracellular calcium concentration (Nitsche et al., 2003). There is strong evidence that in addition to influencing synaptic plasticity through modulation of glutametargic (NMDA and AMPA) receptors, the after-effects of tDCS also involve inhibitory γ- aminobutyric acid (GABA) interneurons (Nitsche et al., 2005; Stagg et

al., 2009). Anodal tDCS-induced reductions in GABA concentration, as measured by magnetic resonance spectroscopy (MRS), have been shown to be highly correlated with motor learning and motor memory processes (Kim et al., 2014b). Furthermore, paired-pulse transcranial magnetic stimulation (TMS) protocols have demonstrated changes to short-term intracortical inhibition (SICI) and intracortical facilitation mechanisms following tDCS indicative of a reduction in GABAergic inhibition (Stagg et al., 2009). Interestingly, a reduced capacity to modulate GABA mediated inhibitory processes in older adults (Levin et al., 2014) has been associated with age-related decline in cognitive and motor function (Gleichmann et al., 2011). This raises the possibility of using tDCS to target deficient inhibitory activity in older individuals (Heise et al., 2014).

Consistent with LTP-like mechanisms, the after-effects of anodal tDCS also appear to be modulated by several~~by a number of~~ other neurotransmitter systems, including acetylcholine, serotonin, and dopamine (Medeiros et al., 2012). A number of studies have confirmed the important role of the dopaminergic system, especially D2 receptors, for cortical neuroplasticity mechanisms (Nitsche et al., 2012). This is important in the context of the present review, as there is an age-dependent degeneration of dopamine neurons (Backman et al., 2006) that has been linked to declines in memory in the elderly (Chowdhury et al., 2012).

Recently there has been interest in the influence of genetic factors on the after-effects of tDCS. In particular, brain-derived neurotropic factor (BDNF) has been shown to play an important role in the mechanisms of LTP- and LTD-like neuroplasticity by regulating protein synthesis at the glutamergic synapse (Chaieb et al., 2014). As such, BDNF secretion, which is decreased in older adults (Li et al., 2008), has been linked to learning and memory processes. Importantly, anodal tDCS applied to mouse motor cortex slices has been shown to enhance BDNF secretion and the receptor ~~tyorosine~~ tyrosine ~~receptor~~ kinase B (TrkB), which are

crucial factors in the augmentation of synaptic plasticity and motor learning (Fritsch et al., 2010). The role of genetic variation in the after-effects of various NIBS protocols, including the BDNF Val66Met polymorphism, has been the subject of a number of recent studies. Met carriers exhibit reduced BDNF secretion and impaired performance on learning and memory tasks. In general, in repetitive TMS protocols Met carriers have exhibited smaller post intervention changes in measures of cortical excitability (MEP amplitudes) than Val/Val homozygotes. The results for tDCS, however, have been inconsistent with studies showing either no differences between Val/Val and Val/Met carriers (Cheeran et al., 2008; Di Lazzaro et al., 2012) or greater post-intervention increases in cortical excitability in Met carriers (Antal et al., 2010; Teo et al., 2014) including a study of older adults (Puri et al., 2015). There are a number of other genetic polymorphisms that may influence the response to brain stimulation protocols and research into their effect in isolation and in interaction with other genes is just beginning (Witte et al., 2012).

As indicated from the above, tDCS effects are complex and result from changes in systems at different levels of description. While progress is being made in understanding tDCS effects at each level, how the levels interact to produce behavioural change is still poorly understood. Furthermore, this research has largely focussed on local changes underneath an electrode, but there is clear evidence from neuroimaging studies that standard tDCS protocols produce widespread changes in cortical activity across a number of connected brain regions (Zheng et al., 2011). These studies have shown that tDCS can modulate both inter-hemispheric and corticospinal functional connectivity (Polania et al., 2012; Sehm et al., 2013). Age-related differences in connectivity patterns that relate to memory performance have also been reported (Sala-Llonch et al., 2014). Importantly, recent research is beginning to examine the relationships between the micro and macro levels of tDCS effects by

combining neuroimaging measures of network connectivity and proton magnetic resonance spectroscopy ($^{1}$H MRS) measures of glutamatergic neurotransmission (Hunter et al., 2015). Although there is still much to discover about the mechanisms underlying tDCS effects, the possibility of enhancing cortical plasticity via cortical stimulation has enormous potential for use as an intervention to enhance cognitive and motor functions in both healthy and patient populations. As a consequence, tDCS protocols have been applied to a number of brain sites including the primary motor cortex (M1), dorsolateral prefrontal cortex, parietal cortex, inferior frontal gyrus, as well as the cerebellum while investigating stimulation effects on a variety of cognitive and motor functions (Brunoni and Vanderhasselt, 2014; Ferrucci and Priori, 2014; Shin et al., 2015). Further, tDCS has been applied to a wide range of neurological disorders including stroke (Marquez et al., 2015), Parkinson's disease (Benninger et al., 2010), chronic pain (Fregni et al., 2006), depression (Arul-Anandam and Loo, 2009), and traumatic brain injury (Ulam et al., 2014).

To date, the majority of tDCS research has been conducted on healthy young adults or patient groups with relatively few studies specifically investigating the effects of non-invasive brain stimulation in older adults. This is somewhat surprising given the possibility that NIBS, especially tDCS, might promote neuroplasticity in the ageing brain. Further, tDCS protocols that are practical for young adults may not be as effective in older populations as ageing has been associated with reductions in cortical synaptic efficacy and connectivity (Morrison and Baxter, 2012; Sala-Llonch et al., 2014). Several TMS studies have also shown an age-dependent reduction in motor cortex plasticity (Todd et al., 2010) for both LTD-like (Freitas et al., 2011) and LTP-like plasticity (Fathi et al., 2010).

The aim of the present meta-analysis and systematic review, therefore, is to provide a quantitative assessment of the capacity of tDCS to modulate cognitive and motor function in the ageing brain. Such a review is important and timely because despite the claims being

made about the capacity of tDCS to enhance performance in young healthy adults, some recent reviews have seriously questioned the ability of tDCS to produce reliable physiological and cognitive performance effects (Horvath et al., 2014; Horvath et al., 2015; Tremblay et al., 2014). Further, our systematic review and meta-analysis compared the effectiveness of tDCS in enhancing cognitive versus motor task performance. The majority of the early studies applied tDCS to the primary motor cortex, as the effects of the stimulation on cortical excitability can be readily measured from changes in motor evoked potentials obtained prior to and following tDCS by TMS. In contrast, tDCS applied to non-motor areas, such as the dorsolateral prefrontal cortex, often relies on hypothesised changes on behavioural measures to confirm that the targeted cognitive region(s) had been stimulated. In addition, we examined whether the timing of stimulation (i.e., before, or during task performance) is important in the effects of tDCS on cognitive and/or motor function, and whether the site of stimulation has differential effects on cognitive functions. Finally, our meta-analysis *focussed* on the mean effect sizes generated by *anodal stimulation*. A recent meta-analysis of tDCS polarity effects (i.e., anodal-excitation and cathodal-inhibition) reported that while the expected pattern was commonly evident in motor studies, in cognitive studies only the anodal effect was consistently observed (Jacobson et al., 2012).

## 2. Methods

### *2.1. Study inclusion and exclusion criteria*

We searched the literature for the past 12 years with assistance from three computerized databases: (a) PubMed, (b) ISI's Web of Knowledge, and (c) Cochrane Database of Systematic Reviews. Our search included five key words and phrases: transcranial direct current stimulation (tDCS), ageing, elderly, cognitive performance, and motor performance. Additional sources involved reference lists of retrieved articles for broad selection criteria (Rosenthal, 1995). Our initial search (April – October 2015) identified 81

full-length studies that discussed tDCS and ageing in conjunction with cognitive and/or motor functions.

Four predetermined inclusion and exclusion criteria follow:

1. The first inclusion criterion involved quantitative evaluations of tDCS effects on cognitive tasks or motor tasks. Thirty-eight studies met this criterion and 43 studies were discarded (e.g., narrative review papers).
2. Second, we evaluated relevance to our specific ageing brain questions. Six studies were discarded because of lack of relevance to our questions focusing on anodal tDCS, cognitive performance, motor performance, and moderator variables. Thirty-two studies were relevant to our purpose.
3. The third criterion concerned data extraction. If studies did not report the necessary values required for coding and extracting tDCS and ageing brain information on cognitive or motor functions, then we excluded the troublesome studies. Seven studies were discarded.
4. The fourth inclusion criterion was an ageing and active tDCS comparison group involving a control (sham) or pretest versus posttest: all 25 studies included a comparison group. tDCS versus control comparisons (e.g., anodal tDCS vs. sham control) were reported as separate results in 22 of the 25 studies. Three studies reported pretest versus posttest comparisons.

The 25 qualified studies were submitted to our meta-analysis. One author (NK) independently coded the 25 studies and extracted data (Berryhill and Jones, 2012; Boggio et al., 2010; Fertonani et al., 2014; Floel et al., 2012; Goodwill et al., 2015; Goodwill et al., 2013; Hardwick and Celnik, 2014; Harty et al., 2014; Heise et al., 2014; Hoff et al., 2015; Holland et al., 2011; Hummel et al., 2010; Jones et al., 2015; Lindenberg et al., 2013; Manenti et al., 2013; Meinzer et al., 2013; Meinzer et al., 2014; Panouilleres et al., 2015;

Parikh and Cole, 2014; Park et al., 2014; Ross et al., 2011; Sandrini et al., 2014; Seo et al., 2011; Zhou et al., 2015; Zimerman et al., 2013). Two authors (JS & JC) confirmed data extractions, and all authors were involved in interpreting the meta-analytic results. Table 1 lists the characteristics of the 25 comparisons involving tDCS, ageing, cognitive performance, and motor performance.

Insert Table 1 about here

*2.2. Outcome measures: cognitive and motor performance*

Consistent with conventional meta-analysis techniques and in line with our research questions, we extracted data on outcome measures from each study. Unfortunately, deriving composite scores based on multiple outcome measures was impossible because of missing correlation values among the various outcomes (Borenstein et al., 2009). Thus, we followed a standard, conservative recommendation to avoid data biasing by selecting only one outcome measure per study that best represented tDCS effects on cognitive and motor functions for the elderly.

To determine anodal tDCS effects on cognitive functions in the ageing brain, we selected three primary outcome measures: (a) memory/working memory (e.g., working memory task, recall task, visual memory, and long-term memory task; eight studies), (b) problem solving and decision making (e.g., risk task and Repeat No-go trial task; two studies), and (c) language production (e.g., semantic word retrieval task and visual picture naming task; four studies). The motor domain outcome measures included: (a) tracking error task (one study), (b) finger tapping (three studies), (c) wrist extension (one study), (d) reaching movement (one study), (e) grooved pegboard test (one study), (f) Jebsen-Taylor Hand Function Test (one study), (g) postural control (one study), (h) visuomotor adaptation

task (one study), and (i) ball rotation task (one study). Table 1 shows a comprehensive listing of the outcome measures for both the cognitive and motor domains.

Fourteen cognitive performance studies and 11 motor performance studies were submitted to our meta-analysis. For cognitive performance studies, nine studies used dorsal lateral prefrontal cortex (DLPFC) as a stimulation site and five studies stimulated other sites (e.g., anterior temporal lobe or inferior frontal cortex). Further, four studies used tDCS prior to a cognitive task and 10 studies applied stimulation during a cognitive task. For motor performance studies, three studies provided tDCS before a motor task whereas eight studies simultaneously used tDCS during a motor task (see Table 2).

Insert Table 2 about here

*2.3. Data synthesis and analysis*

Analysing the set of common tDCS studies involved (a) describing relevant characteristics of studies as well as comparison groups (see Table 1), (b) tDCS treatment protocols (see Table 2), (c) calculating standardized mean difference effect sizes for each comparison, (c) determining an overall effect size (see Table 3), and (d) identifying potential moderator variables (Borenstein et al., 2009; Rosenthal and DiMatteo, 2001). Once potential moderator variables were identified, additional meta-analyses were conducted to measure the contributions of subgroups to effect sizes (Borenstein and Higgins, 2013; Hedges and Olkin, 1985; Sutton et al., 2000).

Insert Table 3 about here

*2.4. Measuring heterogeneity*

Conducting heterogeneity analyses across studies is a critical meta-analytic technique (Hedges and Olkin, 1985; Higgins and Green, 2006; Rosenthal and DiMatteo, 2001). We

conducted three variability tests: (a) Cochran's *Q*, (b) $I^2$, and (c) $T^2$. Higgins and Green argued that $I^2$ represents heterogeneity as a dispersion value with percentage units, and the technique evaluates the evidence beyond a statistical chance occurrence (Higgins and Green, 2006). Further, $T^2$ measures the variance of true effect sizes in a random effects model. A $T^2$ higher value denotes greater heterogeneity (Borenstein et al., 2009).

*2.5. Publication bias and fail-safe N analysis*

Quantitative analyses concerning potential publication bias are helpful in evaluating a meta-analysis. Thus, we conducted three meta-analytic techniques: (a) funnel plots for symmetry, (b) trim and fill with imputed values on a second funnel plot, and (c) classic fail safe *N* determining the number of studies required to nullify an overall effect size (Borenstein et al., 2009; Hedges and Olkin, 1985; Rosenthal, 1995; Rothstein et al., 2005; Sutton et al., 2000).

## 3. Results

*3.1. Overall tDCS effects: standardized mean differences*

A random effects model meta-analysis on the 25 comparisons indicated a significant overall standardized mean difference effect equal to 0.53 ($SE$ = 0.09; $p < 0.0001$; $Z = 5.59$) with a 95% confidence interval of 0.34 − 0.71. This medium positive effect (e.g., large ≥ .80) revealed distinct tDCS treatment effects on cognitive and motor performances by the elderly (Cohen, 1988; Rosenthal and DiMatteo, 2001). Table 3 shows the individual standardized mean difference (i.e., weighted effect size) for each comparison and the values ranged from −1.50 to 1.71.

The forest plot shown in Fig. 1 lists the authors of each individual comparison alphabetically on the left margin and an associated line with a specific value for each study displayed as a circle in the plotting area (black circles = cognitive task; white circles = motor tasks). The values on the x-axis are standardized mean difference effect size. The tick marks,

left and right of the circles are the 95% confidence intervals for each comparison including the overall effect size. The mean effect sizes ranged ± 3 on the x-axis. The red circle at the bottom of the figure equals the overall pooled effect calculated on the 25 comparisons.

Displaying all comparisons in a forest plot allows visual inspection of both tasks. The effect sizes and confidence intervals indicate that various tDCS treatments positively influenced performance on both the cognitive and motor tasks. Further, a confirmation of the robust tDCS effect is found in the ~~22~~ 25 individual effect sizes to the right of the vertical line of no effect (0.00) as well as the combined performance effects observed in older participants following tDCS treatments.

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Insert Figure 1 about here

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Moreover, one comparison study (Boggio et al., 2010) was considered an outlier because the effect value of -1.50 was greater than two standard deviations beyond the standardized mean effect value (red circle). Thus, we removed the outlier study and conducted a subsequent meta-analysis. The overall effect was nearly the same medium value and the standard error decreased slightly ($ES$ = 0.56; $SE$ = 0.08; $p < 0.0001$; $Z$ = 6.77).

*3.2. Measuring heterogeneity*

Variability calculations on the 25 studies that tested elderly participants using tDCS treatment protocols revealed: (a) Q statistic = 55.92 ($p < 0.001$); (b) $I^2$ = 57.08%; and (c) $T^2$ = 0.11 (Table 3). Meta-analytic investigators frequently refer to $I^2$ values when making decisions about the type of model used. Given that $I^2$ indicated a relatively medium amount of dispersion, we followed the traditional approach and conducted a random effects model (Higgins and Green, 2006; Higgins et al., 2003). Thus, the identified significant summary effect (0.53) is robust across the cognitive and motor domain comparisons in our meta-analysis (Borenstein et al., 2009). This statement is confirmed by the relatively small $T^2$.

*3.3. Publication bias and fail-safe N analysis*

Visual inspection of the funnel plot in Fig. 2 displayed each treatment effect size as a function of standard error, and the edges of the funnel indicate probability level = 0.05. This inspection suggests that the included set of tDCS and ageing comparisons were relatively unbiased. Even though the two sides of the funnel are slightly different, mild asymmetry contributes minimally to publication bias. Importantly, each study contributed data from one primary outcome measure. This conventional procedure minimizes data biasing effects (Fanelli, 2009; Rosenthal, 1995; Sterne and Egger, 2001).

Insert Figure 2 about here

Applying the trim and fill funnel plot (Fig. 3) produced an ideal symmetry of effect sizes and standard error with imputed values. Adhering to Duval and Tweedie's guidelines (Duval and Tweedie, 2000), four values were imputed on the left side of the funnel to balance the individual studies on the right side (Borenstein et al., 2009). Each black circle represents a balanced study with a generated effect size plotted as a function of standard error, achieving relatively perfect symmetry. The black diamond on the x-axis is the recalculated overall effect given the imputed scores on the left side. Note that the two overall medium positive effect sizes (i.e., white and black diamonds) are nearly identical.

Moreover, the classic fail-safe *N* analysis provides additional information supporting our conclusion that bias was not a concern. Specifically, 448 null effect findings are necessary to lower our cumulative effect size of 0.53 to an insignificant level (Table 3). Given that the near symmetrical original funnel plot, slightly adjusted imputed plot, and classic fail-safe *N*, we are confident in stating that publication bias was not a serious concern for the 25 comparison studies.

Insert Figure 3 about here

*3.4. Moderator variable analyses*

*3.4.1. Cognitive versus motor functions*

In the first moderator variable analysis, we examined the effects of tDCS on cognitive and motor functions. The subgroup analyses revealed two significant mean effect sizes: (a) cognitive function (*ES* = 0.45; *SE* = 0.12; $p < 0.0001$; $Z = 3.75$; $I^2 = 58.46\%$; $T^2 = 0.11$; 95% CI = 0.21 – 0.68; 14 studies) and (b) motor function (*ES* = 0.65; *SE* = 0.16; $p < 0.0001$; $Z = 4.08$; $I^2 = 58.06\%$; $T^2 = 0.15$; 95% CI = 0.34 – 0.96; 11 studies). Concerning the ageing brain, these findings reveal robust evidence for providing tDCS to the elderly to enhance both cognitive and motor functions.

*3.4.2. Cognitive function: dorsolateral prefrontal cortex brain region versus other brain regions*

A second moderator analysis compared stimulation effects on the dorsolateral prefrontal cortex with other brain areas. These subgroup analyses indicated significant effect sizes for the brain area comparisons: (a) DLPFC (*ES* = 0.39; *SE* = 0.16; $p = 0.018$; $Z = 2.37$; $I^2 = 63.50\%$; $T^2 = 0.14$; 95% CI = 0.07 – 0.71; nine studies) and (b) other brain areas (*ES* = 0.52; *SE* = 0.19; $p = 0.006$; $Z = 2.76$; $I^2 = 57.30\%$; $T^2 = 0.10$; 95% CI = 0.15 – 0.89; five studies).

*3.4.3. Cognitive function: cognitive categories*

In the third moderator variable analysis, the cognitive tasks across studies were placed into the three broad cognitive categories: (a) memory/working memory, (b) problem solving and decision-making, and (c) language production. Two of the subgroup analyses revealed significant mean effect sizes: (a) memory/working memory (*ES* = 0.45; *SE* = 0.12; $p < 0.0001$; $Z = 3.89$; $I^2 = 15.79\%$; $T^2 = 0.02$; 95% CI = 0.22 – 0.67; eight studies) and (b)

language production (*ES* = 0.68; *SE* = 0.23; *p* = 0.003; *Z* = 2.96; $I^2$ = 61.96%; $T^2$ = 0.13; 95% CI = 0.23 – 1.13; four studies). The third moderator analysis on problem solving and decision-making failed to find a significant effect size (*ES* = -0.45; *SE* = 0.98; *p* = 0.647; *Z* = -0.46; $I^2$ = 92.45%; $T^2$ = 1.80; 95% CI = -2.38 – 1.48; two studies). These findings indicate that anodal tDCS appears to function effectively on tasks categorized as working memory and language production.

*3.4.4. Cognitive function: stimulation before versus during cognitive performance*

A fourth moderator variable analysis investigated effects of anodal stimulation on cognitive task performance (i.e., offline: before task initiation; online: during task execution). Both stimulation time periods showed significant mean effect sizes: (a) anodal stimulation before a cognitive task (*ES* = 0.65; *SE* = 0.19; *p* = 0.001; *Z* = 3.34; $I^2$ = 0.00%; $T^2$ = 0.00; 95% CI = 0.27 – 1.03; four studies) and (b) anodal stimulation during a cognitive task (*ES* = 0.38; *SE* = 0.15; *p* = 0.009; *Z* = 2.61; $I^2$ = 68.54%; $T^2$ = 0.14; 95% CI = 0.10 – 0.67; 10 studies). These findings indicate that beneficial effects of tDCS on cognitive function are evident when applied either before or during a cognitive task.

*3.4.5. Motor function: stimulation before versus during motor performance*

Our fifth moderator analysis compared motor performance effects of tDCS on stimulation timing (i.e., before task initiation or during task execution). Applying anodal tDCS before motor task practice revealed a mean effect size of 0.54 (*SE* = 0.16; *p* = 0.001; *Z* = 3.42; $I^2$ = 0.00%; $T^2$ = 0.00; 95% CI = 0.23 – 0.85; three studies). When stimulation was applied during motor task execution a mean effect size of 0.72 (*SE* = 0.24; *p* = 0.003; *Z* = 2.98; $I^2$ = 70.17%; $T^2$ = 0.32; 95% CI = 0.25 – 1.20; eight studies) was evident.

## 4. Discussion

The current meta-analysis investigated the effects of anodal tDCS on cognitive and motor functions in healthy older adults. The use of NIBS to slow or even reverse cognitive

and motor decline associated with ageing has important health and lifestyle implications given the increasing proportion of the population worldwide aged over 65 years. tDCS has become a popular NIBS technique for enhancing cognitive and motor functions because of the low cost, portability, comfort, ease of use, and safety. Therefore, the aim of the present systematic review and meta-analysis was to determine quantitatively whether the interest and excitement surrounding the potential of tDCS to enhance the abilities of healthy older adults is justified.

*4.1. Meta-analytic findings*

Twenty-five studies involving older adults met the criteria for inclusion in the meta-analysis. Overall, there was a robust medium, significant effect size of 0.53 indicating that the application of tDCS enhanced task performances. This an important finding given that the effect sizes of .50 or greater are regarded as clinically meaningful (Sloan et al., 2005).

A comparison across task domains revealed that the benefit from tDCS was larger for motor tasks (mean effect size = 0.65) than cognitive tasks (mean effect size = 0.45). This is consistent with the findings reported by Jacobson et al. (2012) that anodal tDCS produces larger effect sizes for motor domain tasks. In many motor studies, TMS is used to precisely locate target areas in the motor cortex and directly measure tDCS-induced changes in cortical excitability through the amplitude of motor-evoked potentials (MEPs). Localization of non-motor targets, in contrast, is much less precise and any cognitive task is likely to involve a number of cortical areas making it difficult to attribute performance changes to stimulation of a specific cortical region (Tremblay et al., 2014). These factors may have contributed to the lower effect size associated with studies of cognitive function.

Two additional moderator variable analyses focused on the cognitive domain and explored the tDCS effects observed as a function of cognitive task category and the site of stimulation. Interestingly, only language production (mean effect size = 0.68) demonstrated a

clinically meaningful effect size~~s~~ (ES > 0.50), with the ~~. Even though,~~ analysis of the memory/working memory category showing a slightly lower value (SMD = 0,45). ~~identified a significant standardized mean difference (SMD = 0.45), the values fell slightly below the clinically meaningful effect size.~~ Further, tDCS did not significantly influence performances on problem solving or decision-making tasks (mean effect size = -0.45). However, the lack of a significant effect of tDCS on problem solving and decision-making should be treated cautiously because the comparisons displayed high heterogeneity ($I^2$ = 92.45%).

In terms of site of stimulation, moderate effect sizes were evident for stimulation of the DLPFC (mean effect size = 0.39) and other non-motor sites (mean effect size = 0.52). As the DLPFC is critically involved in working memory, a function that is important for a wide range of cognitive functions and shows marked decline in normal ageing, the positive influence of tDCS has encouraging implications for the maintenance of working memory over the ageing process. However, a caveat to this conclusion is warranted. A recent review of 61 studies applying tDCS to the DLPFC found a lack of consistency in outcomes making causal conclusions between DLFPC stimulation and a particular cognitive function difficult (Tremblay et al., 2014). One reason for the inconsistency is that tDCS appears to simultaneously modulate activity in a number of brain areas subserving a variety of cognitive functions with the maximum field strength being located some distance (20-40 mm) from the target area (e.g., DLPFC) (Rampersad et al., 2014).

A final moderator analysis examined the issue of the timing of tDCS administration. That is, whether the beneficial effects of tDCS are more evident when stimulation is applied before (offline) or during (online) task practice. This is an interesting issue because the optimal timing of the delivery of tDCS is important for clinical applications of the technique. A recent study comparing cortical excitability (TMS-evoked MEP amplitudes) in response to anodal tDCS applied to the motor cortex of young volunteers before, during, or after motor

task practice found enhanced excitability only in the before condition (Cabral et al. 2015). ~~Given that the plasticity-inducing effects of tDCS appear to occur following cessation of stimulation and~~ Given the evidence for an age-related reduction in the efficiency of cortical plasticity mechanisms (Morrison and Baxter, 2012), however, it might be expected that older adults would benefit more from ~~off~~online than ~~on~~offline stimulation. Consistent with this hypothesis, Fertonani et al. (2014), ~~however,~~ found that while picture-naming performance in young adults was enhanced by both online and offline stimulation, for older adults improved performance was only evident when tDCS was applied during task practice. A recent meta-analysis of the effects of NIBS on cognitive function in the elderly, however, found that offline designs produced greater benefits than online designs for healthy old adults, but the reverse was apparent in patients with Alzheimer's disease (Hsu et al., 2015). ~~cortical excitability as measured by TMS-evoked MEP amplitudes was enhanced when anodal tDCS was applied to the motor cortex of young volunteers before a motor task, but not when applied either during or after the task (Cabral et al., 2015). A recent meta-analysis of the effects of NIBS on cognitive function in the elderly also found that offline designs produced greater benefits than online designs for healthy old adults, but the reverse was apparent in patients with Alzheimer's disease (Hsu et al., 2015).~~ In the present meta-analysis, cognitive tasks showed greater beneficial effects from offline stimulation (mean effect size = 0.65) than online stimulation (mean effect size = 0.38). For motor tasks, in contrast, the effect size for stimulation applied during task practice was larger (mean effect size = 0.72) than when applied prior to task performance (mean effect size = 0.54). However, considering that only three studies were included in the offline category, this finding should be treated with caution. The smaller effect size for offline stimulation evident for motor tasks may also reflect the influence of regulatory homeostatic plasticity mechanisms that have been shown to actually decrease motor learning relative to sham stimulation when anodal tDCS is applied

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offline (Amadi et al., 2015; Kuo et al., 2008; Stagg et al., 2011). That is, the increased background neural activity produced by anodal tDCS induces LTP-like synaptic changes and when followed by motor learning which also involves LTP-like changes in the same network, homeostatic mechanisms operate to maintain neural activity within a normal functional range and impedes motor learning induced LTP-like plasticity. One potential problem with evaluating offline effects is that studies rarely attempt to control or report what participants are actually doing during the administration of tDCS for 10-20 min. As Horvath and colleagues note (Horvath et al., 2014), even seemingly innocuous activities performed during stimulation, such as reading, talking or texting, may interfere with tDCS effects. There is clearly a need for further research to determine whether applying tDCS prior to, during, or even after (Tecchio et al., 2010) task practice leads to the greatest task performance benefits. As the responsiveness of neural networks is reduced in older adults, the optimal timing of stimulation may differ for young and older adults. A further question of interest is whether, as suggested in the present analysis, the optimal timing differs for cognitive and motor tasks.

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In summary, the present meta-analysis suggests that the application of anodal tDCS has beneficial effects on both cognitive and motor functions in healthy older adults. In particular, ~~clinically meaningful~~ significant positive effects were revealed for motor task performances, and for cognitive tasks involving memory and language production. While cognitive tasks showed a larger effect size when stimulation was applied before task practice, greater beneficial effects on motor tasks were evident for stimulation applied during task performance. For cognitive tasks slightly greater enhancement occurred when cortical areas other than the dorsolateral prefrontal cortex were stimulated. These findings suggest that the application of NIBS in the form of anodal tDCS may be a useful technique for offsetting the decline in cognitive and motor functions associated with normal ageing. Finally, there are encouraging findings coming from studies examining the application of tDCS in a range of

neurological diseases including mild cognitive impairment, Alzheimer's disease, and movement disorders (Floel, 2014).

*4.2. Conceptual models of tDCS*

Our systematic review and meta-analysis focused on articles that investigated the classic excitability assumption according to Shin et al. (2015): anodal tDCS increases excitability. Indeed, uniform learning often accrues as a function of anodal tDCS inducing long-term potentiation-like plasticity. Moreover, assuming that the more stimulation produces increased benefits, optimal protocols are still under investigation. However, caution must rule because cognition and stimulation may function as a non-linear system (Shin et al., 2015).

Granted, noted in the Introduction, the mechanisms of tDCS are far from clear. In a recent review, Shin et al. (2015) stated that motor learning studies show involved cortical structures including the primary motor cortex, pre-motor cortex, supplementary motor area, and parietal association areas. However, researchers are still debating alternative theories and remaining issues. Three popular conceptual models based on the logic of interhemispheric interactions are viable. One alternative is a model proposed by Di Pino et al. (2014) elaborates on a bimodal balance-recovery approach with implications for normal ageing brains. This integrated model includes components of two models: (a) vicariation and (b) interhemispheric competition theories. In the stroke literature, the vicariation model assumes that increased brain activity in the contralesional hemisphere contributes to stroke motor recovery whereas the interhemispheric competition model posits that suppressing brain activity in the contralesional hemisphere facilitates paretic limb recovery. Importantly, Di Pino and colleagues reasoned that the interhemispheric competition model is appropriate for individuals who experienced a less severe stroke resulting in a smaller affected area (Di Pino et al., 2014). For stroke free ageing brains, the interhemispheric competition model is attractive. Coppi and colleagues indicate that reduced interhemispheric interaction associated

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with less brain activity in non-dominant hemisphere may cause motor disabilities of dominant hand in elderly groups (Coppi et al., 2014). Thus, increasing brain activity in motor areas of non-dominant hemisphere may facilitate interhemispheric interaction contributing to motor improvements.

A third interhemispheric interactions model proposed by Bestmann et al. (2015) focuses on the different viable anatomical structures that participants display. Essentially, individualized modeling involves computational neurostimulation to normalize current flow. When the computational modeling discovers the induced physiological and behavioral current flows, tDCS efficacy should accrue (Bestmann et al., 2015). In addition, Brunoni et al. (2012) suggested two approaches for increasing the accuracy of current flow computational modeling: (a) using high-resolution anatomic scans and (b) applying a priori knowledge about tissue anatomy. Taken together, an important consequence of this computational modeling is determining individualized tDCS protocol efficacy in a healthy group of elderly people with apparent normal ageing brains (Brunoni et al., 2012). Finally, applying individualized tDCS protocols based on individual anatomical variations may minimize inter-individual variability in tDCS treatment effects. Such advances are important in healthy ageing people.

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*4.3. Large inter-individual variability in response to tDCS*

While the current meta-analysis shows that anodal tDCS has generally beneficial effects in healthy older adults, there are a number of caveats that should be recognised in using this NIBS technique. An issue of recent concern are reports of high inter- and intra-individual variability in response to NIBS protocols including tDCS (Hinder et al., 2014; Lopez-Alonso et al., 2014; Wiethoff et al., 2014). In two studies, each involving over 50 participants, the expected response to anodal tDCS (i.e. increase cortical excitability) was observed in less than 50% of the participants (Lopez-Alonso et al., 2014; Wiethoff et al.,

2014). A number of factors have now been identified that may contribute to the large variability in individual responses to tDCS protocols (Krause and Cohen Kadosh, 2014). Two of the most important factors appear to be individual differences in anatomy and physiology and differences in the level of excitation of the system at the time of stimulation (state-dependency). Recent studies using imaging and computational modelling have revealed large inter-individual differences in the tDCS-induced electric fields resulting from differences in the thickness of the cerebrospinal fluid and skull (e.g., Kim et al., 2014; Opitz et al., 2015). Thus, the same electrode montage can stimulate different brain areas in different individuals. Importantly, one study reported that a group of older adults (average age 60 yrs) may have a 30% weaker average electric field than a group of 20 year olds (Laakso et al., 2015). This clearly has implications for the application of tDCS to ageing brains. ~~Across studies, findings are showing that the response to tDCS is greatly influenced by differences in individual anatomy and physiology (Kim et al., 2014a) and by the level of excitation of the system at the time of stimulation (state-dependency) (Silvanto et al., 2008)~~.

The assumption that tDCS effects will always occur in a polarity-specific manner has been shown to be incorrect. Rather the response to tDCS is greatly influenced by individual differences in the level of baseline cortical excitability prior to stimulation.(Silvanto et al., 2008). For example, applying anodal tDCS to an area already exhibiting high excitability may activate intrinsic homeostatic plasticity mechanisms causing a reversal of the predicted effects from excitation to inhibition (Moliadze et al. 2012). It has been suggested that individual differences in baseline neuronal activation states reflect differences in the balance between excitatory and inhibitory neurotransmitter systems, glutamate and GABA respectively (Krause and Cohen Kadosh, 2014). There is also evidence that individual differences in baseline task performance will influence the response to tDCS. Learmonth and colleagues (2015) applied anodal tDCS to the posterior parietal cortex of young and older

adults during a spatial attention task. ~~For example, a recent study found no age-related effects in response to anodal tDCS applied to the posterior parietal cortex during a spatial attention task. Rather,~~ Although no age-related effects in response to anodal tDCS were found, response to tDCS was influenced by an individual's baseline task performance with good task performers showing maintenance of task performance, whereas for poor performers tDCS impaired task performance ~~(Learmonth et al., 2015)~~. This study highlights the need for future research to compare the effects of tDCS on high functioning and lower functioning older adults. ~~Given that only a few studies in the present meta-analysis reported individual data, such individual differences in response to anodal tDCS may have been masked by group averaging.~~ Moreover, task difficulty has been shown to influence the response to tDCS with beneficial effects being more likely to be evident when tasks are sufficiently challenging. This suggests the interesting possibility that when young and old participants are compared on the same task, greater tDCS-induced effects might be expected in older adults as the task is likely to be more challenging and motivating to the elderly (Berryhill et al., 2014).

*4.4. Lack of focal stimulation*

Although researchers commonly assume that the behavioural effects of tDCS reflect the function of the targeted stimulated area, as discussed earlier there is clear evidence from neuroimaging studies that standard tDCS protocols produce widespread changes in cortical activity across numerous brain regions (Zheng et al., 2011). Indeed, caution must be exercised because we cannot assume that the area receiving maximum stimulation is directly beneath the electrode, as the level of current delivered to different areas can vary substantially (Rampersad et al., 2014). Small drifts in the position of electrodes that can occur during a 20 min tDCS session can also significantly change the intensity and distribution of the current delivered to the brain (Woods et al., 2015). Thus, conclusively linking a mechanism by which tDCS produces behavioural effects to a specific stimulated brain area is

tenuous (de Berker et al., 2013). However, the focality of stimulation can be improved by reducing the standard electrode size (35 $cm^2$) by one third to 12 $cm^2$ (Bastani and Jaberadeth, 2013) and can be further increased by the use of high-definition small multi-electrode arrays (Edwards, et al, 2013; Saturnino et al. 2015). ~~Moreover, the fact that the current meta-analysis indicated that anodal tDCS can produce widespread beneficial effects across tasks, time, and site of stimulation may be of concern. As noted by de Berker and colleagues, "…there is no theoretical or mechanistic explanation for why depolarizing cells would improve such complex behaviours as perceptual decision-making, mathematical ability, or motor learning" (de Berker et al., 2013).~~

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*4.5. Neural enhancement cost*

An important question is whether there are any side effects associated with enhancing neural function with anodal tDCS. Recently, Brem and colleagues proposed that enhancement through NIBS is a zero-sum proposition (Brem et al., 2014). That is, the induced enhancement of a cognitive or motor function is associated with a cost (Luber, 2014). Although limited, there is some evidence suggesting that using tDCS to enhance a particular cognitive function may result in impairment of other functions (Iuculano and Cohen Kadosh, 2013). One explanation for such side effects is that increasing cortical excitation in one brain area through anodal tDCS may result in inhibition of other brain areas that are part of the same functional network. Support for this view has come from the study of the dynamics of intrinsic networks in the brain (Fox et al., 2005; Wokke et al., 2014). During task performance it has been observed that task relevant networks (task-positive) exhibit increased activity, whereas networks associated with task irrelevant or opposing (task-negative) processes show decreased activity. Strong anti-correlations between task-positive and task-negative networks have been shown to be predictive of cognitive task performance, including working memory (Hampson et al., 2010). ~~Interestingly, anodal tDCS reduced task-~~

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~~related hyperactivity in prefrontal regions in mild cognitive impairment patients producing normalization of abnormal network configurations (Meinzer et al., 2015).~~ This research opens up the exciting possibility of using tDCS to facilitate cognitive and motor functions in older adults by modulating the balance between task-relevant and task-irrelevant networks (Wokke et al., 2014). However, the possibility that enhancing some cognitive or motor abilities in healthy older individuals could be at the expense of other abilities has clear ethical implications and is an important issue in need of systematic evaluation (Hamilton et al., 2011).

*4.6. Limitations*

Even though meta-analytic tests of variability indicated moderate values in the 25 comparison studies, we noted divergent sample sizes (8 – 72 participants) and stimulation parameters: (a) intensity (1 – 2 mA), (b) duration (6 – 37.5 mins), and (c) electrode size (5.3 – 35 $cm^2$). As ~~T~~these stimulation parameters have been shown to influence the efficacy of anodal tDCS (Bastani and Jaberzadeh, 2012)~~.~~ ~~Thus,~~ there is clearly a need for systematically determining the optimal parameters to maximize the beneficial effects of anodal tDCS.

## 5. Conclusions and Future Directions

The findings of this robust meta-analysis indicated that anodal tDCS had significant positive effects on cognitive and motor functions in healthy older adults across a variety of tasks. Although these behavioural effects are promising with respect to ameliorating age-related functional decline, the lack of a complete understanding of the mechanisms by which anodal tDCS produces enhanced cognitive and motor performances is a concern. As noted by de Berker and colleagues, "…there is no theoretical or mechanistic explanation for why depolarizing cells would improve such complex behaviours as perceptual decision-making, mathematical ability, or motor learning" (de Berker et al., 2013).

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Given that the application of anodal tDCS to a specific area appears to cause widespread activation of a number of connected brain regions, then an analysis of the effects of tDCS at the level of neural networks may be profitable (Luft et al., 2014). Combining ~~of~~ neuroimaging with advanced connectivity analysis techniques (e.g., graph theory) ~~will~~ allows the ~~tracking~~ determination of ~~tDCS-induced changes~~ how tDCS-induced changes in localised connectivity patterns affect large-scale brain dynamics.~~to brain networks~~ (Polania et al., 2011). ~~Of particular interest will be how tDCS-induced changes in localised connectivity patterns affect large-scale brain dynamics.~~ For example, ~~S~~stimulating the motor cortex has been shown to increase functional connectivity within that structure (Polania et al., 2012), and increased connectivity within the default mode network and attention network has been reported from stimulation of the DLPFC (Keeser et al., 2011; Pena-Gomez et al., 2012). The application of graph theory to network organisation has also identified the presence of hubs that have a large number of connections and appear essential for brain communication. Luft et al. (2014) suggested that stimulating a hub might maximise the effect of stimulation. This opens the ~~interesting~~ possibility that individualized tDCS protocols can be used to enhance an impaired function (e.g., working memory) by stimulating a particular hub area (e.g., DLPFC) associated with that function. Interestingly, in a recent study anodal tDCS reduced task-related hyperactivity in prefrontal regions in mild cognitive impairment patients producing normalization of abnormal network configurations (Meinzer et al., 2015).

There are, however, a number of methodological issues that need to be resolved before tDCS can be prescribed as a reliable and safe intervention for the restoration of cognitive and motor functions in the elderly. It is likely that this will require the development of cost-effective ways to reduce the variability of tDCS outcomes by providing individualized customized focal stimulation to specific cortical targets.~~Individual MRI scans should be used to reduce the variability of tDCS outcomes because of inherent anatomical differences, and a~~

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~~high definition electrode array to increase the focality of stimulation (Edwards et al., 2013). As neurodegenerative diseases, such as Alzheimer's disease, may be linked with specific disturbances of brain network connectivity, then identification of such abnormalities may allow the development of tDCS protocols to help make progress toward restoring a more 'normal' connectivity pattern.~~

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**Competing Interests**

None

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**Figure Captions**

**Fig. 1. Meta-analysis forest plot of the effects of tDCS on cognitive and motor functions in elderly.** Data derived from a random effects model. Each line and tick mark represents an individual effect size. Black circles are the cognitive studies and white circles are the motor studies.

**Fig. 2. Funnel plot of the comparisons for our random effects model.** The x-axis represents the standardized mean difference (i.e., pooled effect) and the y-axis indicates the standard error associated with each comparison.

**Fig. 3. Best estimate funnel plot with trim and fill values that approximates a symmetrical unbiased distribution.** White circles and white diamond indicate our original 25 comparisons while black circles and black diamond represent imputed comparisons.

**Table 1. Characteristics of each comparison included in the present meta-analysis (studies listed alphabetically)**

| Study | Total N | Mean Age: Years | Gender | Outcome Measure: (Specific Type) |
|---|---|---|---|---|
| Berryhill and Jones (2012) | 25 | 63.7 | N/A | Cognitive: Working memory; memory / working memory |
| Boggio et al. (2010) | 28 | 68.4 | 25 F, 3 M | Cognitive: Risk task; problem solving + decision making |
| Fertonani et al. (2014) | 20 | 66.5 | 10 F, 10 M | Cognitive: Visual picture naming task; language production |
| Flöel et al. (2012) | 20 | 62.1 | 10 F, 10 M | Cognitive: Object-location recall task; memory / working memory |
| Goodwill et al. (2013) | 11 | 63.0 | 5 F, 6 M | Motor: Wrist Extension |
| Goodwill et al. (2015) | 12 | 66.0 | 6 F, 6 M | Motor: Tracking task |
| Hardwick and Celnik (2014) | 22 | 58.0 | 11 F, 11 M | Motor: Reaching task |
| Harty et al. (2014) | 48 | 72.1 | 27 F, 21 M | Cognitive: Repeat No-go trial; problem solving + decision making |
| Heise et al. (2014) | 16 | 73.4 | 7 F, 9 M | Motor: Finger tapping |
| Hoff et al. (2015) | 36 | 66.61 | 16 F, 20 M | Motor: Ball rotation task |
| Holland et al. (2011) | 10 | 69.0 | 7 F, 3 M | Cognitive: Visual picture naming task; language production |
| Hummel et al. (2010) | 10 | 69.0 | 5 F, 5 M | Motor: Jebsen-Taylor Hand Function |
| Jones et al. (2015) | 72 | 64.4 | 49 F, 23 M | Cognitive: Working memory; memory / working memory |

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|---|---|---|---|---|
| Lindenberg et al. (2013) | 20 | 68.2 | 10 F, 10 M | Motor: Finger tapping |
| Manenti et al. (2013) | 32 | 67.9 | 17 F, 15 M | Cognitive: Verbal episodic memory; memory / working memory |
| Meinzer et al. (2013) | 20 | 68.0 | 10 F, 10 M | Cognitive: Semantic Word retrieval; language production |
| Meinzer et al. (2014) | 18 | 68.4 | 9 F, 9 M | Cognitive: Semantic Word retrieval; language production |
| Panouilleres et al. (2015) | 38 | 63.2 | 20 F, 18 M | Motor: Visuomotor adaptation task |
| Parikh and Cole (2014) | 8 | 75.0 | 3 F, 5 M | Motor: Grooved pegboard test |
| Park et al. (2014) | 40 | 69.8 | 27 F, 13 M | Cognitive: Working memory; memory / working memory |
| Ross et al. (2011) | 14 | 65.0 | 7 F, 7 M | Cognitive: Recall task; memory / working memory |
| Sandrini et al. (2014) | 36 | 67.2 | 24 F, 12 M | Cognitive: Recall task; memory / working memory |
| Seo et al. (2011) | 24 | 69.3 | 10 F, 14 M | Cognitive: Working memory; memory / working memory |
| Zhou et al. (2015) | 20 | 63.0 | 9 F, 11 M | Motor: Postural control |
| Zimerman et al. (2013) | 10 | 68.5 | N/A | Motor: Finger tapping |
| | Total $N$ = 610 | $M$ = 67.0<br>$SD$ = 3.7 | | |

Abbreviations. F: female; M: male; N/A: not applicable

**Table 2. tDCS Treatment Protocols**

| Study | Treatment | mA | Electrode Size | Stimulation Site | Stimulation Time (min) | Reference Electrode Site |
|---|---|---|---|---|---|---|
| Berryhill and Jones (2012) | atDCS on L, atDCS on R, sham | 1.5 | 5 × 7 cm | DLPFC | 10* | Ctr cheek |
| Boggio et al. (2010) | atDCS on L + ctDCS on R, ctDCS on L + atDCS on R, sham | 2 | 35 $cm^2$ | DLPFC | 10#test | Ctr DLPFC |
| Fertonani et al. (2014) | atDCS + online, atDCS + offline, sham | 2 | 7 × 5 cm | left DLPFC | 10# test | Ctr shoulder |
| Flöel et al. (2012) | atDCS, sham | 1 | 5 × 7 cm | right temporoparietal | 20# test | Ctr supraorbital |
| Goodwill et al. (2013) | atDCS on non-dominant, atDCS on non-dominant + ctDCS on dominant, sham | 1 | 25 $cm^2$ | M1 | 15# practice | Ctr supraorbital |
| Goodwill et al. (2015) | atDCS on ipsilateral, sham on ipsilateral | 1 | 25 $cm^2$ | ipsilateral M1 | 15# practice | Ctr supraorbital |
| Hardwick and Celnik (2014) | atDCS, sham | 2 | 5 × 5 cm | cerebellum | 15# test | Ips buccinators muscle |

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|---|---|---|---|---|---|---|
| Harty et al. (2014) | atDCS, sham | 1 | 35 $cm^2$ | right DLPFC | 37.5#test | N/A |
| Heise et al. (2014) | atDCS, sham | 1 | 25 $cm^2$ | left M1 | 20* | Ctr supraorbital |
| Hoff et al. (2015) | atDCS, sham | 1 | 7 × 5 cm | right M1 | 20#practice | frontal orbit |
| Holland et al. (2011) | atDCS, sham | 2 | 5 × 7 cm | left IFC | 20#test | Ctr frontopolar cortex |
| Hummel et al. (2010) | atDCS, sham | 1 | 25 $cm^2$ | left M1 | 20* | Ctr supraorbital |
| Jones et al. (2015) | atDCS, sham | 1.5 | 5 × 7 cm | right DLPFC | 10#practice | Ctr cheek |
| Lindenberg et al. (2013) | atDCS on L, atDCS on L + ctDCS on R, sham | 1 | 5 × 7 cm | M1 | 30#test | Ctr supraorbital |
| Manenti et al. (2013) | atDCS on L, atDCS on R, sham | 1.5 | 7 × 5 cm | DLPFC, parietal cortex | 6#test | Ctr supraorbital |
| Meinzer et al. (2013) | atDCS, sham | 1 | 5 × 7 cm | left ventral IFG | 20#test | Ctr supraorbital |
| Meinzer et al. (2014) | atDCS on L, atDCS on L + ctDCS on R, sham | 1 | 5 × 7 cm | left M1 | 30#test | Ctr supraorbital |
| Panouilleres et al. (2015) | atDCS, sham | 2 | 5 × 7 cm | left M1 | 17#test | Ctr supraorbital |
| Parikh and Cole (2014) | atDCS + motor practice, sham + motor practice | 1 | 25 $cm^2$ | left M1 | 20#practice | Ctr supraorbital |

| | | | | | | |
|---|---|---|---|---|---|---|
| Park et al. (2014) | atDCS on L and R + cognitive training, sham + cognitive training | 2 | 5 × 5 cm | DLPFC | 30* | Ctr arm |
| Ross et al. (2011) | atDCS on L, atDCS on R, sham | 1.5 | 5 × 7 cm | ATL | 15#test | Ctr cheek |
| Sandrini et al. (2014) | atDCS + reminder, atDCS + no reminder, sham + reminder | 1.5 | 5 × 7 cm | left DLPFC | 15* | Ctr supraorbital |
| Seo et al. (2011) | atDCS on L, sham | 2 | 5 × 5 cm | left DLPFC | 30* | Ctr arm |
| Zhou et al. (2015) | atDCS, sham | 2 | 35 $cm^2$ | left DLPFC | 20* | Ctr supraorbital |
| Zimerman et al. (2013) | atDCS, sham | 1 | 25 $cm^2$ | contralateral MC | 20#practice | Ctr supraorbital |

Abbreviations. atDCS: anodal transcranial direct current stimulation; ctDCS: cathodal transcranial direct current stimulation; ATL: anterior temporal lobe; CDLPFC: dorsal lateral prefrontal cortex; Ctr: contralateral; IFC: inferior frontal cortex; IFG: inferior frontal gyrus; N/A: not applicable; M1: primary motor cortex; MC: motor cortex; Asterisk (*) indicates anodal stimulation before task performance; Number sign (#) denotes anodal stimulation during task performance (either posttest or task-related practice).

**Table 3. Summary statistics for the 25 comparisons in the meta-analysis.**

| Study | Primary Outcome Measure | Number of Participants per Group: Rx / Control | Standardized Mean Difference | Confidence Interval (95%) | |
|---|---|---|---|---|---|
| Berryhill and Jones (2012) | Improvement during WM task regardless of atDCS site (high edu: Rx vs. low edu: control) | 13 / 12 | 0.83 | 0.01 | 1.65 |
| Boggio et al. (2010) | Total point earned during risk task (atDCS on R + ctDCS on L: Rx vs. sham: control) | 10 / 9 | -1.50 | -2.52 | -0.48 |
| Fertonani et al. (2014) | Verbal reaction time during picture naming task (atDCS online: Rx vs. sham: control) | 20 / 20 | 0.64 | 0.16 | 1.12 |
| Flöel et al. (2012) | Percentage correct response during object-location recall task (atDCS: Rx vs. sham: control) | 20 / 20 | 0.22 | -0.22 | 0.66 |
| Goodwill et al. (2013) | Average tracking error during wrist extension movement (pre atDCS on non-dominant + ctDCS on dominant vs. post) | 11 | 0.67 | 0.02 | 1.33 |

| | | | | | |
|---|---|---|---|---|---|
| Goodwill et al. (2015) | Tracking error with untrained limb (pre atDCS on ipsilateral M1: Rx vs. post) | 12 | 1.71 | 0.82 | 2.60 |
| Hardwick and Celnik (2014) | Error in adaptation phase during reaching movement (atDCS: Rx vs. sham: control) | 11 / 11 | 1.26 | 0.34 | 2.17 |
| Harty et al. (2014) | Error awareness during Repeat No-go trials (atDCS: Rx vs. sham: control) | 48 / 48 | 0.47 | 0.17 | 0.77 |
| Heise et al. (2014) | Average transition time change during alternating index and little finger tapping (atDCS: Rx vs. sham: control) | 16 / 16 | 0.53 | 0.01 | 1.06 |
| Hoff et al. (2015) | Improved number of ball rotation per a minute during ball rotation task (atDCS: Rx vs. sham: control) | 12 / 13 | 0.94 | 0.11 | 1.77 |
| Holland et al. (2011) | Reaction time during picture naming task (atDCS: Rx vs. sham: control) | 10 / 10 | 1.51 | 0.60 | 2.42 |
| Hummel et al. (2010) | Total time during Jebsen-Taylor Hand Function Test (pre atDCS vs. post) | 10 | 0.72 | 0.02 | 1.41 |

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|---|---|---|---|---|---|
| Jones et al. (2015) | Accuracy during WM task (atDCS: Rx vs. sham: control) | 18 / 18 | -0.19 | -0.85 | 0.46 |
| Lindenberg et al. (2013) | Reaction time with right index finger (atDCS on L + ctDCS on R: Rx vs. sham: control) | 20 / 20 | 0.18 | -0.26 | 0.63 |
| Manenti et al. (2013) | RT for general facilitation during long-term episodic memory (atDCS: Rx vs. sham: control) | 32 / 32 | 0.64 | 0.26 | 1.02 |
| Meinzer et al. (2013) | Response time during semantic word retrieval (atDCS: Rx vs. sham: control) | 20 / 20 | 0.18 | -0.26 | 0.62 |
| Meinzer et al. (2014) | Number of errors during semantic word retrieval (atDCS: Rx vs. sham: control) | 18 / 18 | 0.80 | 0.27 | 1.33 |
| Panouilleres et al. (2015) | Movement error during visuomotor adaptation task (atDCS: Rx vs. sham: control) | 13 / 13 | 0.58 | -0.20 | 1.37 |
| Parikh and Cole (2014) | Time to complete the grooved pegboard test (atDCS + motor practice: Rx vs. sham + motor practice: control) | 8 / 8 | -0.50 | -1.24 | 0.23 |

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|---|---|---|---|---|---|
| Park et al. (2014) | Accuracy during WM task (atDCS on L and R: Rx vs. sham: control) | 20 / 20 | 0.53 | -0.10 | 1.16 |
| Ross et al. (2011) | Accuracy during place name recall task (atDCS on L: Rx vs. sham: control) | 14 / 14 | 0.44 | -0.10 | 0.99 |
| Sandrini et al. (2014) | Percentage of word recall (atDCS + reminder: Rx vs. sham + reminder: control) | 12 / 12 | 1.01 | 0.16 | 1.86 |
| Seo et al. (2011) | Accuracy during WM task (atDCS on L and R: Rx vs. sham: control) | 12 / 12 | 0.34 | -0.47 | 1.14 |
| Zhou et al. (2015) | Complexity index during dual task standing (atDCS: Rx vs. sham: control) | 20 / 20 | 0.47 | 0.01 | 0.93 |
| Zimerman et al. (2013) | Slope of improvement during finger-tapping task (atDCS: Rx vs. sham: control) | 10 / 10 | 1.33 | 0.48 | 2.18 |

| **Model** | **Overall Weighted Effect Size** | ***SE*** | **Confidence Level (95%)** | ***Q* Statistic** | $I^2$ | $T^2$ | **Classic Fail-Safe *N*** |
|---|---|---|---|---|---|---|---|
| Random | 0.53 | 0.09 | 0.34 – 0.71 | 55.92 | 57.08% | 0.11 | 448 |

Abbreviations. atDCS: anodal transcranial direct current stimulation; ctDCS: cathodal transcranial direct current stimulation; Rx: treatment; WM: working memory; *SE*: standard error; *Q* statistic: Cochran's heterogeneity statistic; $I^2$: Higgins and Green's heterogeneity statistic; $T^2$: tau-squared heterogeneity statistic.