



Review

Effects of tDCS on motor learning and memory formation: A consensus and critical position paper



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HIGHLIGHTS

- We review investigations of whether tDCS can facilitate motor skill learning and adaptation.
- We identify several caveats in the existing literature and propose solutions for addressing these.
- Open Science efforts will improve standardization, reproducibility and quality of future research.

ABSTRACT

Motor skills are required for activities of daily living. Transcranial direct current stimulation (tDCS) applied in association with motor skill learning has been investigated as a tool for enhancing training effects in health and disease. Here, we review the published literature investigating whether tDCS can facilitate the acquisition, retention or adaptation of motor skills. Work in multiple laboratories is underway to develop a mechanistic understanding of tDCS effects on different forms of learning and to optimize stimulation protocols. Efforts are required to improve reproducibility and standardization. Overall, reproducibility remains to be fully tested, effect sizes with present techniques vary over a wide range, and the basis of observed inter-individual variability in tDCS effects is incompletely understood. It is recommended that future studies explicitly state in the Methods the exploratory (hypothesis-generating) or hypothesis-driven (confirmatory) nature of the experimental designs. General research practices could be improved with prospective pre-registration of hypothesis-based investigations, more emphasis on the detailed description of methods (including all pertinent details to enable future

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modeling of induced current and experimental replication), and use of post-publication open data repositories. A checklist is proposed for reporting tDCS investigations in a way that can improve efforts to assess reproducibility.

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1. Introduction

Noninvasive brain stimulation (NIBS) techniques, most commonly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been used to modulate motor and cognitive functions in human subjects (Pascual-Leone et al., 1994b; Wassermann et al., 1998; Jahanshahi and Rothwell, 2000; Maeda et al., 2000; Gangitano et al., 2002; Butefisch et al., 2004; Marshall et al., 2006; Duque et al., 2007; Brunoni et al., 2012; Perceval et al., 2016) (Fig. 1). TMS-based investigations have included the use of repetitive (primarily 1, 5 or 10 Hz) and patterned (continuous or intermittent theta burst; cTBS or iTBS, respectively) stimulation protocols. Transcranial electrical stimulation (TES) techniques have included direct (tDCS) or alternating current (tACS) (Pollok et al., 2015; Krause et al., 2016), or random noise (tRNS) (Saiote et al., 2013)

stimulation. Since published findings using rTMS, TBS, tACS and tRNS for enhancing motor learning remain particularly sparse (Fig. 1) the primary focus of the review will be on tDCS-based interventions. It has been argued that rTMS and tDCS can either enhance or decrease excitability in targeted cortical regions depending on the parameters of stimulation employed (Chen et al., 1997; Galea et al., 2009; Labruna et al., 2016; Woods et al., 2016) and the underlying intrinsic state of the stimulated brain networks (Silvanto et al., 2008a; Silvanto and Pascual-Leone, 2008; Sandrini et al., 2011; Dayan et al., 2013). Animal and human studies suggest that tDCS modulates the threshold for action potentials (Fritsch et al., 2010), GABAergic function (Fritsch et al., 2010; Stagg and Nitsche, 2011; Bachtiar et al., 2015), and LTP-like mechanisms when paired with a biologically-relevant stimulus. The ability to influence LTP-like mechanisms has been invoked as the rationale for modulating learning behavior. The role

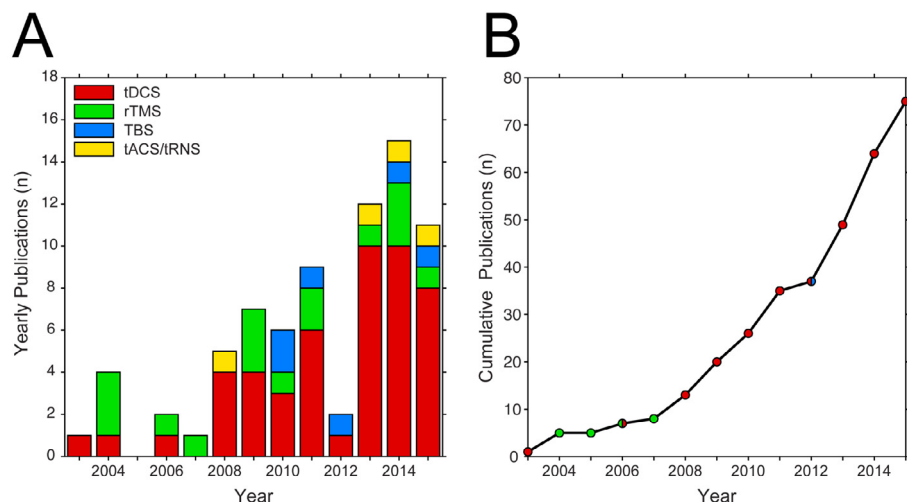


Fig. 1. Publications of studies investigating NIBS-based enhancement of motor learning or memory formation. (A) Yearly publications grouped into categories of different non-invasive brain stimulation techniques between 2003 and 2015. Categories consist of transcranial direct current stimulation (tDCS; red; $n = 49$), repetitive transcranial magnetic stimulation (rTMS; e.g. – 1, 5 or 10 Hz; green; 15), patterned theta-burst stimulation (TBS; e.g. – intermittent or continuous TBS; blue; $n = 6$), or transcranial alternative current or random noise stimulation (tACS/tRNS; yellow; $n = 4$). (B) Cumulative publications by year. Marker color indicates the majority stimulation type used in studies for that year. (tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; TBS = theta-burst stimulation; tACS = transcranial alternating current stimulation; tRNS = transcranial random noise stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the glia in tDCS-mediated effects represents a new area of investigation (Gellner et al., 2016).

tDCS has also been used as a tool to gain insight into possible causal relationships between altered activity in relatively large regions of the brain and particular behaviors (Nitsche et al., 2008). More specifically, tDCS has been used to study effects on, and mechanisms of, motor learning (Nitsche et al., 2003; Antal et al., 2004; Reis et al., 2009; Galea et al., 2011). In a previous consensus document, it was stated that “Improved understanding of the involvement of a brain region in a type of behavior was followed by attempts to modify activity... to secondarily influence performance, learning and memory functions” (Reis et al., 2008). Several recommendations from that paper have been advanced in the literature. For example, many studies have utilized multi-session rather than single-session tDCS application (Hashemirad et al., 2016), greater emphasis has been placed on monitoring long-term effects of tDCS on motor learning (Hashemirad et al., 2016), evidence of dissociation of tDCS effects applied to distinct brain regions on different stages of motor learning (Galea et al., 2011; Reis et al., 2015; Wymbs et al., 2016) has begun to emerge, and mechanisms underlying tDCS effects are starting to be elucidated (Lang et al., 2003; Kuo et al., 2008; Fritsch et al., 2010; Stagg et al., 2011a; Kuo et al., 2013). Below, we summarize results from tDCS studies aiming to improve motor learning in healthy humans without performing a critical review of each individual investigation, discuss new challenges and limitations to be considered, and propose strategies to move forward.

1.1. Motor learning

The acquisition and retention of new motor skills, and adaptation of previously learned ones are fundamental to our daily lives (Debas et al., 2010). Commonly used skills such as typing or playing a musical instrument are acquired and improved through years of repetitive practice (Dayan and Cohen, 2011). Although initially stabilized through consolidation processes (Muellbacher et al., 2002), acquired skills remain adaptive throughout the lifespan as dynamic interactions between intrinsic (e.g. – body morphology, muscle strength, injury, etc.) and extrinsic (e.g. – tools, task constraints) factors require frequent updating of how we interact with changing environments (Wolpert et al., 2011) through reconsolidation processes (Censor et al., 2012). In the laboratory, motor learning is commonly explored using paradigms focusing on the acquisition and retention of new motor skills, or the adaptation of existing ones to environmental disruptions. Motor skill learning is typically achieved with prolonged training, resulting in slow performance gains underpinned by an improved speed-accuracy relationship and/or a reduction in performance variability (Shmuelof et al., 2012). Conversely, motor adaptation is typically achieved over brief training periods, where performance levels are restored to prior maximums following exposure to an environmental perturbation (Shmuelof et al., 2012). Here, we focus on these most commonly studied types of motor learning, as both have been used as the substrate for neuromodulation. However, it should be kept in mind that the categorization of skill learning and adaptation is applied rather broadly and may engage error-dependent, use-dependent, reinforcement, and/or strategic learning to different extents (Krakauer and Mazzoni, 2011) with shared or independent underlying mechanisms.

From a behavioral standpoint, motor skill learning can be deconstructed into several component features that occur over different timespans. Learning is initiated by experience that is accrued over one or more practice or training periods (Dayan and Cohen, 2011). Performance improvements that occur over shorter time periods, such as within a single training session or day, are typically referred to as online learning (Reis et al., 2009). Over

longer periods of time, such as over several hours, days or training sessions, motor memories may transition to a consolidation phase (Walker et al., 2003; Stickgold, 2005; Gais et al., 2007, Marshall and Born, 2007). Behavioral expressions of consolidation may include: (1) a greater resistance to interference caused by other learned skills (i.e. – stability) (Krakauer and Shadmehr, 2006); (2) observed performance improvements at re-test in the absence of additional practice (i.e. – offline gains) (Reis et al., 2009); or (3) reductions in performance decrements experienced with the passage of time (i.e. – retention) (Abe et al., 2011).

Even once acquired motor skills are consolidated and retained as stable, long-term motor memories must maintain some capacity to be flexible and responsive to unpredictable biological or environmental changes that may occur in the future (Sandrini et al., 2015). Each time a given skill is executed, retrieval of these previously consolidated motor memories may initiate a cascade of plasticity mechanisms that enable their composition to be modified in order to maintain skill performance optimization over the long term (Censor et al., 2010; Censor et al., 2014a; Censor et al., 2014b; Censor et al., 2016; Dayan et al., 2016; Wymbs et al., 2016). It has been reported that existing motor memories can be modified through reconsolidation, which may repeat as needed across the lifespan (Sandrini et al., 2013; Censor et al., 2014b; Wymbs et al., 2016).

Measuring motor skill learning is not a trivial task. Most motor skills require the optimization of a speed-accuracy trade-off dependent upon specific task constraints. One approach to estimating learning is to reduce this feature to a single dimension by instructing participants to favor one factor over the other, or employing strict accuracy- or speed-related task requirements. An alternative approach is to use more neutral instructions or employ tasks that allow for natural variation of this interaction across the study population. In this case, the speed-accuracy trade-off is then explicitly modeled in performance or skill learning estimates. Another crucial factor in the experimental study of motor learning is the information participants have access to about the task and their performance. The specific nature and resolution of information available to participants will determine if learning is driven by factors such as sensory feedback error signals, cognitive strategies, or reward maximization. Thus, variants of the same basic task may assess very different learning processes. This may be particularly important for a technique like tDCS (which may exert its effect through the alteration of thresholds for neuronal discharge; Fritsch et al., 2010) as observed effects may be highly dependent on the specific context in which it is applied.

Currently, the most frequently used tasks to investigate motor skill learning in experimental settings are: (1) sequential finger tapping tasks (SFTT; which can include either implicit or explicit sequence structure) (Ghilardi et al., 2009; Nitsche et al., 2010; Song and Cohen, 2014; Reis et al., 2015); and (2) the sequential visual isometric pinch force task (SVIPT) (Reis et al., 2009). In a sense, these tasks are complimentary in that for the SFTT, the main unit of action is rather trivial for a healthy subject to accomplish (i.e. – pressing a keyboard key or button), while the required sequence of actions are typically complex in structure (between 8 and 15 items in length with controls on smaller intra-sequence patterns). Alternatively, the SVIPT requires execution of a precision pinch force action that is more difficult to elicit than a key-press (Waters-Metenier et al., 2014). Thus, there is a greater emphasis placed upon accurate performance of the unit action within an explicit sequence context in the SVIPT than in most variants of SFTTs. A general advantage of these learning tasks is that their complexity can be manipulated in a manner conducive to studying learning over long time periods (i.e. – months and years). Furthermore, competing sequences can be used to investigate consolidation and re-consolidation processes, as well.

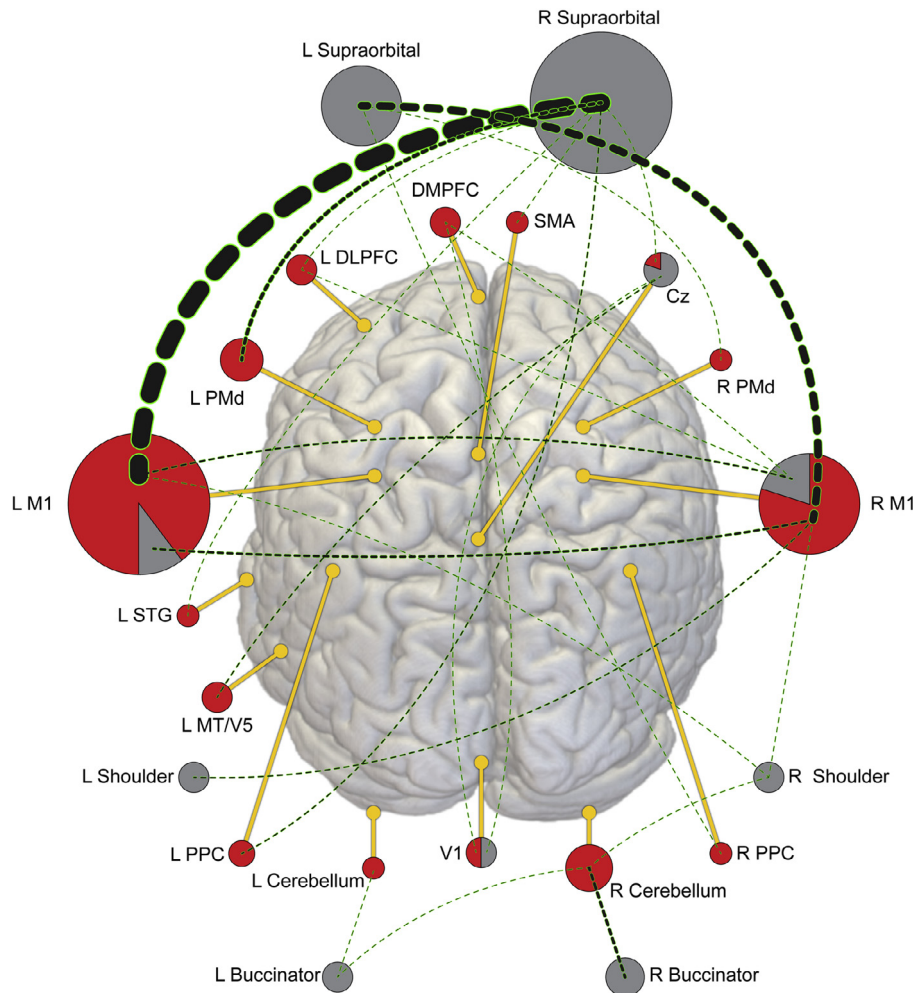


Fig. 2. Proportion of tDCS montages utilized across 84 motor learning experiments (from 53 publications). Circles for each location are proportionally filled with red (anode) and grey (cathode) to represent the relative number of studies the anode or cathode was placed at that location (i.e. – filled red circles were used as anode locations only, grey circles as cathode locations only, red and grey pie charts as both). The diameter of each circle is relative to the proportion of experiments that location was used in. Dashed lines represent montage connections between anode and cathode, with the line weighted relative to the proportion of experiments that particular montage was used in. L = left; R = right; M1 = primary motor Cortex; PMd = dorsal premotor cortex; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; SMA = supplementary motor area; STG = superior temporal gyrus; MT/V5 = middle temporal visual area; PPC = posterior parietal cortex; V1 = primary visual cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Adaptation of highly-learned, target-directed pointing or shooting movements to environment perturbations has been regularly investigated (Orban de Xivry and Shadmehr, 2014). In this case, visual or proprioceptive feedback of generated movements is manipulated to produce a large error between a motor plan and sensory feedback. This error signal elicits an adaptive response that returns performance to pre-perturbation levels (Shadmehr et al., 2010). The applied perturbations can be designed to affect either limb kinematics or dynamics, and typically involve rotating visual feedback representations of the movement (Krakauer et al., 1999) or applying external forces to the moving limb via a robotic manipulandum (Smith et al., 2000), respectively. As these tasks involve basic reaching movements that have been highly learned over a participant's lifetime, performance levels typically return to baseline within a single training session.

Motor skill learning and adaptation are associated with functional and structural changes to a distributed brain network that includes primary motor (M1) and somatosensory (S1), dorsal (PMd) and ventral premotor (PMv), supplementary motor (SMA) and posterior parietal cortex (PPC), as well as the cerebellum and basal ganglia (Pascual-Leone et al., 1994a; Scholz et al., 2009; Landi et al., 2011). Thus, several candidate brain networks are

accessible to tDCS or rTMS for investigating neuromodulatory effects on different features of motor learning. Furthermore, NIBS techniques are crucial for demonstrating that specific networks play an antecedent role in learning, as opposed to functional changes that emerge as a consequence (Diedrichsen and Kornysheva, 2015). To date, the primary region of interest for modulating online learning and retention of skill acquisition has been the contralateral, ipsilateral or bilateral M1 (Fig. 2). In some cases, montages with electrodes positioned over PMd or the cerebellum have also been used, with cerebellum montages primarily used in relation to adaptation learning (Table 1). While tDCS electrodes have been placed overlying specific scalp locations, it should not be assumed that the underlying brain region is independently, specifically or selectively stimulated (Woods et al., 2016). Additionally, tDCS can modulate different stages of learning, best tested over multiple days.

1.2. Online motor performance and skill learning

Investigation of tDCS effects on online motor skill learning, that is performance gains observed during training, has focused primarily on stimulation montages where the anode is applied to a region

Table 1
Investigations of tDCS-based enhancement of motor skill acquisition over a single day of training.

Reference	Anode Locations	Cathode Locations	Intensity (mA)	Anode Current Density (mA/cm ²)	Duration (min)	Stim Application Timing (relative to training)	Sample Size (avg. per group)	Task Type	Cohort	Enhanced Online Learning Effect	Enhanced Offline Learning Effect	Double-blind?
Nitsche et al. (2003)	L M1 L PMd L DLPFC DMPFC	R Supraorbital R Supraorbital R M1 R M1	1	0.03	15	Concurrent	20	Sequence Learning (SFTT)	Adult ^a	YES	N/A	NO
Vines et al. (2008)	R M1 R M1	L Supraorbital L M1	1	0.06	20	Between training blocks	16	Sequence Learning (SFTT)	Adult	YES	N/A	NO
Kuo et al. (2008)	L M1	R Supraorbital	1	0.03	10	Pre-training	20	Sequence Learning (SFTT)	Adult	NO	NO	NO
Tecchio et al. (2010)	R M1	R Shoulder	1	0.03	15	Between training blocks	22	Sequence Learning (SFTT)	Adult	NO	YES	NO
Nitsche et al. (2010)	L PMd	R Supraorbital	1	0.03	15	Post-training	8	Sequence Learning (SFTT)	Adult	NO	YES	NO
Kang and Paik (2011)	L M1 L M1	R Supraorbital R M1	2	0.08	20	Concurrent	11	Sequence Learning (SFTT)	Adult	NO	YES	YES
Stagg et al. (2011b)	L M1	R Supraorbital	1	0.03	10	Pre-training, Concurrent	7.3	Sequence Learning (SFTT), Reaction Time (Simple)	Adult	YES	NO	NO
Kantak et al. (2012)	L M1 L PMd	R Supraorbital R Supraorbital	1	0.13	15	Concurrent	13	Sequence Learning (SFTT)	Adult	YES	YES	NO
Karok and Witney (2013)	L M1 R M1	R M1 L Supraorbital	1.5	0.06	10	Concurrent	20	Sequence Learning (SFTT)	Adult	YES	YES	NO
Cuypers et al. (2013)	L M1	R Supraorbital	1, 1.5	0.04/0.06	20	Concurrent	13	Sequence Learning (SFTT)	Adult	YES	YES	YES
Zimmerman et al. (2013)	L M1	R Supraorbital	1	0.04	20	Concurrent	9.7	Sequence Learning (SFTT)	Aged	YES	YES	YES
Amadi et al. (2015)	L M1	R Supraorbital	1	0.03	20	Pre-training, Concurrent	13	Sequence Learning (SFTT)	Adult	NO	N/A	NO
Wade and Hammond (2015)	L PMd	R Supraorbital	1	0.04	14	Concurrent	10	Sequence Learning (SFTT)/Action Observation	Adult	YES	NO	NO
Ambrus et al. (2016)	L M1	R Supraorbital	1	0.03	13	Concurrent	17	Sequence Learning (SFTT)	Adult	NO	NO	NO
Krause et al. (2016)	L M1	R Supraorbital	1	0.03	10	Between training blocks	13.2	Sequence Learning (SFTT)	Adult	YES	N/A	YES
Antal et al. (2004)	L MT/V5 V1 L M1	Cz Cz R Supraorbital	1	0.03	10	Concurrent	7	Visuomotor Learning (Tracking; Arm)	Adult	YES	N/A	NO
Antal et al. (2008)	L MT/V5 L M1	Cz R Supraorbital	1	0.03	10	Pre-training	13	Visuomotor Learning (Tracking; Arm)	Adult	YES	N/A	NO
Matsuo et al. (2011)	L M1	R Supraorbital	1	0.03	20	Between training blocks	14	Visuomotor Learning (Circle Drawing)	Adult	YES	YES	NO
Shah et al. (2013)	L Cerebellum R M1	L Buccinator L Supraorbital	1	0.13	15	Concurrent	8	Visuomotor Learning (Tracking; Ankle)	Adult	YES	N/A	YES
Foerster et al. (2013)	L M1 L PMd SMA R Cerebellum	R Supraorbital R Supraorbital R Supraorbital R Shoulder	2	0.10	13	Concurrent	18	Visuomotor Learning (Handwriting)	Adult	YES	N/A	YES
Goodwill et al. (2013)	L DLPFC R M1 R M1	R Supraorbital L Supraorbital L M1	1	0.04	15	Pre-training, Concurrent	11	Visuomotor Learning (Tracking; Arm)	Aged ^b	YES	NO	YES

(continued on next page)

Table 1 (continued)

Reference	Anode Locations	Cathode Locations	Intensity (mA)	Anode Current Density (mA/cm ²)	Duration (min)	Stim Application Timing (relative to training)	Sample Size (avg. per group)	Task Type	Cohort	Enhanced Online Learning Effect	Enhanced Offline Learning Effect	Double-blind?
Sriraman et al. (2014)	R M1	L Supraorbital	1	0.13	15	Pre-training, Concurrent	12	Visuomotor Learning (Tracking; Ankle)	Adult	YES	YES	NO
Zhu et al. (2015)	L DLPFC	R Supraorbital	1.5	0.06	20	Concurrent	13.5	Visuomotor Learning (Golf Putting)	Adult	YES	NO	NO
Saiote et al. (2013)	L M1	R Supraorbital	1	0.03	10	Concurrent	10	Visuomotor Learning (Isometric Force)	Adult	NO	N/A	NO
Boggio et al. (2006)	L M1 R M1	R Supraorbital L Supraorbital	1	0.03	20	Between training blocks	6.5	Dexterity (Jebsen-Taylor Hand Function Test)	Adult	YES	N/A	NO
Hummel et al. (2010)	L M1	R Supraorbital	1	0.04	20	Concurrent	10	Dexterity (Jebsen-Taylor Hand Function Test)	Aged	YES	YES	YES
Kidgell et al. (2013)	R M1 R M1	L Supraorbital L M1	1	0.04	13	Between training blocks	11	Dexterity (Purdue Pegboard Task)	Adult	YES	YES	YES
Convento et al. (2014)	R M1 L M1 R PPC L PPC	L Supraorbital R Supraorbital L Supraorbital R Supraorbital	2	0.08	10	Between training blocks	12	Dexterity (Jebsen-Taylor Hand Function Test)	Adult	YES	N/A	YES
Ishikuro et al. (2014)	DMPFC	V1	1	0.03	15	Concurrent	7	Dexterity (Pegboard Task)	Adult	YES	N/A	NO
Bastani and Jaberzadeh (2014)	L M1	R Supraorbital	0.2	0.02	10	Between training blocks	9	Dexterity (Purdue Pegboard Task)	Adult	NO	NO	NO
Pavlova et al. (2014)	L M1 R M1 L PMd R PMd	R Supraorbital L Supraorbital R Supraorbital L Supraorbital	0.5	0.03	10	Concurrent	12	Dexterity (Spring Compression)	Adult	YES	NO	NO
Hoff et al. (2015)	R M1	L Supraorbital	1	0.03	20	Concurrent	12	Dexterity (Ball Rotation Task)	Aged	YES	NO	NO
Galea et al. (2009)	L M1	R Supraorbital	1	0.0400	30	Concurrent	9	Thumb Movement (Opposite)	Adult	YES	N/A	NO
Bortoletto et al. (2015)	R M1	L Supraorbital	1.5	0.0600	20	Concurrent	44	Thumb Movement (Abduction)	Adult	NO	N/A	NO
Floel et al. (2008)	L STG	R Supraorbital	1	0.0286	20	Concurrent	19	Associative Verbal Learning Task	Adult	YES	NO	YES
Tanaka et al. (2009)	L M1	R Supraorbital	2	0.0571	10	Concurrent	10	Reaction Time (Simple)	Adult	YES	N/A	NO
Lindenberg et al. (2013)	L M1 L M1	R M1 R Supraorbital	1	0.0286	30	Concurrent	20	Reaction Time (Choice)	Adult	NO	NO	NO
Zuchowski et al. (2014)	R Cerebellum	R Buccinator	2	0.0571	42.9	Concurrent	10	Conditioning (Eyeblink)	Adult	YES	N/A	YES
Soekadar et al. (2014)	R M1	L Supraorbital	1	0.0417	7	Concurrent	10	Mu-rhythm Modulation BCI	Adult	NO	NO	NO

SFTT = sequential finger tapping tasks; L = left; R = right; M1 = primary motor Cortex; PMd = dorsal premotor cortex; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; SMA = supplementary motor area; STG = superior temporal gyrus; MT/V5 = middle temporal visual area; PPC = posterior parietal cortex; V1 = primary visual cortex.

^a The inclusive age range for study cohorts listed as "Adult" is 18–35 years.

^b The inclusive age range for study cohorts listed as "Aged" is 55–88 years.

of the scalp overlying the M1 contralateral to the practice hand and the cathode placed on the supraorbital (SO; sometimes referred to as “unilateral”) or M1 (sometimes referred to as “bilateral”) region of the opposite hemisphere. Other montages used have included anode placement over the cerebellum, PMd, PPC (specifically area MT/V5), and dorsomedial (DMPFC) or dorsolateral prefrontal cortex (DLPFC) (for more complex tasks) (Table 1). Stimulation parameters across these studies included median intensities of 1 mA (range = 0.2–2 mA), target current densities of 0.04 mA/cm² (0.0167–0.1327 mA/cm²) and durations of 15 min (7–42.9 min). tDCS montage information and stimulation parameters for individual studies can be found in Tables 1–3. More remains to be learned about optimal parameters for eliciting specific behavioral effects. For example, it has been reported that tDCS applied with the same polarity may have opposing motor cortical excitability effects for different stimulation intensities (Batsikadze et al., 2013). However, as different behavioral tasks have been employed in these studies the relationship between neurophysiological changes and resulting behavioral changes (which may vary across task domains) remains uncertain (Lopez-Alonso et al., 2015a).

The effects of tDCS on online sequence learning have been a particular area of interest (Nitsche et al., 2003; Kuo et al., 2008; Vines et al., 2008; Reis et al., 2009; Nitsche et al., 2010; Tecchio et al., 2010; Kang and Paik, 2011; Stagg et al., 2011b; Kantak et al., 2012; Cuyper et al., 2013; Karok and Witney, 2013; Amadi et al., 2015; Reis et al., 2015; Wade and Hammond, 2015; Ambrus et al., 2016). In an initial study, Nitsche et al. (2003) showed that tDCS with the anode over M1 applied concurrently with training improved online implicit learning of a motor sequence, while stimulation applied with the anode over PMd, DMPFC and DLPFC did not (Nitsche et al., 2003). Similar effects have been reported for explicit sequence learning, which may be GABA-mediated (Stagg et al., 2011a; Stagg et al., 2011b; Amadi et al., 2015). Interestingly, stimulation with the anode applied over M1 prior to training appears to decrease subsequent learning rates (Stagg et al., 2011a; Stagg et al., 2011b; Amadi et al., 2015), although whether or not this is mediated through a meta-plastic or homeostatic effect remains unclear (Kuo et al., 2008). Kantak et al. (2012) attempted to further dissociate tDCS-related effects for explicit versus implicit learning. In this study, tDCS was delivered with the anode applied over M1 or PMd based upon previous work regarding the relative roles these areas play in explicit (where PMd is highly critical) versus implicit (where M1 is highly critical) learning. Stimulation delivered with the anode applied over M1 during an implicit motor sequence task resulted in greater online improvements compared with sham, as well as greater retention 24 h later. In contrast, tDCS applied with the anode over PMd showed no online effects relative to sham, but in fact impaired retention at 24 h. Finally, Cantarero et al. (2015) showed that applying tDCS stimulation with the anode over the ipsilateral cerebellum during skill learning (SVIPT task) in young healthy individuals augmented online skill acquisition via a reduction in error rates (Cantarero et al., 2015). This effect appeared to be robust, as it was present in every session for three consecutive days (the duration of the study). Interestingly, there were larger offline declines in the group receiving this type of tDCS, possibly due to a reduction in memory stability or that there was more accumulated knowledge to be lost. Despite this, the overall skill gains remained larger at one week follow up (Cantarero et al., 2015). Other previous work has shown significant online learning enhancement effects of tDCS applied with the anode located over M1 for early training sessions only (Reis et al., 2009).

Online tDCS-mediated effects for visuomotor skill learning (non sequential) for both the upper (Antal et al., 2004; Antal et al., 2008; Matsuo et al., 2011; Foerster et al., 2013; Zhu et al., 2015) and lower (Shah et al., 2013; Sriraman et al., 2014) limb have also been investigated. Earlier work by Antal et al. (2004), showed that stim-

ulation with the anode located over contralateral M1 or area MT/V5 (an extrastriate area that has been implicated in motion processing) applied during learning improved performance in a visuo-motor tracking task when applied concurrently with training (Antal et al., 2004). Application of tDCS on these locations is consistent with known parietofrontal networks involved in these behaviors (Johnen et al., 2015). Using a naturalistic golf-putting task, Zhu et al. (2015) observed that cathodal stimulation applied over left DLPFC indirectly improved putting performance relative to sham stimulation (Zhu et al., 2015). This effect was particularly pronounced when participants were subjected to a multi-tasking constraint where putting and verbal working memory tasks were performed simultaneously. Overall, these results suggest that secondary network effects of stimulation (i.e. – alteration of information processing within the set of interconnected cortical areas) may play a more significant role in real-world environments where different cognitive and learning processes constantly interact.

Online training-induced improvements in non-dominant hand dexterity on the Purdue Pegboard and Jebsen-Taylor tests can be facilitated by tDCS (Kidgell et al., 2013; Bastani and Jaberzadeh, 2014; Convento et al., 2014). Kidgell et al. (2013) found that tDCS applied with the anode over the non-dominant M1 using a unilateral (cathode over contralateral SO) or bilateral (cathode over contralateral M1) montage resulted in similar dexterity improvements (assessed with the Purdue Pegboard Test) in the non-dominant hand compared with sham stimulation. Using the same task, Bastani and Jaberzadeh (2014) investigated the effect of repeated offline application (up to 3) of relatively low intensity (0.2 mA) and duration (10 min) tDCS with the anode applied to the dominant (left) M1 on corticospinal excitability and behavior (Bastani and Jaberzadeh, 2014). Not surprisingly, given our understanding of the need for synchronous application of tDCS with training (Fritsch et al., 2010), no behavioral effects were observed. Of note however, corticospinal excitability was significantly facilitated up to 24 h depending on the interval between subsequent stimulation applications, which had been reported previously (Monte-Silva et al., 2013). This finding suggests that cumulative effects of stimulation may be sensitive to the time between tDCS application and training. It also underscores the lack of a clear relationship between the neurophysiological and the behavioral effects of tDCS—changes in one may not predict or reflect changes in the other. Convento et al. (2014) found that offline tDCS with the anode applied to contralateral non-dominant M1 or ipsilateral PPC resulted in improved dexterity function in the non-dominant hand as well, with PPC and M1 stimulation having specific effects on action planning and execution, respectively (Convento et al., 2014).

A series of studies have looked at online learning and adaptation effects over the life span (Hummel et al., 2010; Goodwill et al., 2013; Zimerman et al., 2013; Hardwick and Celnik, 2014; Hoff et al., 2015). Hummel et al. (2010) investigated motor performance effects of tDCS using a crossover design in a cohort of older adults. When real or sham tDCS with the anode over the contralateral M1 was applied concurrently with performance of the Jebsen-Taylor hand function test (JTT) they observed a significant performance improvement relative to sham that lasted for over 30 min, and that the size of the effect correlated positively with age. The final group performance levels of the cohort were similar to those observed previously in a group of healthy young subjects. A later study by Zimerman et al. (2013) using very similar stimulation parameters looked instead at the effects of tDCS with the anode applied over M1 on sequence learning in aged adults. Again, performance gains were observed when the stimulation was applied to contralateral M1 concurrently with training, with effects remaining significant up to 24 h later.

Goodwill et al. (2013) assessed whether there was a differential effect of contralateral versus bilateral M1 stimulation with

Table 2
Studies investigating tDCS-based enhancement of motor skill learning and retention over multiple days of training.

Reference	Anode Locations	Cathode Locations	Intensity (mA)	Anode Current Density (mA/cm ²)	Duration (min)	Stim Application Timing (relative to training)	Sample Size (avg. per group)	Task Type	Training Period (Days)	Enhanced Online Learning Effect	Enhanced Offline Learning Effect	Double-blind?
Reis et al. (2009)	L M1	R Supraorbital	1	0.04	20	Concurrent	12	Sequence Learning (SVIPT)	5	YES ^a	YES	YES
Schambra et al. (2011)	L M1	R Shoulder	1	0.04	20	Concurrent	15.5	Sequence Learning (SVIPT)	3	N/A ^a	YES	NO
Saucedo Marquez et al. (2013)	R M1	L Shoulder	1	0.04	20	Concurrent	15	Sequence Learning (SFTT)/ Visuomotor Learning (Isometric Pinch Force)	3	Mixed (SFTT only)	YES (Pinch Force)	YES
Waters-Metenier et al. (2014)	R M1	L M1	2	0.06	25	Concurrent	13	Sequence Learning (SFTT)/Motor Synergy Hand Configuration	4	YES ^a	YES	YES
Cantarero et al. (2015)	R Cerebellum	R Buccinator	2	0.08	20	Concurrent	11	Sequence Learning (SVIPT)	3	YES	NO	YES
Reis et al. (2015)	L M1	R Supraorbital	1	0.06	15	Concurrent, Post-training	15.9	Sequence Learning (SVIPT)	3	NO	YES	YES
Naros et al. (2016)	R M1	L SO	1	0.06	20	Pre-training	10	Visuomotor Learning (Tracing)	3	Mixed (Bilateral M1 only)	YES	NO
Ciechanski and Kirton (2016)	R M1	L M1	1	0.04	20	Concurrent	6 ^b	Sequence Learning (SFTT)/ Dexterity (Purdue Pegboard Task & Jebsen Taylor Hand Function Test)	3	YES	NO	YES

SFTT = sequential finger tapping tasks; SVIPT = sequential visual isometric pinch force task; L = left; R = right; M1 = primary motor Cortex.

^a Online effects occurred on Day 1 of training only.

^b All participants in this study were male and female adolescents with a mean age of 14.0 (±3.2) years.

Table 3
Studies investigating tDCS-based enhancement of motor skill adaptation in healthy subjects.

Reference	Anode Locations	Cathode Locations	Intensity (mA)	Anode Current Density (mA/cm ²)	Duration (min)	Stim Application Timing (relative to training)	Sample Size (avg. per group)	Task Type	Cohort	Enhanced Online Learning Effect	Enhanced Offline Learning Effect	Double-blind?
Hunter et al. (2009)	L M1	R Supraorbital	1	0.03	17	Concurrent	14	Adaptation (Force-field)	Adult	NO	NO	NO
Orban de Xivry et al. (2011)	L M1	R Supraorbital	1	0.04	20	Concurrent	8.6	Adaptation (Force-field)	Adult	YES	NO	NO
Galea et al. (2011)	L M1	R Supraorbital	2	0.08	15	Concurrent	9.5	Adaptation (Screen Cursor Rotation)	Adult	YES (Cerebellum)	YES (M1)	YES
Herzfeld et al. (2014)	L M1	R Supraorbital	2	0.08	25	Concurrent	12.75	Adaptation (Force-field)	Adult	YES	NO	YES
Hardwick and Celnik (2014)	R Cerebellum	R Buccinator	2	0.08	15	Concurrent	11	Adaptation (Screen Cursor Rotation)	Aged	YES	NO	NO
Avila et al. (2015)	R Cerebellum	L Buccinator	1.5	0.13	15	Pre-training, Concurrent	10	Adaptation (Saccade)	Adult	YES	NO	YES

L = left; R = right; M1 = primary motor Cortex; PPC = posterior parietal cortex.

concurrent training on an upper limb visuomotor tracking task. Here, the group of older adults displayed similar performance gains and increased learning rates were observed for both contralateral and bilateral M1 stimulation, relative to sham. Furthermore, both montages resulted in the facilitation of corticospinal excitability and a decrease in observed short-interval intracortical inhibition (SICI). Complementary work by Zimerman et al. (2014) reported that cathodal stimulation applied to M1 ipsilateral to the learning hand actually impaired learning. Finally, a recent study by Hardwick and Celnik (2014) compared the effects of tDCS with the anode located over the ipsilateral cerebellum between healthy younger and older individuals during a visuomotor adaptation (screen cursor rotation) task (Hardwick and Celnik, 2014). As expected, the group of older adults showed slower adaptation rates compared to younger adults when receiving sham tDCS. Older participants who received real tDCS, however, displayed faster learning rates that were similar in magnitude to the young group.

In summary, these studies suggest that tDCS applied with the anode over M1 or the cerebellum in a single training session may have broad-ranging effects on sequence learning or skill learning, respectively. Furthermore, this stimulation may be an effective tool in facilitating motor learning and adaptation in older healthy adult populations. More work is needed to evaluate the relative size of the augmentation effect of tDCS in aged versus young adult populations, as well as replicability of the above findings.

1.3. Offline motor skill learning and retention

Several studies, a majority of which have focused on sequence learning, have investigated offline motor skill learning and retention over multiple (typically at least three) days of training (Table 2) (Reis et al., 2009; Schambra et al., 2011; Saucedo Marquez et al., 2013; Waters-Metenier et al., 2014; Cantarero et al., 2015; Reis et al., 2015; Naros et al., 2016). Reis et al. (2009) found that tDCS with the anode located over M1 applied concurrently with training over five consecutive days resulted in significant enhancement of offline skill gains and retention compared with sham in the sequential visual isometric pinch-force task (SVIPT) (Reis et al., 2009). While learning within sessions was not significantly different between the two groups, learning over the five sessions was facilitated in the group receiving real stimulation. Furthermore, this difference remained present when skill was retested three months later, suggesting that these gains had successfully consolidated and remained stable over the long-term. In a follow-up study, effects mediated by consolidation processes were further supported, as offline skill gains induced by real tDCS were found to be dependent upon the passage of time as opposed to requiring overnight sleep (Reis et al., 2015). Concurrent application of tDCS with training also appears crucial for these effects to emerge as stimulation applied post-training only did not induce offline skill gains, consistent with findings in animal models that tDCS alone does not elicit LTP unless it is associated with a second input delivered to the motor cortex (Fritsch et al., 2010). Modifications made to the montage used here (cathode placed over contralateral supraorbital location) to an alternative montage with extracephalic cathode location (ipsilateral shoulder) resulted in reduced effects of stimulation (Schambra et al., 2011). In agreement with modeling predictions, this finding suggests that the montage configuration is the primary determinant of the applied current density distribution, and plays an important role in resulting behavioral effects (de Berker et al., 2013; Bestmann, 2015; Woods et al., 2016). Finally, tDCS applied with the anode located over the cerebellum increased skill learning in this task through the enhancement of online as opposed to offline components. In particular, the larger gains were driven to a greater extent by reductions in error rates as opposed to changes in movement time.

This suggests that specific task constraints may play a role in determining the motor network areas of interest (Cantarero et al., 2015). For example, tDCS with the anode placed over the cerebellum applied concurrently with training for a task with very precise timing requirements enhanced offline improvement, as opposed to online learning as observed in prior studies (Wessel et al., 2016).

Saucedo Marquez et al. (2013) conducted a crossover design that investigated the decomposable elements of the SVIPT task, sequence learning (sequential finger tapping) and visual isometric pinch force (Saucedo Marquez et al., 2013). Following three days of training in each task with concurrent application of sham or real tDCS applied with the anode over M1, they observed that real stimulation improved online sequence learning, but only skill retention for the pinch force task. In addition to task-specific learning effects, these findings suggest that different learning processes interact with tDCS stimulation in non-additive ways as task complexity increases. Waters-Metenier et al. (2014) looked at task-specific effects of bilateral M1 stimulation, in this case on the learning of novel hand movement synergy patterns and finger-tapping sequences (Waters-Metenier et al., 2014). In this case, tDCS improved both synergy and sequence learning with long-term retention of the effects persisting for at least 4 weeks following training. Furthermore, bilateral M1 stimulation effects showed task- and effector-based generalization to untrained hand synergies and finger sequences, and the untrained hand, respectively. This generalization is most likely the result of polarity specific effects on each hemisphere (Naros et al., 2016).

A recent study also suggests that tDCS can influence motor learning in children with rather large effects (Ciechanski and Kirton, 2016). Here, a cohort of 24 school-aged children trained on the Purdue Pegboard Test (PPT) with their left hand over a period of three consecutive days while receiving either real (1 mA with the anode located over M1, or 1 or 2 mA tDCS with the cathode located over right M1), or sham tDCS ($n = 6$ per group). The children were tested on the PPT, JTT and SRTT immediately prior to the commencement of training on Day 1, and then retested immediately following the completion of training on Day 3. A second retest was performed 6 weeks after the completion of training. Interestingly, all three stimulation groups showed a substantial increase in performance following training relative to the sham group (effect sizes in stimulation group ranged from 2.58–3.44). These performance improvements also generalized to the untrained tasks (JTT and SRTT), and remained significant after 6 weeks.

Although preliminary, the results in both aged adults and children suggest that the magnitude of tDCS-related motor learning augmentation, as well as polarity-specific effects of the stimulation may vary across the lifespan. More work is needed to evaluate the replicability of these findings. Finally, it should be noted that in some studies online improvements are not seen, such as in several of the studies conducted over multiple days that emphasize offline effects (see Table 2).

1.4. Adaptation

tDCS-related effects on adaptation have also been studied in young healthy adults (Hunter et al., 2009; Galea et al., 2011; Orban de Xivry et al., 2011; Herzfeld et al., 2014; Avila et al., 2015) (Table 3). Galea et al. (2011) compared the effects of tDCS applied with the anode over the cerebellum versus M1 during concurrent adaptation to 30-degree rotation of visual feedback. Here, cerebellar tDCS resulted in faster initial adaptation to the perturbed task environment, while M1 stimulation showed no effect in this regard. In contrast, a dissociative effect emerged when M1 stimulation resulted in improved retention of the newly acquired visuomotor transformation, as subjects receiving this stimulation adapted faster when the perturbation was reintroduced following a wash-

out period. Interestingly, in a force-field reaching task that assesses adaptation to perturbed upper limb dynamics, tDCS applied with the anode over the cerebellum increased error-dependent learning and facilitated adaptation, while M1 stimulation had no effect (Herzfeld et al., 2014). Furthermore, tDCS applied with the anode over M1 did not improve retention. In addition to the work above, this suggests that M1 and the cerebellum play complementary roles with respect to different learning processes, and that tDCS can be used to influence these processes in a task-dependent manner.

1.5. Neurorehabilitation

A central aim of neurorehabilitation has been to apply principles derived from motor learning research to treatment protocols in the rehabilitation clinic. The underlying premise is that the same factors that enable the nervous system to reorganize when a new motor skill is being learned or an existing one adapted, are important drivers of the nervous system response to a sudden loss of or substantial decrement in existing motor function caused by injury or disease. In the past few years, a series of small proof-of-principle studies have investigated the augmenting effects of tDCS on motor functional gains (Hummel et al., 2005) observed during therapeutic rehabilitation protocols currently used following stroke. While initial work was largely limited to traditional physical or occupational therapy (Kim et al., 2010; Lindenberg et al., 2010), more recently it has been applied during constraint-induced movement or robotic arm training therapy (Bolognini et al., 2011; Hesse et al., 2011; Giacobbe et al., 2013; Triccas et al., 2015; Rocha et al., 2016; Figlewski et al., 2017). In one of the first studies performed, Lindenberg et al. (2010) combined tDCS (anode located over ipsilesional and cathode over contralesional M1) with an occupational and physical therapy regiment over a period of five days. A significant improvement in motor function was observed in the tDCS group relative to sham as assessed by the upper extremity portion of the Fugl-Meyer Assessment and Wolf Motor Function test. In a similar study, Kim et al. (2010) found that ten days of tDCS (cathode located over the contralesional M1 and anode over ipsilesional supraorbital region) combined with occupational therapy resulted in greater improvement in upper limb impairment and activities of daily living measures when compared with sham stimulation. Furthermore, this effect persisted for up to six months and a positive correlation was found between the initial disability and the degree of improvement.

Investigations of the effect of tDCS on constraint-induced movement therapy (CIMT) suggest that bihemispheric (cathode located over contralesional M1 and anode located over ipsilesional M1; Bolognini et al., 2011) or unihemispheric (cathode located over contralesional supraorbital and anode located over ipsilesional M1; Rocha et al., 2016) tDCS applied during this regiment increases corticospinal excitability, reduces transcallosal inhibition from contralesional to ipsilesional M1, and improves upper extremity functional motor gains. In fact, improved outcomes observed with CIMT combined with unihemispheric tDCS have been recently confirmed in a larger population of stroke patients (Figlewski et al., 2017). Findings in relations to robot arm training have been more mixed. In some instances, the application of tDCS has resulted in no significant added benefit (Hesse et al., 2011; Triccas et al., 2015), while in others it resulted in increased corticospinal excitability and improved behavioral kinematics (Giacobbe et al., 2013).

2. Meta-analyses and systematic reviews of the literature

Hashemirad et al. (2016) reviewed the effects of tDCS with the anode placed over M1 on motor sequence learning in healthy adults. 13 of 140 reviewed articles (9.2%) met the eligibility criteria (one or more sessions of unilateral or bilateral tDCS over M1 con-

currently with SFTT or SVIPT task training, and inclusion of a negative control group receiving either sham tDCS plus task training or training only). Following data extraction for each included study, effect-sizes (Cohen's *d*) were determined, and results were grouped according to design characteristics such as montage, and single or multiple training sessions. Across all studies and results, the median effect-size was 0.71 with a total range of -0.02 to 1.70). Thus, while moderate effects were typically observed, the effects across all studies ranged from trivial to large. It should be noted however, that despite attempts by Hashemirad and colleagues to constrain the inclusion criteria in a manner that homogenized the study population included in the analysis, several important methodological factors remained uncontrolled for necessitating grouping.

The authors conclude that the effects of tDCS applied with the anode over M1 on sequential motor learning may depend on learning stages (Dayan and Cohen, 2011), be to some extent task- or montage-specific (Schambra et al., 2011), and that multiple tDCS sessions present advantages over single session applications on both finger tapping and SVIPT tasks. Similarly, the effects on long-term retention might be task specific with different retention effects reported in the finger tapping versus SVIPT tasks (Reis et al., 2009; Saucedo Marquez et al., 2013; Waters-Metenier et al., 2014; Reis et al., 2015). Of note, the relatively small number of studies fitting the inclusion criteria is a clear illustration of the challenges faced when attempting to perform quantitative reviews of tDCS effects on motor learning (Antal et al., 2015; Nitsche et al., 2015). Other meta-analyses focusing on effects of a single tDCS session have reported few significant physiological (Horvath et al., 2015a) and no significant cognitive effects (Horvath et al., 2015b), although questions regarding methodology used in these analyses have been raised (Antal et al., 2015).

A recent meta-analysis was performed on neurorehabilitation studies in stroke where tDCS was applied concurrent with training over multiple sessions (Tedesco Triccas et al., 2016). 8 of 81 reviewed articles (9.9%) met the eligibility criteria and were subjected to further analysis. The results of the meta-analysis revealed trivial to small effects in most cases, ranging from 0.01 to 0.38 (Cohen's *d*). Again, the authors stated that wide variation in experimental factors including heterogeneity upper extremity impairments in patient populations, tDCS stimulation parameters, different types of applied upper extremity therapy regiments, and different end-point measures used to evaluate outcomes present a major challenge to interpreting the findings.

When evaluating findings in systematic reviews and meta-analysis findings, it should be kept in mind that in the absence of systematic critical assessment of the quality of individual studies, and understanding of the biases that they may be prone to, interpretation remains uncertain (Bastian, 2016). A concerted effort by investigators in clinical research to address these issues has culminated in the PRISMA statement (Liberati et al., 2009), which included guidelines and a checklist for best practices (see <http://www.prisma-statement.org/> for more information).

3. Caveats and future considerations

There has been a substantial increase in the number of investigations using tDCS over M1 to influence motor learning since the previous consensus document in 2008 (Reis et al., 2008). Since then, a number of scientific, methodological and social caveats have emerged that deserve closer scrutiny by those interested in using this technique. Many of these caveats are applicable to the broader realm of basic and clinical science, while others are more specific to the use of tDCS.

Scientific caveats include understanding that application of tDCS with one of the electrodes placed over a specific region may not influence that region or may result in behavioral changes

through nonspecific (i.e. – poor spatial targeting or focality) or distant secondary effects on other interconnected cortical areas (Dayan et al., 2013), infrequent use of modeling to guide stimulation montages (de Berker et al., 2016) or overly simplified modeling assumptions that neglect the folding of the cortex and consequences on stimulation effects (i.e. – decreasing the threshold for hyperpolarization of neurons on one side of a gyrus but depolarization on the other). Systematic determination of the optimal timing of stimulation for inducing long-lasting effects, and how this varies across individuals, is another avenue where more research is needed (Martin et al., 2014; Manenti et al., 2016). Indeed, a more coordinated effort where experimental parameters and modeling assumptions are iteratively refined is required (Brunoni et al., 2012; Bestmann, 2015). With the emerging use of more elaborated and higher density electrode montages, modeling work will be beneficial to customizing stimulation montages in a manner that better standardizes current density distributions across subjects (Bestmann, 2015). More tightly controlled dosing, may prove to be an important factor in reducing inter-individual variability of effects and increasing overall effect-sizes (Cancelli et al., 2015). A high-definition tDCS montage (four cathode electrodes surrounding a single anode electrode) has been recently used to study motor adaptation for the first time (Doppelmayr et al., 2016). More elaborate arrays employing up to 82 independent stimulation channels are now commercially available and future research on motor learning is likely to occur (Cancelli et al., 2015).

Neuromodulatory after-effects induced by tDCS on motor cortical excitability appear to be relatively stable over prolonged time courses (Lopez-Alonso et al., 2015b) but the nature and magnitude of these effects are variable across individuals (Nitsche and Paulus, 2001; Hamada et al., 2013; Wiethoff et al., 2014; Nettekoven et al., 2015). One study explored whether the magnitude of response to different NIBS paradigms (including tDCS) predicted motor learning gains in subsequent behavioral training sessions where no stimulation was received, but no significant relationship was observed (Lopez-Alonso et al., 2015a). One possible source of inter-individual variability highlighted by several investigators has been dosing. Modeling work suggests that a priori knowledge of an individual's scalp, skull and brain anatomy obtained from MRI scans and neuronavigation devices can be used to optimize electrode array design and placement, and stimulation intensity with the aim of minimizing differences in current density distribution across subject populations (Datta et al., 2012; Truong et al., 2013; Cancelli et al., 2015; Parazzini et al., 2015; Saturnino et al., 2015). Another source of inter-individual variability for both excitability and behavioral changes may be the brain state-dependent nature of these effects, meaning that the history of endogenous activity of a brain region may be crucial to the effects of stimulation (Silvanto et al., 2008a) and consequent activation of homeostatic and non-homeostatic metaplasticity mechanisms (Amadi et al., 2015; Muller-Dahlhaus and Ziemann, 2015). More complete investigation of these proposed factors represents an important hurdle for increasing the effectiveness of stimulation protocols. Incorporating knowledge of negative findings (Horvath et al., 2015b), which are currently under-reported due to publication bias (Shiozawa et al., 2014; Mancuso et al., 2016; Vannorsdall et al., 2016) is an important scientific caveat that must be addressed in order to facilitate future research progress.

Motor learning is a rather complex process in itself, with different forms (i.e. – use-dependent, error-based, reinforcement, strategic learning) and likely different underlying neural substrates. Many of the tasks employed to determine the effects of tDCS on learning either have several variants or include different forms of learning. These circumstances limit the information that can be drawn from the effects of tDCS on those tasks. For instance, it is

possible that tDCS changes learning because it improves knowledge of the dynamics of the task at hand, or because it improves the strategic approach to that task. Depending on the specific task variant or learning strategies employed by a given individual, tDCS applied to one region may or may not influence task learning. Therefore, a better understanding of motor learning processes, and the tasks used to assess them, will be critical to determine whether NIBS can or cannot manipulate behaviors that are potentially impactful to daily life. Similarly, the issue of generalization is of clear relevance to rehabilitation and remains a major challenge. In addition to investigating the efficacy of tDCS in enhancing specific quantitative features of skill learning, improving our understanding of the effects of tDCS on the generalization of learning across different skills will also be an important scientific endeavor (Waters-Metenier et al., 2014).

Maturation of the tDCS field since the previous consensus document (Reis et al., 2008) and the focus on enhancing human motor learning have overall raised the bar of methodological and design requirements in tDCS studies. Present problems in the field include: (1) insufficient use of double-blind designs (see above, for example only 25 out of the 60 published studies on tDCS effects on motor learning in healthy adults reviewed here utilized double-blind designs) and positive controls (stimulation of other cortical regions); (2) insufficient differentiation and understanding of design and claims when carrying out exploratory (hypothesis-generating) versus confirmatory (hypothesis-driven) research (with the former suggesting trends and providing data for prospective power analysis, and the latter, strengthened by preregistration, allowing one to draw conclusions for particular effects; Finkel et al., 2015); (3) insufficient efforts to reduce false-positive rates in studies geared to provide proof of principle data to power subsequent clinical trials; (4) scarcity of pre-registration agreements including the hypothesis statement, experimental design, power analysis and data processing pipeline for confirmatory, hypothesis-driven research studies (see for example <https://blogs.royalsociety.org/publishing/registered-reports/>); (5) insufficient prepublication and sharing of materials (Lauer et al., 2015; Morey et al., 2016), particularly in relation to negative results; (6) insufficient post-publication repositories of data (see for example Campbell et al., 2002) and in general (Nosek et al., 2015) to allow additional analyses; (7) seldom use of experimental designs with replications built in (Cohen et al., 1997; Nosek et al., 2015; Anderson et al., 2016; Gilbert et al., 2016); and (8) use of appropriate sample size based on prospective power analysis for studies claimed to be hypothesis-driven (Landis et al., 2012). A transition towards Bayesian adaptive experimental designs may help in this endeavor, as well.

Another important discussion surrounding tDCS research is related to how reproducibility of reported effects should be evaluated. A special mention should be made to the expression of the general reproducibility problem in science (Collins and Tabak, 2014) to tDCS studies of motor learning. There are three levels of reproducibility: methods, results and inferential (Goodman et al., 2016). Methodological reproducibility requires “provision of enough detail about study procedures and data so the same procedures could . . . be exactly repeated”. More importantly, in order to evaluate methodological reproducibility, there should be “. . . agreement about the level of detail needed in the description of the measurement process, . . . the degree of processing of the raw data . . .” and the “completeness of the analytic reporting”. Such agreement does not exist at the present time in the tDCS field. Development of standards of consistency in methodological reporting would represent an important step forward. To start addressing this problem, we propose a checklist with reporting standards for tDCS studies (Table 4). Reproducibility of results refers to replicability once the tools for methodological replication are fully provided and

Table 4
Reporting checklist for tDCS studies. Modified with permission from (Chipchase et al., 2012).

Experimental Design Factors:			
Controls used	<input type="checkbox"/> None	<input type="checkbox"/> Sham	<input type="checkbox"/> Active
Blinding used	<input type="checkbox"/> None	<input type="checkbox"/> Single	<input type="checkbox"/> Double
Hypothesis statement	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If Hypothesis-based:			
Power-analysis statement	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Pre-registration	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Exploratory-based	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Sample-size estimation (i.e. – power analysis)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Participant Factors:			
	Reported?	Controlled?	
Number of subjects	<input type="checkbox"/>	<input type="checkbox"/>	
Age of subjects	<input type="checkbox"/>	<input type="checkbox"/>	
Gender of subjects	<input type="checkbox"/>	<input type="checkbox"/>	
Handedness of subjects	<input type="checkbox"/>	<input type="checkbox"/>	
Subjects prescribed medication	<input type="checkbox"/>	<input type="checkbox"/>	
Use of CNS active drugs (e.g. anti-convulsants)	<input type="checkbox"/>	<input type="checkbox"/>	
Neuropsychological evaluation	<input type="checkbox"/>	<input type="checkbox"/>	
Any medical conditions	<input type="checkbox"/>	<input type="checkbox"/>	
History of specific repetitive motor activity	<input type="checkbox"/>	<input type="checkbox"/>	
<u>Years of Education completed</u>	<input type="checkbox"/>	<input type="checkbox"/>	
Stimulation Factors:			
	Reported?	Controlled?	
Scalp position of tDCS electrodes	<input type="checkbox"/>	<input type="checkbox"/>	
MRI-based localization of tDCS electrodes	<input type="checkbox"/>	<input type="checkbox"/>	
Electrode type (size and geometry)	<input type="checkbox"/>	<input type="checkbox"/>	
Current density of applied stimulation	<input type="checkbox"/>	<input type="checkbox"/>	
Type of stimulator used (e.g. brand)	<input type="checkbox"/>	<input type="checkbox"/>	
Stimulation intensity	<input type="checkbox"/>	<input type="checkbox"/>	
Stimulation ramp time	<input type="checkbox"/>	<input type="checkbox"/>	
Stimulation duration	<input type="checkbox"/>	<input type="checkbox"/>	
Number of Sessions	<input type="checkbox"/>	<input type="checkbox"/>	
If Multiple Sessions:			
Time interval between sessions	<input type="checkbox"/>	<input type="checkbox"/>	
Subject attention (level of arousal) during testing	<input type="checkbox"/>	<input type="checkbox"/>	
Subject activities during stimulation	<input type="checkbox"/>	<input type="checkbox"/>	
<u>tDCS-induced sensations</u> (i.e. – itching, pain, heat, pinching, burning)	<input type="checkbox"/>	<input type="checkbox"/>	
Analysis & Statistics factors:			
Effect-size(s) reported	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Raw data uploaded to publicly accessible data repository	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Analyzed data uploaded to publicly accessible data repository	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Full analysis protocol including custom scripts uploaded to publicly accessible data repository	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

agreed upon. Importantly, replicability is best tested for stochastic data using Bayesian paradigms of accumulating evidence more than binary criteria of successful or unsuccessful replication (Goodman et al., 2016). Clearly, “statistical significance by itself tells very little about whether one study has “replicated” the results of another”. Finally, inferential reproducibility refers to “drawing of qualitatively similar conclusions from either an independent replication of a study or a reanalysis of the original study”. Please, see Goodman and Ioannidis for a full discussion (Goodman et al., 2016).

A unique concern that has emerged with transcranial electrical stimulation techniques, is that the simplicity, low-cost nature of, and public access to the technology has led to the emergence of a popular do-it-yourself movement where individuals participate in self-experimentation without oversight. Such data is not part of well-designed experimental protocols (Fitz and Reiner, 2015; Riggall et al., 2015; Wexler, 2016). An additional worrisome aspect

of this movement is that no studies have investigated the long-term effects associated with chronic tDCS use (for further reading please see the International Federation for Clinical Neurophysiology position statement on do-it-yourself TES applications at <http://bit.ly/1TLZqSH>).

As nuanced understanding of the possibilities and limitations of a given experimental technique matures, critical evaluation amongst experts leads to the progressive refinement of standards associated with its use. Used alone, tDCS has quite a large parameter space. On one hand, this flexibility is one of the main features supporting the general use of tDCS across several disciplines and purposes. However, this has resulted in substantial variation in stimulation parameters across individual studies and laboratories, and has presented a challenge to the convergence upon field-wide standards. Furthermore, when used in conjunction with different behavioral tasks (or even variants of a single task) this dimensionality substantially grows. This makes the careful acquisition and availability of metadata covering all aspects of how a study is carried out crucial to identifying which factors play significant roles in determining tDCS effects, and in which proportions. With such metadata in hand, an interesting approach to addressing the issue of heterogeneity of stimulation protocols and tasks could be to directly account for the heterogeneity within statistical models through inclusion of stimulation parameters, electrode montages and task variants as covariates. In this way, meta-analyses could serve as important tools for identifying which experimental factors predominantly explain significant levels of inter- or intra-individual variability (Lopez-Alonso et al., 2015b; Horvath et al., 2016).

4. Conclusions

The 2008 consensus concluded: “In summary, the scarce studies performed so far point to the encouraging conclusion that noninvasive brain stimulation can contribute to the understanding of mechanisms underlying motor learning and motor memory formation and raise the exciting hypothesis that this increased understanding could in the future result in the development of new strategies to enhance specific stages of learning and memory processing in healthy humans and in patients with brain lesions”. A growing body of work continues to support the use of noninvasive brain stimulation as a tool for neuromodulation of motor learning. However, the larger literature has raised numerous and substantial caveats to be considered that are not trivial to resolve. More work is required to understand mechanisms underlying the effects of tDCS and substrates of inter-individual variability, to optimize dosing and methodological designs. Additionally, improved understanding of motor skill learning processes and standardization of tasks will help reduce inter-study variability, as the scientific approach to manipulating motor learning will become more precise. Emerging efforts for improving transparency, full reporting of data and all analyses carried out, replication and data sharing through repositories will be important to answering these questions.

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