REVISITING THE EFFECTIVENESS OF TRANSCRANIAL DIRECT CURRENT BRAIN STIMULATION FOR COGNITION: EVIDENCE, CHALLENGES, AND OPEN QUESTIONS

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REVISITING THE EFFECTIVENESS OF TRANSCRANIAL DIRECT CURRENT BRAIN STIMULATION FOR COGNITION: EVIDENCE, CHALLENGES, AND OPEN QUESTIONS

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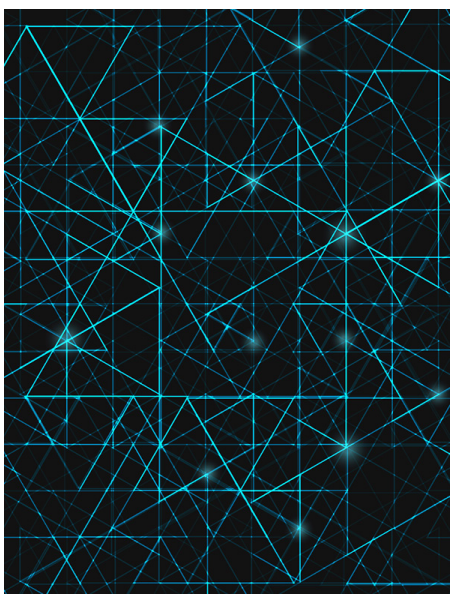

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The aim of this Frontiers Research Topic is to assemble a collection of papers from experts in the field of non-invasive brain stimulation that will discuss (1) the strength of the evidence regarding the potential of tDCS to modulate different aspects of cognition; (2) methodological caveats associated with the technique that may account for the variability in the reported findings; and (3) a set of challenges and future directions for the use of tDCS that can determine its potential as a reliable method for cognitive rehabilitation, maintenance, or enhancement.

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EDITORIAL
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Editorial: Revisiting the Effectiveness of Transcranial Direct Current Brain Stimulation for Cognition: Evidence, Challenges, and Open Questions

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Keywords: transcranial direct current stimulation (tDCS), neuroenhancement (NE), noninvasive brain stimulation, cognition and emotion, neurorehabilitation

Editorial on the Research Topic

Revisiting the Effectiveness of Transcranial Direct Current Brain Stimulation for Cognition: Evidence, Challenges, and Open Questions

Over the past 15 years, there has been an explosion of interest in the use of noninvasive brain stimulation approaches to study the brain. Some studies have suggested that transcranial Direct Current Stimulation (tDCS) in particular can elicit positive effects on performance for many aspects of cognition, including working memory, attention, executive function, language, and numerical competence. A growing literature further indicates that tDCS can provide potentially long-lasting benefits for patient rehabilitation, ameliorating wide-ranging conditions such as aphasia, pain, major depression, tinnitus, and migraine, among others.

It is well-accepted that tDCS is a well-tolerated, noninvasive technique that involves the application of low levels of direct current (1–2 mA, 10–30 min) through electrodes placed on the scalp to alter the neural activity of underlying neural populations. It is often assumed that during and immediately after application, cortical excitability increases under the anode electrode because of neuron soma depolarization, whereas cortical excitability decreases under the cathode electrode because of neuron soma hyperpolarization (Purpura and McMurtry, 1965; Nitsche and Paulus, 2000, 2001)—however, both the outcomes and mechanisms of tDCS are more complex (Giordano et al., 2017; Jamil et al., 2017; Kronberg et al., 2017). Long-term effects of tDCS have been linked to neuroplasticity following LTP-like changes in synaptic strength between stimulated neurons involved in task performance (Reato et al., 2010; Rahman et al., 2015). An advantage of the procedure relative to other brain stimulation techniques is its reliable sham manipulation: active tDCS is silent, does not induce muscle twitches, and it is not immediately distinguishable from sham stimulation, thus allowing for double blinded studies (but see Giordano et al., 2017). Critically, the existing availability of devices that can administer tDCS, its ease of use, and its excellent safety profile underscore the potential of tDCS as a tool for improving cognitive performance in healthy populations, stabilizing cognition in those who are at high risk for cognitive decline, and providing adjuvant therapy for those in need of cognitive rehabilitation.

Nevertheless, despite these recent advances in the use of the procedure, the precise neurobiological mechanisms underlying tDCS effects in humans remain insufficiently understood. Tempering the enthusiasm for this methodology, a number of recent quantitative reviews of both neurophysiological and cognitive studies using tDCS have raised questions regarding

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its effectiveness to induce reliable neuroplastic changes that measurably affect cognition in neurotypical or patient populations (Horvath et al., 2014, 2015a,b). Additional concerns pertain to the replicability of the findings reported in the existing literature and the specification of the precise conditions under which positive tDCS effects can be obtained (Mancuso et al., 2016). Overall, there is a great deal of variability in the robustness of tDCS-linked cognitive outcomes that may be largely attributed to small and heterogeneous sample sizes, the scarcity of data on dose-response effects, and substantial methodological diversity across laboratories. These limitations are exacerbated by the aforementioned lack of understanding of the precise mechanistic effects of a given tDCS protocol on the brain over short- and long-timeframes and in the context of particular tasks.

As researchers using tDCS, we are acutely aware of the limitations in interpretation and application imposed by these gaps in knowledge about the procedure and we are highly motivated to fill them. To satisfy this goal, this Frontiers Research Topic brings together 11 articles from leading experts in the field of non-invasive brain stimulation that aim to address several of the above-mentioned questions associated with tDCS, as well as examine the strength of the evidence regarding the potential of tDCS to modulate different aspects of cognition.

The resulting collection of articles is divided into two clusters centered around (a) methodological issues and perspectives and (b) the influence of individual and group differences in guiding tDCS effects. The first part of the E-book begins with a review by Esmaeilpour et al. of the outcomes of human trials using tDCS in psychiatric populations that helps situate the current literature regarding effectiveness of experimental designs and tDCS stimulation protocols. Harty et al. provide a strong rationale for use of mediation and moderation analyses when examining interactions between tDCS interventions, neural dynamics, and behavior. In turn, Minarik et al. focus on the importance of appropriate sample sizes to ensure replicability of tDCS findings, while highlighting the likelihood of overestimating effect sizes based on the published literature to date. Two additional papers in this section examine the effects of current polarity, intensity, and stimulation site for tDCS effects. Karuza et al. examine the consequences of parametric variations in current polarity and stimulation intensity for a cognitive control task, whereas Weinberger et al. review how interactions among task demands, tDCS polarity, and stimulation site can measurably enhance flexible thinking.

The second group of papers takes a sharp look at several individual and group differences factors that can determine the strength of tDCS effects, consideration of which is required to advance the interpretability of tDCS research. Wiegand et al. point out the essential role of genetically-determined variations in neural activity in predicting tDCS outcomes, which is particularly notable in studies of executive function. Likewise, Hsu et al. show that baseline differences in working memory performance interact with task difficulty and other state-dependent individual differences factors to determine responsiveness to tDCS. Rosen et al. similarly show that individual level of expertise determines whether anodal tDCS will enhance or impede performance in a jazz improvisation task. The last three papers highlight the importance of such individual and group differences factors for tDCS outcomes in clinical settings. Two empirical papers, one by McConathey et al. and a second by Norise et al., demonstrate how baseline measures of patient severity and task specificity can determine the efficacy of tDCS for the treatment of aphasia. Lastly, Mervis et al. review the extent of anodal or cathodal tDCS-guided improvements for different aspects of cognition in schizophrenia.

We are pleased with the breadth of topics covered in this collection and the issues addressed. Yet it is clear that each article raises a series of new questions in need of answers that will require much future research. For this goal to be achieved, it is critical to develop appropriate statistical methods and power analyses that will allow sufficient consideration of complex interactions among an extensive set of factors shown to drastically influence tDCS outcomes. Additionally, substantial work on the neurobiological mechanisms associated with tDCS effects in the brain is acutely needed. We hope this compilation will serve as a starting point for these investigations by framing the challenges and future directions for the use of tDCS that can determine its potential as a reliable method for cognitive rehabilitation, maintenance, or enhancement.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Notes on Human Trials of Transcranial Direct Current Stimulation between 1960 and 1998

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Background: Transcranial direct current stimulation (tDCS) is investigated to modulate neuronal function including cognitive neuroscience and neuropsychiatric therapies. While cases of human stimulation with rudimentary batteries date back more than 200 years, clinical trials with current controlled stimulation were published intermittently since the 1960s. The modern era of tDCS only started after 1998.

Objectives: To review methods and outcomes of tDCS studies from old literature (between 1960 and 1998) with intention of providing new insight for ongoing tDCS trials and development of tDCS protocols especially for the purpose of treatment.

Methods: Articles were identified through a search in PubMed and through the reference list from its selected articles. We included only non-invasive human studies that provided controlled direct current and were written in English, French, Spanish or Portuguese before the year of 1998, the date in which modern stimulation paradigms were implemented.

Results: Fifteen articles met our criteria. The majority were small-randomized controlled clinical trials that enrolled a mean of approximately 26 subjects (Phase II studies). Most of the studies (around 83%) assessed the role of tDCS in the treatment of psychiatric conditions, in which the main outcomes were measured by means of behavioral scales and clinical observation, but the diagnostic precision and the quality of outcome monitoring, including adverse events, were deficient by modern standards. Compared to modern tDCS dose, the stimulation intensities used (0.1–1 mA) were lower, however as the electrodes were typically smaller (e.g., 1.26 cm^2), the average electrode current density (0.2 mA/cm^2) was approximately 4× higher. The number of sessions ranged from one to 120 (median 14). Notably, the stimulation session durations of several minutes to 11 h (median 4.5 h) could markedly exceed modern tDCS protocols. Twelve studies out of 15 showed positive results. Only mild side effects were reported, with headache and skin alterations the most common.

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Conclusion: Most of the studies identified were for psychiatric indications, especially in patients with depression and/or schizophrenia and majority indicated some positive results. Variability in outcome is noted across trials and within trials across subjects, but overall results were reported as encouraging, and consistent with modern efforts, given some responders and mild side effects. The significant difference with modern dose, low current with smaller electrode size and interestingly much longer stimulation duration may worth considering.

Keywords: tDCS, electric stimulation therapy, human, brain, review

INTRODUCTION

Transcranial direct current stimulation (tDCS) consists of applying a weak direct current on the scalp, a portion of which crosses the skull (Datta et al., 2009) and induces cortical changes (Fregni and Pascual-Leone, 2007; Nitsche et al., 2008). The investigation of the application of electricity over the brain dates back to at least 200 years, when Giovanni Aldini (Zaghi et al., 2010) recommended galvanism for patients with deafness, amaurosis and "insanity", reporting good results with this technique especially when used in patients with "melancholia". Aldini also used tDCS in patients with symptoms of personality disorders and supposedly reported complete rehabilitation following transcranial administration of electric current (Parent, 2004).

These earliest studies used rudimentary batteries and so were constant voltage, where the resulting current depends on a variable body resistance. Over the 20th century, direct voltage continued to be used but most testing involved pulsed stimulation, starting with basic devices where a mechanical circuit that intermittently connected and broke the circuit between the battery and the subject and evolving to modern current control circuits including Cranial Electrotherapy Stimulation and its variants (Guleyupoglu et al., 2013). Interest in direct current stimulation (or tDCS) resurged with the studies of Priori et al. (1998) and Nitsche and Paulus (2000) that demonstrated weak direct current could change cortical response to Transcranial Magnetic Stimulation, thereby indicating that tDCS could change cortical "excitability". Testing for clinical and cognitive modification soon followed (Fregni et al., 2005, 2006). Developments and challenges in tDCS research, including applications in the treatment of neuro-psychiatrics disease since 1998 have been reviewed in detailed elsewhere (Brunoni et al., 2012).

This historical note aims to explore earlier data on human trial using current controlled stimulation (tDCS) before 1998 with the goal of informing ongoing understanding and development of tDCS protocols. As expected, we found variability in the quality of trial design, data collection and reporting in these earlier studies. Nonetheless, many clinical findings are broadly consistent with modern efforts, including some encouraging results but also variability across subjects. We also describe a significant difference in dose with lower current, smaller electrodes and much longer durations (up to 11 h) than used in modern tDCS.

METHODS

Literature Search

For our searching methodology, we included articles that: (a) investigated the clinical effects of transcranial direct current stimulation; (b) were published before 1998; (c) human studies; (d) written in English, Spanish, Portuguese or French; (e) controlled current for stimulation. We also excluded articles if they were reviews or meta-analysis, as well as studies that involved invasive procedures or other methods of electrical stimulation.

To identify relevant studies, we searched PubMed using the keywords (*brain polarization*), (*transcranial direct current stimulation*) and (*electric stimulation therapy*) along with (*brain*). We also searched the reference list of all selected articles to identify other relevant articles that we might have missed during the primary PubMed search. Initially, AP and PS conducted the search but, if there were any unresolved issue, FF was consulted. Most of the articles were not available online; therefore they were retrieved at *Francis A. Countway Library of Medicine* (Harvard, Cambridge, MA, USA).

The data was collected using a semi-structured form for each study. The following variables were extracted: (a) title; (b) year of publication; (c) Journal; (d) number of participants in the study; (e) their pre-existing condition; (f) medications; (g) intensity of the applied current; (h) duration of each session; (i) number of sessions; (j) total duration of stimulation; (k) position of the electrodes; (l) electrode size; (m) the strategy of stimulation; (n) clinical effects; (o) side effects; (p) trial design; (q) conclusion; and (r) main outcome. Some of these data were shown in **Table 1**. Because we only found 15 articles fulfilling the inclusion criteria, and included articles had with incomplete and variable reporting details, it was not prudent to conduct quantitative analysis.

Terminology

For the purpose of this study we combine typical terminology used in modern tDCS with literature with conventions in classic literature. tDCS always requires a positive (anode) and negative (cathode) electrode on the body. The term "active" indicates the electrode which is considered by the investigator to exert behavioral effects, presumably by modulating cortex under the electrodes, while "return" electrode indicate the counter polarity electrode which is presumed to have no or less consequential effect. The anode electrode is presumed to

generate an excitatory influence, while the cathode a local inhibitory influence. This concept pervades historical to modern tDCS design, though modern neurophysiology, imaging and computational modeling suggest that how and which brain regions are modulated by tDCS is much more complex. One electrode must always be on the head. In modern literature, an electrode below the head is "extra-cephalic" and typically placed on the forearm. In older literature, "scalp-positive" or "scalp-negative" is used to indicate the use of an extra-cephalic electrode, typically placed on the hand or foot with the anode or cathode, respectively, on the head. For example, "scalp-positive" is comparable to "active anode electrode with extra-cephalic return". For all the limitations in this terminology, here we respect nomenclature as used in the original reports. Electrode dimensions are assumed to refer to contact area between the electrolyte (sponge) and skin.

RESULTS

Figure 1 displays the diagram of search strategy and its results. **Table 1** indicates the final selected studies. Given these 15 articles, the oldest where current was controlled was written in 1964. The majority of articles were small studies with number of patients varying from 1 to 107 (mean, 26 subjects). Approximately half of the studies (8 out of 15) were randomized controlled trials, but there were also two single blind and five open the studies. Most of the studies involved patients with psychiatric disorders, mainly major depression and schizophrenia (**Figure 2B**). Only four studies were performed using exclusively healthy subjects. Eight out of 15 studies were performed in United Kingdom and United States (**Figure 2B**). Positive results were obtained in most of the analyzed studies (**Table 1**).

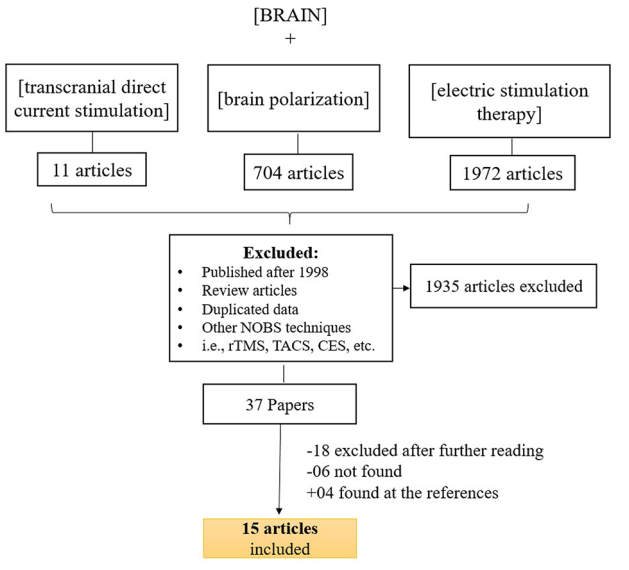

FIGURE 1 | Search strategy for inclusion, exclusion criteria of this study. To identify relevant studies, we searched PubMed using the keywords (*brain stimulation*), (*transcranial direct current stimulation*) ad (*electric stimulation therapy*) along with (*brain*).

tDCS Parameters

The intensity of electric current varied between studies. The median of most commonly used intensity was 0.33 mA for each anode; typically ranging from 0.1 mA (Redfearn et al., 1964) to 0.5 mA (Nias and Shapiro, 1974) for each anode. However, Lippold and Redfearn (1964) applied 3 mA in one single patient. The most common electrode montage was: active electrode(s) above eyebrow and reference electrode in extra-cephalic position (e.g., leg, hand; **Figure 2A**). The active electrodes were most commonly placed in the frontal—especially supraorbital—but also in occipital areas of the scalp and vertex. Apart from the leg and arm, other locations for the return electrode were also used such as the mastoid bone or collarbone. Historically, the approach of applying a stimulation over orbital fissures originated from two other failed trials conducted by Lippold and Redfearn (1964) and trial and error in electrode placement, current intensity and stimulation duration. They found that largest modification in mood and alertness would be produced when anode is placed over an orbital fissure and cathode at an extra-cephalic location (e.g., leg, thigh or arm). The essential differences between the two failed trials and the successful one was location of electrodes, lower applied current with longer duration of stimulation (Lippold and Redfearn, 1964) which was used in most of studies on depression afterwards.

Only 8 out of 15 studies specified the precise dimensions of the electrodes; in those ones the smallest active electrode was of 0.1 cm^2 and the smallest reference electrode was of 0.2 cm^2. The reference electrode area was often larger than the active ones, from approximately 30% (Lifshitz and Harper, 1968) to 50% bigger (Baker, 1970), but in some cases was the same (Elbert et al., 1981a). The use of a larger return electrode compared to active electrode is in line with modern conventions (Woods et al., 2016), though even the larger active and return electrodes are smaller than used in modern tDCS.

Most of studies employed several sessions of stimulation, with a median of 14 sessions. The quantity of session varied from one single to 120 sessions. The median of the total duration of stimulation was 30 h. Redfearn et al. (1964) conducted the longest study, with 960 h as the total time of stimulation.

The mean duration of session was 4.5 h (4 h and 30 min) with a maximum of 11 h (Redfearn et al., 1964) of electrical stimulation. Due to the long duration of stimulation in several studies, the devices were portable and patients were able to move around the hospital or go home (Lippold and Redfearn, 1964; Redfearn et al., 1964; Ramsay and Schlagenhauf, 1966; Baker, 1970). The regimen of sessions varied across articles—daily sessions or several days interval between sessions. In average, stimulation protocols consisted of applying 0.33 mA for 6 h per session that was continued up to 14 days.

In most included studies, stimulation apparatus was made of low voltage dry batteries in a pack with a potentiometer manually adjusted to produce a constant current. In a later study (Elbert et al., 1981b), an optocoupled system driven by the analog output provided constant current which had a ramp up period of 6 s to increase current from 0 mA to 0.25 mA. In all the studies, electrodes were metallic, either pure silver or silver chloride disks covered with saline soaked

TABLE 1 | tDCS studies published between 1960 and 1998.

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration of stimulation	Electrode	Findings	Side effects
Lippold et al. (1964), UK	32	Depression/ Schizophrenia	Uncontrolled double-blind	Anodes over each eyebrows and cathode over right knee	0.1 to 3 mA*	0.5 to 5** h (duration of stimulation varied in subjects based on their condition and improvement).	1.26 cm^2 Chloride silver discs covered with saline-soaked gauze	In scalp-positive polarization patients became more alert and more involved with the environment; in scalp-negative polarization quietness and withdrawal was seen. They have often found an effect at 0.25 mA for each anode whereas there had repeatedly been no effect at 0.15 mA scalp positive stimulation***.	Tremor during scalp-positive, nausea, sleepiness
Costain et al. (1964), UK	24	Depression	Controlled double-blind, crossover	Anodes over each eyebrows and cathode over one knee	0.25 for each anode % current was started from 0.1 for each eyebrow and gradually increased	8 h per day for 12 days	1.26 cm^2 Silver discs covered with saline-soaked gauze	Improvement of anxiety, agitation and somatic symptoms.	Faint, blue flashes, skin sensitivity, mild headaches
Redfearn et al. (1964),UK	29	Refractory depression	Open label	Anodes over each eyebrows and cathode over one knee	0.1 to 0.25 for each anode	0.5 to 11** (duration for each person was based on side effects), 5 times a week for 6 months.	1.26 cm^2 Chlorided silver discs covered with saline-soaked gauze	13 cases showed clinical improvement that lasted only 1–2 days. It has been suggested that a dosage of 0.4 mA in each lead for period on 8 h per day was more effective in many patients.	Mild headache, skin sensitivity
Ramsay et al. (1966), USA	20	Depression	Open label	Anodes over each eyebrows and cathode over one knee	0.15 to 0.3 for each anode	4 to 6** h per day. Total stimulation time varies.	–	14 definitely improved, 4 equivocal improved, 2 did not improve.	Few side effects reported (does not mention which)
Herjanic et al. (1967)	20	Depression/ Schizophrenia	Uncontrolled open label	-	0.1 to 0.5	–	–	All patients improved their depressive symptoms.	None reported
Lifshitz and Harper (1968), USA	5	Schizophrenia	Controlled double-blind crossover	Anodes over eyebrows and cathodes over homolateral thighs.	0.33 for each channel of stimulation	6 h per day for two weeks only on week days followed by two week rest period.	Pure silver electrodes covered by surgical gauze soaked with normal saline. Anode = 1 × 2.5 cm and cathode = 2 × 4 cm	No significant effects either for scalp positive or scalp negative stimulation.	Skin irritation was fairly marked for 3 patients. Skin lesion consisted of erythema, papules and pustules which principally appeared under negative electrode.

(Continued)

TABLE 1 | Continued

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration of stimulation	Electrode	Findings	Side effects
Sheffield et al. (1968), Australia	6	Healthy	Controlled double blind	Anodes over eyebrows and cathode over one leg	0.25 for each lead % current started from 0.03 mA and gradually increased in 90 minutes	3 h, each person was stimulated twice (positive and negative) in different days.	Chlorided silver discs covered with saline soaked lint pads. Anode= 0.5 inch diameter, cathode= 0.75 inch diameter.	Happier and more alert with scalp-positive polarization but results don't show significant changes in mood in subjects compared to control.	Moody and sleepy with scalp-negative polarization
Carney et al. (1970), Australia	119	Depression	Open label, uncontrolled	–	0.25	–	–	Improvement in excited behavior and mood; relapse on stopping treatment and improvement on recommencing.	None reported
Arfai et al. (1970), USA	19	Depression	Controlled double blind clinical trial	Anodes over eyebrows and cathodes over thighs	0.25 for each independent channel	8 h/day during 6 days each week (totally 12 applications)	Chlorided silver discs	No significant effects.	None reported
Hall et al. (1970), USA	18	Healthy	Controlled double-blind	Anodes over each eyebrows and cathode over knee	0.15 and 0.3 for each lead	2 h, each person was stimulated 3 times (scalp positive, scalp negative and sham) in different days.	Metallic mesh electrodes. Skin was rubbed by alcohol and local anesthetic was used.	No significant effect.	None reported
Baker et al. (1970), Rhodesia	107	Depression	Random group of patients treated with brain polarization.	Anodes over each eyebrows and cathode over upper arm or forearm	0.4 for each lead % current started with 0.2 mA and gradually reached 0.4 in half an hour	5 h** per day for 6 to 8 sessions.	Silver plates covered with lint soaked in saline and gel was used for skin Anode= 10 cm^2 and cathode= 20 cm^2.	84% reported sustained improvement. Anxiety was not relieved.	Skin sensitivity, tachycardia and migraine
Nias and Shapiro (1974), UK	1	Schizophrenia with depression	Double blind controlled clinical trial	Anodes over each eyebrows and two cathodes attached to right knee	0.4 for each lead	3–4 h per day for 14–120 sessions.	–	Improvement with negative and worsening with positive stimulation	Tingling on the forehead.
	1	Alcoholism with depression			0.5 for each lead			Improvement with positive stimulation	
Elbert et al. (1981a), Germany	48	Healthy	Single-blinded	Anode over vertex and cathodes over earlobes	0.26	1 h in a session (half of task was done in cathodal and the rest was done in anodal stimulation).	1.5 cm diameter Silver discs	Vertex positive current tends to develop faster reaction times and higher skin conductance responses than vertex-negative currents.	None reported

(Continued)

TABLE 1 | Continued

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration of stimulation	Electrode	Findings	Side effects
Elbert et al. (1981b), Germany	32	Healthy	Single-blinded	Anode over vertex and cathode over collarbone to both sides which were linked	0.25	1 h in a session (half of it was anodal and the other half was cathodal stimulation).	1.5 cm diameter Silver discs	Results suggest that subjects reacted after a shorter interval when negative pole was applied compared to positive stimulation.	None reported
Korsakov (1989), Russia	48	Schizophrenia	Open label clinical trial	Anode over occipital cortex OR anode over frontal CORTEX cathode = mastoid	0.05 to 0.2	–	Silver cup electrodes	Cathodal on occipital cortex increased visual sensitivity (discrimination of the brightness of a pair of light flashes), anodal decreased.	None reported

= 3 mA was used just for one person and it was applied while putting local anesthetic under electrode. **= Device was portable and patients could go about their normal hospital business and returning to the lab at pre-arranged times. *= They had two other failed trials before the present study. The essential difference between this trial and two others were electrodes placed over eyebrows, currents were lower and they were passed for much longer time.*

gauze or lint. Electrode contact and current was checked in pre-arranged times especially in studies with longer duration of stimulation.

Clinical and Side Effects

Twelve studies reported positive results. With the exception of Arfai et al. (1970), all other studies with melancholic or depressive patients showed some positive results using tDCS. The most common side effects reported were headache and skin sensitivity. Half of the studies did not mention any side effects.

DISCUSSION

Across the limited historical use of tDCS between 1960 and 1998, there was little standardization of electrical parameters of stimuli. The lack of methodological rigidity on some parameters such as reference electrode position, number of sessions, the target area, current strength, electrode size and duration of each session might explain some contradictory findings between the studies. There was often limited information on subject inclusion and recruitment, in one case, not even the place of origin of the study was apparent (Herjanic and Moss-Herjanic, 1967).

The values of the current intensity used in the selected historical tDCS trials, from 0.1 mA to 0.5 mA (median 0.33 mA) for each anode(s), were overall lower than those ones used contemporarily in clinical trials, which vary between 1–3 mA (median 2 mA; Bikson et al., 2016). Potentially maximum current was constrained by hardware limitations (battery voltage), especially with the need for portability (small size and weight) and long duration operation (hours per session). Smaller electrodes were used in historical tDCS trials, but this may have marginal or no effects in resulting brain current density, compared to the linear loss with reduced current intensity (Miranda et al., 2009). Nitsche et al. (2008) demonstrated that, when stimulations durations are limited to several minutes, an intensity of 0.6 mA is required to induce a significant change in average cortical excitability detectable by TMS. Total stimulation charge was determined by the current and time. The neurophysiological consequence of lower-intensity stimulation but with longer period (e.g., hours) is unknown. In most cases included here the total charge applied (e.g., 4.5 h times 0.25 mA for each anode = 8100 mC[1]) was above that is used in modern tDCS (e.g., 2 mA for 20 min = 2400 mC). The side effect profile of the included historical trials, to the extent they were monitored and reported was mild.

Most of the studies placed the active electrode above the eyebrow and the reference one on the leg, or on the arm. This position of the active electrode approximates locations used in modern human trials. However, the "reference" electrode is now more commonly placed on the head; extra-cephalic "return" electrodes are sometimes used. Modern computational modeling studies suggest the use of extra-cephalic electrode produce significant current flow in deep and mid-brain structures (DaSilva et al., 2011). Indeed, Redfearn et al. (1964) suggested

[1]Mili-Coulomb (mC).

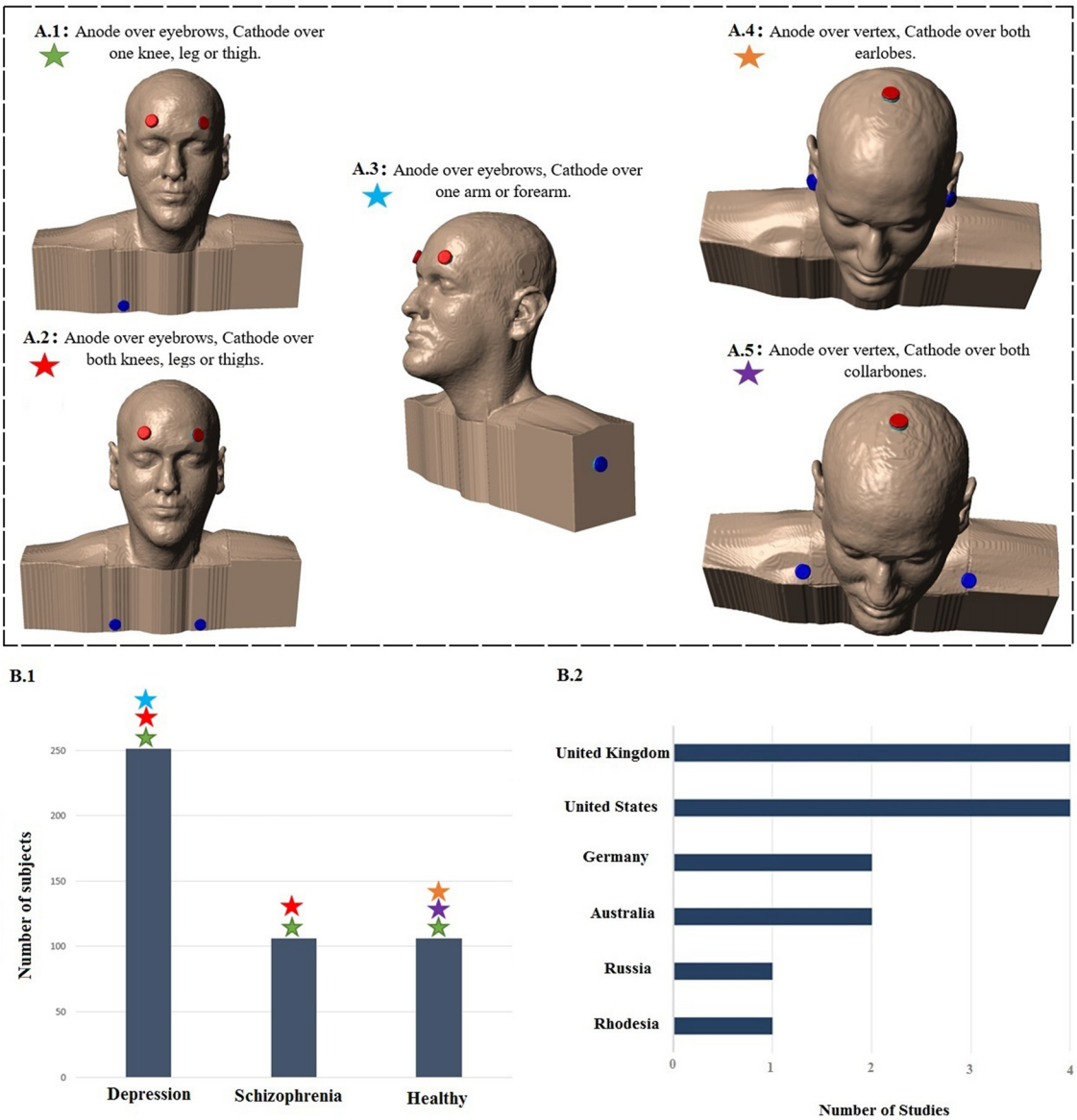

FIGURE 2 | Summary of study parameters on human trials using transcranial direct current stimulation (tDCS) in old literature (from 1960 to 1998). Models of commonly used montages of tDCS in early studies **(A)**; red: anode electrode(s), blue: cathode electrode(s). Total number of subjects in each group of patients participating in studies using aforementioned montages **(B.1)** and leading countries conducting tDCS studies in early stage with number of published articles **(B.2)**.

that highest current density in extra-cephalic stimulation could be in brainstem and supported it by evidence of respiratory depression caused by applying 3 mA cathodal stimulation in a normal subject.

Historical tDCS trials employed from 1 to 120 sessions with a median of 14 sessions, and a median of 4.5 h (20 min to 11 h) of electrical stimulation per session, resulting in a total duration of the trial with a median of 30 h (150 min to 960 h). Currently, it is known that stimulation duration of 20–30 min is more than enough to induce cortical excitability chances and consequently clinical improvements rather than hours of stimulation that would compromise patient's compliance in clinical daily practice (imagine a patient using tDCS for hours at home).

The Use of Outcomes

The Hamilton Depression Rating Scale—HDRS (Hamilton, 1960), recognized as the gold standard in modern depression trials, although contemporary to the majority of early tDCS reviewed was not adopted. Rather early tDCS studies favored clinical outcomes and depression self-rating scales, more subjective and of difficult comparability. Only one study used the HDRS (Arfai et al., 1970). Other more objective measures used

in depression trials were: laboratory changes (norepinephrine, serotonin, beta-endorphin and cholinesterase) and cardiac frequency. In the other conditions addressed, also subjective and objective outcomes assessment was conducted. Among the validated outcomes, the Benton Visual Retention Test (Benton, 1946) was used to evaluate the improvement in short-term memory in alcoholic patients. Tests of reaction to light stimuli were performed within a schizophrenic group of patients. Other studies took into account laboratory changes in hormone levels, self-report scales and several clinical outcomes such as remission of symptoms, improvement in terms of re-hospitalization and/or further treatment and medical evaluation.

Trial Design

The majority of the retrieved articles consisted of double blind controlled clinical trials, which is considered as the "gold standard" for intervention studies. On the other hand, some of them were inadequately reported, therefore making difficult to assess their quality. In a few of these studies, the blinding status was not clearly defined especially in those allocating patients with major depression. In fact, without an appropriate blinding, the results might be biased by a decrease of the placebo effect, as well as an increase of the number of false-positive results and over-estimate of the magnitude of an association. Another aspect to take into account is the high electrical density used that might have precluded blinding process. In most historical trials, the number of subjects was relativity small (indicating cautious interpretation of the results), this remains the case in modern tDCS pilot trials on new indications.

Adverse Effects

It is difficult to draw a reliable evaluation of the side effects from these works as the majority of articles did not post how many healthy subjects or patients were affected, and when multiple intensities were used did not correlate adverse events with intensity. There were no reports of subjects needing to terminate a session or receive medical care for injury. In contemporary tDCS trials, the most common side effects using standard protocols and montages—all transitory—are a mild tingling followed by itching and headache (Brunoni et al., 2011). Autonomic reactions are considered unlikely according to recent systematic review (Schestatsky et al., 2013). Historical studies lacked systematic questionnaire searching for adverse events, which might underestimate detection of occurrence.

Synopsis

In conclusion, we found 15 studies with semi-systematic approaches before the year of 1998, considered the time point of contemporary tDCS. For dosage, the use of multi-hour stimulation session, albeit with modestly reduced current intensity is a significant deviation from modern protocols. The use of supra-orbital active electrode(s) with an extra-cephalic return is another feature in these older studies, though rarely used in modern tDCS.

It is difficult to draw firm meta-conclusions from the analysis of the 15-included studies. This is due to lack of information regarding patient's diagnosis and stimulation parameters as well as varied scientific rigor in design study. The most common type of patients addressed was from the psychiatric field. The occurrence of unusual adverse events i.e., papules, pustules and faint, might be related to longer duration of stimuli and higher density but also other conditions apart from the stimulation itself, such as stimulus-induced anxiety and unrelated events in patients.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

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OPINION
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Transcranial Electrical Stimulation and Behavioral Change: The Intermediary Influence of the Brain

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Keywords: transcranial electrical stimulation, trancranial direct current stimulation, behavior, neurophysiology, mediation analysis, moderation analysis

INTRODUCTION

Numerous studies have shown that transcranial electrical stimulation (tES) can modulate a wide-range of behavioral processes (Coffman et al., 2014; Harty et al., 2014; Sarkar et al., 2014; Pasqualotto, 2016), and ameliorate deficits in several neuropsychiatric disorders (for reviews see Kekic et al., 2016; Lefaucheur et al., 2017). These promising outcomes, in conjunction with the fact that the approach is safe and inexpensive, have generated enthusiasm for its viability as both an investigative and neuroenhancement tool. However, concerns about the variability and reproducibility of tES effects have constrained progression with its application (Jacobson et al., 2012; Berlim et al., 2013; Horvath et al., 2015). Many factors may contribute to the variability and poor reproducibility of findings. Some of these have already been discussed elsewhere such as insufficient statistical power, methodological differences across studies, experimenter error, inadequate sensitivity and test-retest reliability of the outcome measures (Horvath et al., 2015; Open Science Collaboration, 2015). However, one factor that we believe has received insufficient consideration to date concerns the extent to which the assumptions relating to the targeted brain region are supported (Bikson and Rahman, 2013; Miniussi et al., 2013; Plewnia et al., 2015; Harty et al., 2017). In the present article, we highlight the importance of accounting for states and traits of the neurophysiological milieu when assessing the effects of interventions such as tES on behavior. We present hypothetical scenarios relating to the use of transcranial direct current stimulation (tDCS), but the discussed logic equally applies to other electrical and magnetic stimulation techniques. We additionally propose that mediation and moderation analyses constitute valuable and elegant statistical approaches for assessing the dynamic interaction between these interventions, the brain, and behavior.

A FUNDAMENTAL ASSUMPTION OF tDCS RESEARCH

The primary objective of most tDCS studies is to establish an association between the application of weak electric currents to specified locations on the scalp and changes in a behavioral index of interest. An implicit assumption of this approach is that the electric currents modulate neural activity in the regions beneath the scalp locations and accordingly affect behaviors supported by these neural regions. A corollary of this assumption has been that the efficacy of tDCS for modulating behavior has typically been evaluated by assessing the direct effect of tDCS (Active vs. Sham) on the behavior of interest (**Figure 1A**, top panel). A limitation of this approach is that it disregards the fact that the impact of tDCS on behavioral outcomes will inevitably depend on how the neurophysiological milieu of each individual responds to the tDCS. This is a particularly pertinent consideration given the growing literature demonstrating how various states and traits of the neurophysiological milieu can influence the impact of tDCS on behavior

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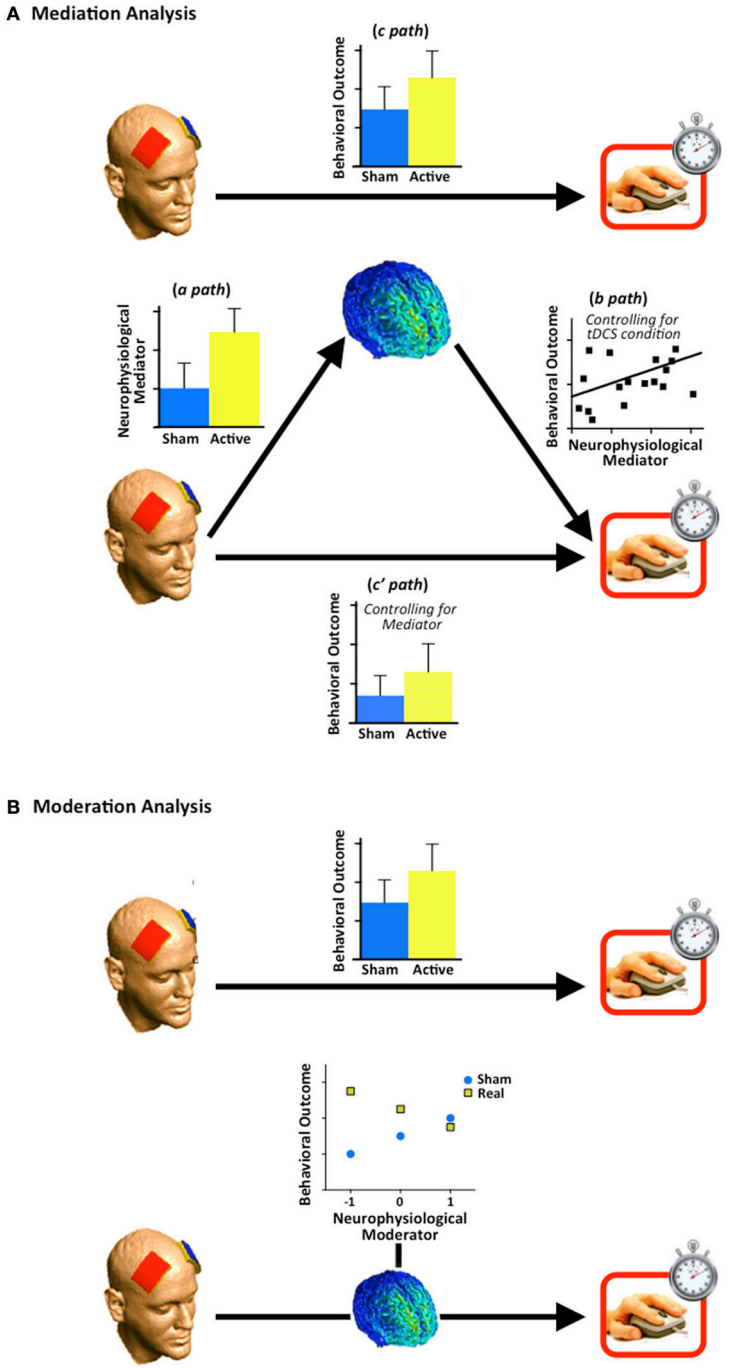

FIGURE 1 | Schematics for mediation and moderation analyses. (A) Upper panel: A linear regression examining the relationship between transcranial direct current stimulation (tDCS; Active vs. Sham) and the behavioral outcome measure (*c path*). One can proceed to the analyses in the lower panel regardless of whether a significant relationship is observed here. Lower panel: The effect of tDCS condition on the neurophysiological index is evaluated with a linear regression (*a path*). The relationship between the neurophysiological index and the outcome variable is evaluated with another linear regression, which also includes the tDCS condition as a predictor (*b path*). The effect of tDCS condition on the outcome variable is re-evaluated using a linear regression that also includes the neurophysiological mediator as a predictor (*c' path*) The bar chart for the *c' path* represents the adjusted means when the impact of the neurophysiological mediator is controlled for. Finally, the mediation hypothesis is evaluated through one of the three approaches outlined in the main text; **(B)** Upper panel: A linear regression examining the relationship between tDCS condition and the behavioral outcome measure (*c path*). Lower panel: In accordance with standard convention for moderation analyses (Aiken and West, 1991), the estimated value of the outcome variable for each condition is reported at the mean, one standard deviation below the mean and one standard deviation above the mean, of the proposed moderating variable. This example shows a significant moderation effect: the impact of the tDCS condition on the behavioral outcome changes according to the value of the neurophysiological index (i.e., the moderator). Note that the heatmap shown for the neurophysiological index in both **(A,B)** is for illustrative purposes only, and does not reflect neural activity obtained from a neurophysiological assay.

(Krause and Cohen Kadosh, 2014; Li et al., 2015). Accordingly, both tDCS *and the neurophysiological milieu* should be regarded as critical antecedents to tDCS-related behavioral effects. Given the pivotal role of the neurophysiological milieu in determining tDCS-related behavior outcomes, we propose that relevant neurophysiological measures should be acquired and accounted for more routinely when examining the efficacy of tDCS for modulating a given behavior. We furthermore advance that the mediating and moderating roles of the neurophysiological milieu can be efficiently evaluated using mediation and moderation analyses (Hayes, 2009).

CONCEPTUAL OVERVIEW OF MEDIATION AND MODERATION ANALYSES

Mediation Analysis

Mediation analysis is a form of regression that can be used to simultaneously evaluate the direct effect of tDCS on behavior and the indirect effect of stimulation on behavior through the brain. In the simplest version of this statistical model, the tDCS condition (e.g., Active vs. Sham) is the independent variable, an implicated brain index constitutes the mediating variable, and the behavioral index of interest constitutes the outcome variable (**Figure 1A**).

First, we determine whether there is a significant difference in the behavioral index for each tDCS condition (called *c path),* as indexed by simple linear regression. This relationship represents the direct effect of stimulation on behavior, and the majority of tDCS studies to date have focused solely on this bivariate relationship. Second, we investigate whether there is a significant difference in the brain index for each tDCS condition (called *a path)*. A significant relationship here implies that the implicated brain index was significantly modulated by tDCS. Next, we evaluate whether the brain index (mediating variable) is a significant predictor of the behavioral index (*b path*) when tDCS condition is also included in the model (called *c' path*).

Finally, the mediation hypothesis is evaluated. The three most common approaches for determining whether there is a mediation effect are the following: (1) establish that the regression coefficients for the *a path* and the *b path* are both significant different from zero (test of joint significance; Kenny et al., 1998); (2) use bootstrapping with replacement to derive a distribution of the product of the *a path* and *b path* regression coefficients, and confirm that the 95% confidence intervals of the distribution do not overlap zero (Hayes, 2009; Mackinnon and Fairchild, 2009); or (3) determine that the product of the regression coefficients from the *a path* and *b path* is significantly different from zero when evaluated using the Sobel test (for details, see Sobel, 1986). If a mediation effect is established, it can be claimed that the proposed mediating brain index mediates the relationship between tDCS condition and behavior.

To underscore the value of measuring theoretically implicated neural indices and including them in mediation analyses, we provide the following simplified hypothetical research scenario. Let us assume that we are interested in determining the effect of tDCS applied to the dorsolateral prefrontal cortex (dlPFC) on working memory, which is assumed to rely on the dlPFC (Brunoni and Vanderhasselt, 2014). The prevailing approach to determine an effect in this context would be to examine the effect of tDCS (Active vs. Sham) on working memory performance using some form of a bivariate analysis. This analysis may or may not reveal a tDCS-related change in working memory performance. The lack of a behavioral change will likely leave us pondering several different possibilities about why no effect was observed. For example, we might wonder whether or not we succeeded to stimulate the targeted brain region. And, if not, was this attributable to one of the many parameters of the tDCS protocol (e.g., intensity or duration of the stimulation, size or location or the electrodes) being unsuitable? We might also have doubts regarding our assumption about the involvement of the targeted region to begin with. We might question whether our potential to pick up on a main effect was hampered by variability in the flow and distribution of the electric current across subjects, or by one of the many other inter-individual differences that are known to affect responsiveness to tDCS (e.g., Krause and Cohen Kadosh, 2014; Li et al., 2015). Similarly, we might contemplate whether different individuals within the study sample could have employed different cognitive strategies, and in turn different brain regions, to carry out the task. Variation in strategy use is a particularly pertinent consideration when appraising the effects of tDCS on behavior as we know that the currents involved in tDCS will not elicit neural firing. Rather, they only modulate the likelihood of firing within populations of neurons that are already naturally engaged by ongoing activity. Therefore, any tDCS-related effects on behavior are critically contingent on subjects' intrinsic recruitment of the target brain region to perform the task. We are thus left with several different questions that cannot be resolved when behavioral indices are our only outcome measure.

In contrast, by quantifying the response of the dlPFC to tDCS with an appropriate neurophysiological assay (e.g., pre- to post-change in blood-oxygen level-dependent (BOLD) response), and including this in a mediation analysis we can gain insights to inform many of these questions. For instance, the assumption about the role of the dlPFC in working memory, the assumption that the employed tDCS protocol is successfully modulating this area, and the extent to which this is common across subjects can all be verified. It is important to underscore that an initial significant direct effect (*c path*) is not a critical requisite for advancing with a mediation analysis (Hayes, 2009). For instance, we may not observe a direct effect of tDCS on working memory, but by pursuing with the mediation analysis we may find that tDCS was associated with an increase in activity in the dlPFC (*a path*) and this change in activity was in turn associated with an improvement in working memory (*b path*). If we substantiate the mediation hypothesis through one of the aforementioned approaches, we can formally infer that the tDCS-related change in dlPFC activity mediated the tDCS-related change in working memory. This hypothetical example serves to demonstrate how it is imperative to be cautious about drawing conclusions about the efficacy of tDCS for modulating behavior with the prevailing bivariate analyses. This point is particularly relevant when only small to medium sample sizes are under question,

which has been the case for the vast majority of tDCS studies to date. Furthermore, this example highlights how the systematic assessment of theoretically implicated brain indices and their inclusion in a mediation model could reduce the chances of spurious conclusions in tDCS research.

Moderation Analysis

Moderation analysis is also a form of regression analysis, but here the objective is to determine whether the relationship between the independent and dependent variables changes as a function of a third variable (i.e., statistical interaction), known as the moderator (**Figure 1B**). Thus, while mediation analyses can provide insight on how behavioral effects are achieved (e.g., a change in activity within the neurophysiological milieu), moderation analyses can determine particular conditions for which the effects will hold. In the context of the hypothetical experiment described above, it is plausible that an effect of tDCS, or lack thereof, on working memory performance may be driven by a subset of subjects who had particular baseline neurophysiological characteristics, such as, for example, lower than average gray matter (GMD) density in the dlPFC. Here, moderation analyses could provide an elegant unified framework for demonstrating that the relationship between tES and behavior is moderated by individual differences in the GMD of the targeted region. Accordingly, we would be able to make a more refined interpretation regarding the efficacy of tDCS: the reported effect of tDCS applied over dlPFC on working memory was particular to a select group of individuals with low GMD in the target region. Identifying these kinds of caveats has important implications for the translational potential of tDCS research and the development of individualized protocols.

In summary, most tDCS research is based on the assumption that weak direct currents applied to the scalp will stimulate the underlying brain regions, resulting in a detectable change in associated behavioral indices. However, we have argued that this and other assumptions need to be formally verified by acquiring data regarding the actual states and traits of the targeted neural region. We suggest that the inclusion of theoretically implicated neurophysiological indices in mediation and moderation models constitute valuable approaches for enhancing the inferential power of tDCS research, by revealing how and for whom tDCS is effective. Exploiting these approaches should also yield information for guiding the design of more effective and personalized tDCS protocols. More generally, the nuanced insights that these approaches afford should reduce the likelihood of spurious conclusions, and accordingly improve the prospects for reproducibility in the field.

On a final note, mediation and moderation analysis can be readily implemented using open source plug-ins for common statistical software packages such as SAS, SPSS (e.g., Process by Hayes, 2013, MEMORE by Montoya and Hayes, 2017), and R (e.g., The Lavaan package; Rosseel, 2012). In addition to the basic forms of the mediation and moderation models we discussed here, these plug-ins provide other analysis templates with varying levels of complexity, including moderated mediation and mediated moderation, as well as options to incorporate multiple mediators, moderators and covariates.

AUTHOR CONTRIBUTIONS

SH wrote the article and helped to conceive the opinion. FS helped to conceive the opinion and provided feedback on drafts of the article. RK helped to conceive the opinion and provided feedback on drafts of the article.

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The Importance of Sample Size for Reproducibility of tDCS Effects

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INTRODUCTION

Cheap, easy to apply, well-tolerable, with the potential of altering cortical excitability, and for testing causalities—these are attributes that have made transcranial direct current stimulation (tDCS) a highly popular research tool in cognitive neuroscience. Since its reintroduction over 15 years ago by Nitsche and Paulus (2000), the number of publications reporting tDCS results has risen exponentially (a Scopus® literature search indicates over 500 such journal articles published in 2015 alone). Recently however, the efficacy of tDCS to alter cognitive performance has been called into question, in particular among healthy participants, but also in certain clinical samples (Horvath et al., 2015; Hill et al., 2016; Mancuso et al., 2016). A number of empirical studies reported not having been able to detect any facilitatory effects of anodal tDCS or inhibitory effects of cathodal tDCS on various cognitive processes (e.g., Wiethoff et al., 2014; Minarik et al., 2015; Sahlem et al., 2015; Horvath et al., 2016; Vannorsdall et al., 2016). In fact, in a recent meta-analysis Horvath et al. (2015) argue that in young, healthy participants there is no effect of tDCS on cognition whatsoever, whereas other meta- analyses do find specific modulation of cognitive processes by tDCS; however, these effects seem to be rather weak (Hill et al., 2016; Mancuso et al., 2016). In a recent commentary the field of tDCS research was even called a research area of bad science (Underwood, 2016) in desperate need of further meticulous evaluation. Although there seems to be some inconsistency of effects there is also current work by Cason and Medina (2016) suggesting no evidence for p-hacking (strategic testing and analysis procedures to increase likelihood of obtaining significant effects) in tDCS research. However, Cason and Medina (2016) find average statistical power in tDCS studies to be below 50%. Therefore, one potential reason for the reported inconsistencies might be that sample size is usually very small in most tDCS studies (including those from our research group). Whilst this issue is not specific to tDCS studies (in fact Button et al., 2013 estimate the median statistical power in neuroscience in general being only 21%), it could lead to weaker effects often not being detected, and consequently meta- analyses suggesting small or no efficacy of tDCS. In addition, the assessment of the real effect of tDCS is further complicated by potential publication bias (file drawer problem) leading to over-reporting significant tDCS findings. That is, a publication bias favoring studies with significant effects might lead to an inflation of the reported efficacy of tDCS. Thus, depending on which studies are included in systematic reviews and meta- analyses (i.e., findings published in peer-reviewed journals; unpublished nil-effects; nil-effects reported as an additional finding in papers with the actual focus on another, significant, effect, etc.), small sample size in tDCS research could lead to both under—and overestimation of tDCS efficacy. Some current meta-analyses (e.g., Mancuso et al., 2016), however, include an estimation of publication bias (e.g., using the "trim and fill" procedure in which funnel plots are used for determining whether there is a bias toward studies with significant effects in the literature included in the meta- analysis); and overall

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effect size can then be adjusted accordingly. Taking publication bias into account it becomes evident that efficacy of tDCS is rather weak (Mancuso et al., 2016).

As indicated by quite some inconsistency in literature on the efficacy of the stimulation, the field of tDCS research is clearly struck by the replication crisis that we also find in psychology and neurosciences in general (Button et al., 2013; Open Science Collaboration, 2015). But how to estimate efficacy of tDCS, if it is not clear, how many unsuccessful experimental attempts end up in the file drawer? As discussed above, one possibility is to adjust for publication bias in meta- analyses. Another strategy is pre-registering tDCS studies and reporting their outcome, independent of whether the results are significant or not—be it in peer reviewed journals or platforms such as the Open Science Framework (https://osf.io); this can result in more accurate estimates of efficacy. Moreover, allowing open access to the acquired data (open data) offers the opportunity that researchers could pool raw data from experiments with small samples but similar experimental designs. By doing so, they overcome the problem of under-powering, an issue that seems so fundamental in tDCS research.

Therefore, to investigate the effect of sample size on tDCS efficacy and to contribute to increased research transparency we designed a simple, pre-registered study (https://osf.io/eb9c5/?view_only=2743a0c4600943c998c2c37fbfb25846) with a sufficiently large number of young, healthy volunteers estimated with *a priori* power analysis. Furthermore, we make all the acquired data publicly available. In a choice reaction time task (CRT) participants underwent either anodal or cathodal tDCS applied to the sensorimotor cortex. Jacobson et al. (2012) suggest that for the motor domain with tDCS over sensorimotor cortex anodal-excitation and cathodal-inhibition effects (AeCi) are quite straight forward, whereas in other cognitive domains AeCi effects seem not particularly robust. Since we stimulated the sensorimotor cortex we decided to contrast anodal with cathodal tDCS (instead of sham stimulation) for obtaining the largest possible effect. We expected anodal stimulation to result in faster response times compared to cathodal tDCS in accordance with findings by Garcia-Cossio et al. (2015). To demonstrate the importance of sample size for finding the predicted effect, random samples of different sizes were drawn from the data pool and tested statistically. This way the probability of identifying the predicted effect was obtained as a function of sample size.

MATERIALS AND METHODS

A power analysis (Faul et al., 2007) for an independent-sample *t*-test was conducted assuming one-tailed testing, an effect size of $d = 0.6$, 80% power and alpha error probability of $\alpha = 0.05$. This analysis suggested a total sample size of at least 72 participants.

We tested 75 participants, randomly assigned to either anodal tDCS (24 female and 14 male; mean age: 22 year [SEM = 0.61]) or cathodal tDCS (19 female and 18 male; mean age: 22.8 year [SEM = 0.59]). The groups did not differ in age [$t_{(73)} = 0.89$, $p = 0.38$] or gender distribution ($\chi^2 = 1.07$, $p = 0.30$). All volunteers were right handed, had normal or corrected to normal vision, and did not meet any exclusion criteria for tDCS (Nitsche et al., 2003; Woods et al., 2016). The study was approved by the local ethics committee and conducted according to the Declaration of Helsinki.

Volunteers performed a CRT task. In each trial either a diamond (requiring left button press) or a square (requiring right button press) was presented in the center of a monitor for 100 ms followed by an inter-trial interval with a length of 1700–2100 ms. The experiment started with a 2-min training block comprising 60 trials. This was followed by a baseline block of 120 trials. Then tDCS was started. After 4 min of stimulation another block of 120 trials was performed while tDCS continued until the end of the experiment.

In a between-subjects design either anodal or cathodal tDCS was delivered to the left motor cortex. The stimulation electrode was applied with its center at 10-20-electrode position C3. The return electrode was placed above the right orbita. tDCS was delivered at 1 mA (with a ramp-up time of 20 s and ramp-down of 2 s) over 8 min in total. Since we conducted the task during tDCS and did not test during a potential after-effect of tDCS we assumed a total stimulation time of 8 min to be sufficient. We, however, cannot exclude that longer stimulation duration might produce a larger effect. A TCT tDCS stimulator (TCT Research Limited, Hong Kong) with 35 cm^2 large sponge electrodes soaked in saline water was used.

For each participant the median RT of correctly responded trials only was calculated for the baseline block and the stimulation block separately. Then RT differences between the stimulation block and the baseline block were obtained (ΔRT) and used for statistical analysis. Percentage of correctly responded trials was used as a measure of task accuracy.

PRE-REGISTRATION, OPEN DATA AND OPEN MATERIAL

This is a pre-registered study. The project description is available on open science framework (https://osf.io/eb9c5/?view_only=2743a0c4600943c998c2c37fbfb25846).
Presentation® raw data log files as well as processed data for each volunteer are accessible here: https://osf.io/xnyar/?view_only=2743a0c4600943c998c2c37fbfb25846. Data documentation can also be found there. We also provide open access to a Matlab® script we used to draw random samples of different size and perform t-statistics on them, the required input files for this procedure, and its results (https://osf.io/eurcq/?view_only=57080ff7b15f492fa1c343e26c113133).
Open material (Presentation® code and stimulus material) can be found here: https://osf.io/nw2hj/?view_only=e083cfb8fc81424ca02e916b40c0378c.

RESULTS

All requirements for parametric testing were met. As predicted, ΔRT was significantly different between anodal and cathodal tDCS [$t_{(73)} = -1.91$, $p = 0.03$ [one-tailed], $d = 0.45$], with anodal stimulation resulting in faster RTs than cathodal tDCS

(see **Figure 1A**). Additional one-sample *t*-tests indicate that compared to baseline anodal tDCS resulted in significantly faster RTs [$t_{(37)} = -3.49$, $p = 0.001$, $d = 1.15$], whereas no such effect was obtained for cathodal stimulation [$t_{(36)} = -0.71$, $p = 0.48$, $d = 0.27$]. RTs of the baseline block did not differ significantly between the two groups [$t_{(730} = 0.66$, $p = 0.51$, $d = 0.15$].

To demonstrate the drastic effect of sample size on the probability of detecting the above mentioned effect on RTs we drew random samples of different sizes from our pool of participants and conducted the statistics as described above. For each sample size between 12 and 68 participants we drew 500 samples and each time performed a *t*-test comparing anodal and cathodal stimulation. As depicted in **Figure 1B**, with very small sample sizes we found statistically significant effects in less than 20% of the cases. Notably, with a sample size of 12 the opposite significant effect was found in two instances, i.e., faster RTs in cathodal than anodal tDCS. Even with a sample size of 60 participants, the hypothesized effect was detected only in 51% of the cases.

For each sample size the average effect size d was calculated over only those randomizations that showed a significant effect (e.g., the 15.4% of tests for sample size 12, etc.). Average effect size as a function of sample size is depicted in **Figure 1C**, with very high effect sizes for small samples (that still led to a significant *t*-test) to medium and small effect sizes with samples larger than 60 participants. When we, however, averaged all 500 obtained effect sizes for each sample size, independent of whether the *t*-test was significant or not, we observed a relatively stable mean effect size around $d = 0.45$—a value fairly representative for the real effect in our data (**Figure 1C**).

Task accuracy data were not normally distributed; therefore a Mann-Whitney-*U*-test was performed. There was no significant effect of tDCS on task accuracy ($z = -0.34$, $p = 0.37$ [one-tailed], $r = 0.04$).

DISCUSSION

Our results suggest that tDCS over the sensorimotor cortex modulates response times in a CRT task, with anodal tDCS leading to faster RTs compared to cathodal stimulation. It is important to point out, however, that in this study there was no sham stimulation condition included. Hence and also because a training effect could have distorted RT differences from baseline to stimulation conditions, it is impossible to conclude whether only anodal, only cathodal or both stimulation conditions have an impact on cognition. This is despite anodal tDCS leading to a significant reduction in RTs compared to baseline, while cathodal tDCS showing no difference to baseline. Jacobson et al. (2012) found that for stimulation of the motor cortex effects of excitation

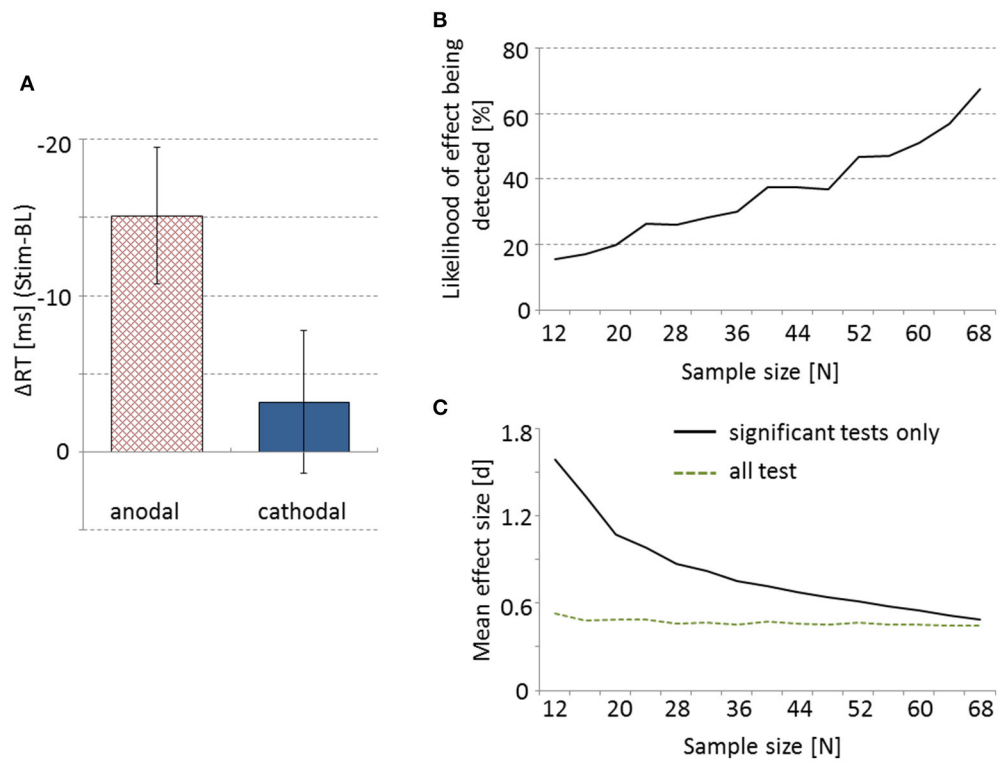

FIGURE 1 | Anodal tDCS leads to significantly larger response time reduction from baseline to post-stimulation compared to cathodal stimulation (A). Error bars represent SEM. **(B)** Percentage of 500 random draws at given sample sizes in which the effect shown in **(A)** can be obtained. **(C)** The solid line depicts mean effect size d as a function of sample size for randomizations where a significant effect was obtained only. The dotted line represents effect size d averaged over all the 500 random draws at each sample size.

by anodal tDCS and inhibition by cathodal stimulation are fairly consistent. Therefore, it is rather unlikely that in this study a larger overall effect would have been obtained if only one active stimulation condition was compared to sham.

Most importantly, however, here we demonstrate how essential a sufficiently large sample size is for finding an effect of tDCS on cognitive processes in healthy, young participants. With sample sizes of up to 20 participants we found a significant modulation of RTs by tDCS in less than 20% of tests. This very nicely resembles the anecdotal impression (from personal communication with colleagues) of only roughly every fifth tDCS experiment with small sample sizes finding a predicted effect. Even a sample size of 60 participants produced the significant difference between anodal and cathodal tDCS in only 51% of randomizations. That might be somewhat surprising, since in this research field such a sample size would probably be considered as rather large. However, an *a priori* power-analysis suggested a sample size of 72 participants in order to achieve 80% probability of detecting an effect with an effect size of $d = 0.6$. The actual effect size that we found in our experiment was only at $d = 0.45$. This means that *post-hoc* even with our sample of 75 participants the experiment was slightly under-powered. Here, however, it should be noted that sufficient sample size might be substantially smaller in within-subjects designs.

Under-powered tDCS studies might have a range of negative consequences. First, the number of false negatives can be increased. Meta- analyses, therefore, could underestimate the efficacy of tDCS, based on the number of reported false negative results. Moreover, there might be more false positive results, detecting non-existing effects by chance. In our randomization procedure we found significant but reversed effects in a few very small samples (12 participants). This would lead to irreproducible results further counteracting efficacy estimates in meta- analyses. Finally, only fairly vast effects stand a chance of becoming statistically significant in small samples (see **Figure 1C**). Due to publication bias, studies reporting significant results are more likely to become published in peer-reviewed journals. On a single study level this can lead to an overestimation of effect sizes. Since *a priori* power-analyses assuming these large effect sizes will erroneously suggest relatively small sample sizes, this file drawer problem can have negative impact on the planning of follow-up experiments and replication attempts. If, however, studies are pre-registered and data are open access, failed attempts can be taken into account. As suggested in our analysis the mean effect size over all the attempts (successful as well as unsuccessful ones) is a relatively stable measure of the true effect, even in small samples. Alternatively, meta- analyses correcting for publication bias (e.g., applying "trim and fill" procedures; see Mancuso et al., 2016) give a more accurate measure of overall effect size as well.

Although we only investigated effects of tDCS delivered to sensorimotor cortex on performance in the motor domain, it is plausible that studies using other stimulation parameters and other cognitive tasks are similarly affected by sample size. Since Jacobson et al. (2012) suggest that in cognitive domains other than the motor domain tDCS does not show these clear AeCi effects it is likely that tDCS studies investigating non-motor cognition might even be more affected by sample size issues than demonstrated in the current study. Additionally, task difficulty might influence tDCS efficacy in higher cognitive functions as well (Jones and Berryhill, 2012).

Open data can further contribute to a better evaluation of tDCS efficacy. The pooling of data from several studies with small samples but similar experimental designs will create large data sets that allow the estimation of efficacy much more precisely. This way, small tDCS data sets can best contribute to accurate and rigorous testing of the method. Another advantage is that accessible data can be re-analyzed with statistical methods that are more robust against smaller sample sizes. For instance, the replication rate in psychological studies seems higher than originally reported (Open Science Collaboration, 2015) when Bayes statistics are used for data analysis (Etz and Vandekerckhove, 2016).

CONCLUSION

We conclude and recommend that tDCS studies need to be planned more carefully, particularly when it comes to estimation of the to-be-tested sample size. *A priori* power analyses are an important tool for doing so. While due to publication bias, effect sizes in single studies carried out with small samples might be substantially overestimated, meta- analyses—if also including studies reporting a lack of effects in very small samples—might underestimate efficacy. Therefore, it seems most appropriate to assume small to intermediate effect sizes (between $d = 0.4$ and $d = 0.5$ according to Cohen, 1988) when planning a tDCS study with healthy young participants and performing *a priori* power analysis. Moreover, we recommend open, accessible data so that small data sets can be potentially merged or analyzed using for example Bayes statistics.

AUTHOR CONTRIBUTIONS

Each author contributed to designing the study, recording and analyzing the data, interpreting the results and writing the manuscript. BB and PS implemented the study.

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Mapping the Parameter Space of tDCS and Cognitive Control via Manipulation of Current Polarity and Intensity

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In the cognitive domain, enormous variation in methodological approach prompts questions about the generalizability of behavioral findings obtained from studies of transcranial direct current stimulation (tDCS). To determine the impact of common variations in approach, we systematically manipulated two key stimulation parameters—current polarity and intensity—and assessed their impact on a task of inhibitory control (the Eriksen Flanker). Ninety participants were randomly assigned to one of nine experimental groups: three stimulation conditions (anode, sham, cathode) crossed with three intensity levels (1.0, 1.5, 2.0 mA). As participants performed the Flanker task, stimulation was applied over left dorsolateral prefrontal cortex (DLPFC; electrode montage: F3-RSO). The behavioral impact of these manipulations was examined using mixed effects linear regression. Results indicate a significant effect of stimulation condition (current polarity) on the magnitude of the interference effect during the Flanker; however, this effect was specific to the comparison between anodal and sham stimulation. Inhibitory control was therefore improved by anodal stimulation over the DLPFC. In the present experimental context, no reliable effect of stimulation intensity was observed, and we found no evidence that inhibitory control was impeded by cathodal stimulation. Continued exploration of the stimulation parameter space, particularly with more robustly powered sample sizes, is essential to facilitating cross-study comparison and ultimately working toward a reliable model of tDCS effects.

Keywords: tDCS, cognitive control, prefrontal cortex, Flanker task, neurostimulation

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INTRODUCTION

With the recent surge in use of transcranial direct current stimulation (tDCS) has come a growing uncertainty about the reliability of this neuromodulatory technique. TDCS, a form of non-invasive electrical brain stimulation, hinges on a simple premise: *hypo*-polarization of a cortical area should increase neuronal excitability, while *hyper*-polarization should induce the opposite effect. Within the motor domain, this rationale has been largely supported at the neurophysiological level: when primary motor areas are hypo-polarized by positive current administered during anodal stimulation (A-tDCS), motor-evoked potentials (MEPs) recorded from peripheral muscles tend

to increase in magnitude, indicating a boost in cortical excitability. In contrast, hyper-polarization of these areas via negative current administered during cathodal stimulation (C-tDCS) tends to diminish the amplitude of MEPs, indicating cortical inhibition (Nitsche and Paulus, 2000; see also, Fregni et al., 2006; Furubayashi et al., 2008; Jefferson et al., 2009; Stagg et al., 2009). Extended to the cognitive domain, it was thus assumed that improvement of a cognitive function could be achieved by anodal stimulation of the substrate underlying that function. Conversely, cathodal stimulation of the underlying substrate should lead to decrements in that function.

Several recent findings have called into question this basic premise—on which the design and interpretation of all tDCS studies hinge—thereby creating a wave of confusion. Of most pressing importance for the future of brain stimulation research, the effects of tDCS are demonstrably sensitive to seemingly subtle variations in task, stimulation parameters, and characteristics of the individuals being tested. In one well-known example from the motor domain, Batsikadze et al. (2013) charted the effects of stimulation intensity (1 mA vs. 2 mA) for both A- and C-tDCS of primary motor cortex. A-tDCS at the highest stimulation intensity produced an increase in MEPs while A-tDCS at 1 mA produced no significant change relative to baseline amplitude. Unexpectedly, C-tDCS at 2 mA *also* induced an excitatory effect (compared to the suppressed MEPs observed for C-tDCS at the level of 1 mA). Thus, the excitatory and inhibitory effects of tDCS may depend not only on the polarity of current, but also on the intensity level of stimulation. In accordance with these findings, a number of meta-analyses and review articles offer in-depth discussions of other sources of variation associated with tDCS both within and outside the motor domain (Nitsche et al., 2008; Jacobson et al., 2012; Filmer et al., 2014; Horvath et al., 2014; Li et al., 2015; Price et al., 2015). These factors include: electrode position and size (e.g., Bikson et al., 2010), timing of task relative to stimulation period (e.g., Nozari et al., 2014), duration of stimulation (e.g., Nitsche and Paulus, 2001), cognitive demand involved in task (e.g., Antal et al., 2007; Gill et al., 2015), skull thickness and subcutaneous fat content (Datta et al., 2012), and a genetic polymorphism associated with prefrontal dopamine (Plewnia et al., 2013; Nieratschker et al., 2015).

In acknowledging the challenges faced by the field of tDCS research, our aim is not to encourage the abandonment of this tool but rather to stress the value of more comprehensive experimental approach. We propose that a thorough exploration of the stimulation parameter space is essential to facilitating cross-study comparison and ultimately working toward a reliable model of tDCS effects. These steps are especially crucial for tDCS investigations in the cognitive domain, for which, relative to the motor domain, there exists greater variability in experimental design and potentially greater complexity in the neural systems engaged at task. Below, we highlight the extent of methodological variation within one sub-field of cognitive tDCS research (cognitive control), thereby motivating our own experimental approach.

Broadly construed, *cognitive control* underlies our capacity to interact flexibly with our surroundings in a goal-directed manner. More precisely, this term refers to processes such as the selection and maintenance of relevant information, shifting between tasks, and the inhibition of prepotent responses (Miller and Cohen, 2001). A combination of lesion and functional neuroimaging studies have implicated a network of cortical and subcortical brain regions as the seat of these essential functions. In particular, a host of tDCS studies have stimulated prefrontal cortex in order to affect performance on tasks of working memory, set-shifting and inhibitory control. Experimenters have examined these processes via different stimulation sites (e.g., F7- contralateral mastoid placement: Nozari et al., 2014; Fz-left cheek: Hsu et al., 2011; F3- right supraorbital (RSO): Ohn et al., 2008; the crossing point between T3-Fz and F7-Cz-RSO: Cattaneo et al., 2011; the crossing point between T4-Fz and F8-Cz: Ditye et al., 2012), and at different current intensities (e.g., 1 mA: Fregni et al., 2005; 1.5 mA: Nozari et al., 2014; 2.0 mA: Vanderhasselt et al., 2013). On top of these differences, a recent review of polarity effects on executive function (Jacobson et al., 2012) found that only half of the tDCS studies surveyed examined both cathodal *and* anodal effects. In some cases, experimenters did not include a sham stimulation condition as a control (e.g., Ditye et al., 2012). While studies generally show a boost in cognitive control during A-tDCS administered to the prefrontal cortex, it is unclear whether an equal and opposite effect would be obtained during C-tDCS under otherwise identical experimental conditions. Moreover, experimenters rarely probe dose-dependent changes in stimulation intensity (but see, Iyer et al., 2005; Hoy et al., 2013; Horvath et al., 2016), leaving open the question of whether behavioral effects might change, such as by flipping directions or diminishing across intensity levels (as in Batsikadze et al., 2013).

Against this backdrop, in which we have an abundance of data but great variation in how those data were obtained, the field is thus faced with a host of interpretation issues. To illustrate: Hoy et al. (2013) reported that anodal stimulation of left prefrontal cortex significantly improved participants' speed on a simple work memory task (the "2-back"), but not on a more difficult version of the task (the "3-back"). They did not test the effects of cathodal stimulation. In contrast, Fregni et al. (2005) reported improved accuracy but not speed on 3-back task performed during anodal stimulation. They also tested the effects of cathodal stimulation, but found no significant effect. Finally, Zaehle et al. (2011) reported polarity-*dependent* changes in accuracy on a 2-back task (accuracy was superior for A-tDCS relative to C-tDCS), but polarity-*independent* changes in RT (reaction time was equally facilitated for A-and C-tDCS relative to sham). Though these three studies are, in fact, more closely related than is typical (i.e., they made use of the F3 electrode montage and comparable current intensity), their remaining dissimilarities still make it challenging to pinpoint the source of non-overlapping results. Can they be traced to important differences in task structure, timing of stimulation, duration of stimulation, current polarity, or some combination of these factors? In an era when replicability is increasingly a focus in psychological research (Open Science Collaboration, 2015; Anderson et al., 2016), careful consideration of these features is critical.

The present study represents a crucial step toward disentangling two basic but still crudely understood stimulation

parameters within the domain of cognitive research: current polarity and stimulation intensity. While we propose the systematic variation of stimulation parameters constitutes an important contribution to the field, we fully acknowledge the limitations of this approach. Specifically, between-subject manipulations, which are useful in minimizing stimulation timing and task familiarity effects, may require prohibitively large sample sizes. Indeed, this limitation becomes even more essential when considering that the behavioral effects of tDCS may be quite small (Minarik et al., 2016).

Bearing in mind this trade-off between a comprehensive approach and lowered statistical power, we examine here performance on the Eriksen Flanker, a cognitive control task that taps into the capacity for selective attention and response inhibition (Eriksen and Eriksen, 1974), and one whose rapid pace enables us to collect a rich data set (over 550 trials). As this task has been associated with activation in prefrontal cortex (e.g., Casey et al., 2000; Ullsperger and von Cramon, 2001; Bunge et al., 2002), we selected an electrode montage thought to target prefrontal cortex in the left hemisphere: F3- RSO. In particular, we chose this montage due to its common use in studies of tDCS during various cognitive control tasks (Fregni et al., 2005; Ohn et al., 2008; Hoy et al., 2013). While the Flanker task has also been employed in a handful of other tDCS studies (Weiss and Lavidor, 2012; Nozari et al., 2014; Zmigrod et al., 2016), our design enables us to examine both the effects of current polarity (i.e., A-tDCS and C-tDCS relative to sham stimulation) and dose-dependent stimulation (i.e., to ask whether cognitive control increases or decreases monotonically from 1, to 1.5, to 2 mA). Specifically, we test the dual hypotheses that A-tDCS will improve performance on the Eriksen Flanker in a dose-dependent manner while C-tDCS will worsen performance in this way. To this end, we extract an index of cognitive control by comparing, for each participant, reaction times for trials that require response inhibition relative to those that do not strongly engage this process. By charting the parameter space of tDCS during this task, we hope to open the door to further methodological research while also serving as a launching pad for exciting theoretical questions about the behavioral consequences of suppressing and exciting cognitive control capacities.

MATERIALS AND METHODS

Participants

One hundred and one participants recruited from the University of Pennsylvania community completed the study in exchange for $20. All were right-handed, native speakers of English between the ages of 18 and 30. They were approximately matched for education level (at minimum, all completed secondary schooling). Participants were not pregnant or currently taking psychotropic/anticonvulsive drugs. They reported no history of head trauma, seizures, or neurologic or psychiatric disease. All participants gave informed consent in accordance with the University of Pennsylvania Institutional Review Board. Of the original 101 participants who completed the study, 11 of them achieved an accuracy score less than chance performance (50%) on one or more trial types (C-tDCS: $n = 2$; S-tDCS: $n = 4$; A-tDCS: $n = 5$). As this performance suggests failure to follow task instructions, they were excluded. All analyses reported below examine the remaining 90 participants (10 per group). Corresponding demographic information is provided in **Table 1**. Though not precisely matched, sex ratios did not differ significantly by polarity manipulation (A-tDCS vs. S-tDCS: $\chi 2 = 0.28$, $p = 0.60$; C-tDCS vs. S-tDCS: $\chi 2 = 0.08$, $p = 0.79$). Furthermore, the inclusion of sex as a predictor in statistical models comparing polarity groups did not impact the pattern of significant results reported below.

Stimuli

Participants performed a nonlinguistic version of the Flanker task described in Nozari et al. (2014). An equal number ($n = 188$) of *congruent*, *incongruent*, and *no-go* trials were presented centrally as black text on a white background and measured approximately 0.5° × 4.5° (**Figure 1**). Each trial contained a row of five angle brackets. In *congruent* trials, the center bracket and the four flanking brackets faced the same direction (equal number of < < < < < and > > > > >). In *incongruent* trials, the center bracket and the four flanking brackets faced the opposite direction (equal number of > > < > > and < < > < <). For both *congruent* and *incongruent* trials, participants were instructed to press the left or right arrow keys to indicate the direction in which the center bracket was facing. In *no-go* trials, the four flanking brackets were constructed from dashed

TABLE 1 | Summary of age and sex across experimental conditions.

Polarity	Intensity (mA)	Mean age *(SD)*	# Female
Anodal	1	21.0 (3.6)	6
Anodal	1.5	20.8 (1.9)	6
Anodal	2	21.7 (3.1)	7
Sham	1	21.1 (2.1)	3
Sham	1.5	21.2 (2.7)	9
Sham	2	20.2 (2.5)	5
Cathodal	1	22.3 (3.5)	6
Cathodal	1.5	21.5 (2.6)	6
Cathodal	2	22.6 (4.2)	6

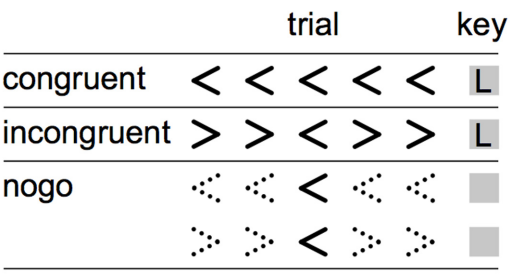

FIGURE 1 | Visualization of trials types in the Eriksen Flanker. During the congruent and incongruent trials (*top and middle rows*), participants responded to the direction of the middle arrow. During the nogo trials, signaled by dashed flanker arrows (*bottom rows*), participants were instructed to suppress any button press.

rather than solid lines; the bracket orientations were equally distributed between the four patterns used for *congruent* and *incongruent* trials. For these trials, participants were instructed not to make any key response. Each trial was displayed for 800 ms, followed by a fixation cross with a variable ISI drawn from a uniform distribution (500–150 ms). Trial order was randomized. Participant responses were indicated by pressing the left and right arrow keys with two fingers on the dominant hand and were recorded during the entire trial and fixation period.

Procedure

We randomly assigned participants to one of nine between-subject experimental manipulations: three stimulation conditions (anode, sham, cathode) crossed with three stimulation intensity levels (1.0, 1.5, 2.0 mA). We varied stimulation intensity within the control groups in order to rule out the (admittedly unlikely) possibility that participants in the sham condition might, even after only 30 s of stimulation, be sensitive to differences along this dimension.

Participants were blind to their assigned condition. Experimental procedures were identical across participants (**Figure 2**). First, the experimenter applied the electrodes. Next, the experiment script was initiated; participants were informed of the task format and directed to make their responses as quickly and as accurately as possible. Once they finished reading the instruction screen (indicated by hitting the space bar), the experimenter began stimulation. The Flanker task began after an initial fixation period of 3 minutes during which the participant sat quietly. Stimulation was delivered through 5 cm × 5 cm (25 cm^2) electrodes, placed in saline-soaked sponges and held on the head with a rubber strap. A continuous current of 1.0, 1.5, or 2.0 mA, depending on experimental condition, was generated with battery-operated continuous current stimulator (Magstim Eldith 1 Channel DC Stimulator Plus, Magstim Company Ltd., Whitland, Wales). In cathode and sham stimulation conditions, the cathode was placed over the left dorsolateral prefrontal cortex, F3 using the International 10–20 System, and the anode was placed over the right supraorbital sinus. Electrode placement was reversed for the anodal stimulation condition. In the non-sham conditions, current was increased to the target level over 30 s, held constant for 20 min (the entirety of the Flanker task + 3 min of initial fixation), and decreased to 0 over 30 s. In the sham condition, current was increased to the target level over 30 s, held constant for only 30 s, decreased to 0 over 30 s, and was maintained at 0 for the remaining 19 min 30 s. Approximately 10 min after the termination of the Flanker task, participants completed a written questionnaire in which they were asked to rate on a scale of 1–10 the extent to which they experienced the following physical sensations during the task: tingling, itching, burning, pain, headache, and change in vision.

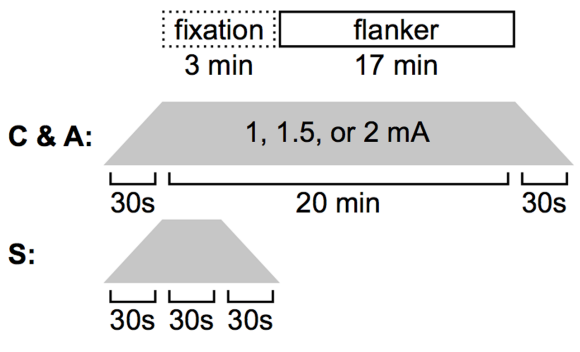

FIGURE 2 | Stimulation timing. During A- or C-tDCS, 3 min elapsed before the Flanker task was initiated. Both stimulation and the behavioral task were terminated after 17 min. In the sham condition, current was ramped up, held steady, and ramped down in 30 s increments.

Analyses

In preparation for analysis, we removed the first 10 trials from each participant to minimize task start-up effects (data loss 1.8%). Motivated by prior literature (e.g., Nozari et al., 2014), this pre-determined step ensured that results would not be driven by initial reaction times (RTs), which are likely to be heavily influenced by acclimation to task structure. We also excluded RTs less than 200 ms (data loss 0.04%). All results reported below hold without these trial exclusions (removal of the first 10 trials and RTs < 200 ms). Due to near-ceiling effects on accuracy on the Flanker task (mean performance = 96.7%, SE = 0.5), all subsequent analyses were carried out using reaction time (RT) on correct trials as the dependent measure (**Figure 3**).

We next implemented a linear mixed effects model (LMM) using the *lmer()* function (library *lme4*, v. 1.1–7; (Bates et al., 2014) in R (v. 3.2.2; R Development Core Team, 2015). LMMs represent a powerful, flexible tool for better estimating the generalizability of experimental findings to the broader population. Their strength lies in their ability to properly handle correlated observations (i.e., the fact that RTs for congruent and incongruent trials, collected for each subject, are necessarily non-independent) while also explicitly accounting for inter-individual variation alongside primary effects of interest. In the statistical models presented below, for example, we can evaluate the significance of our predictors of interest (stimulation condition, intensity level, and trial type) while also adding a random effects term that accounts for the possibility that, regardless of experimental manipulation, participants will be generally slower or show a smaller interference effect than others. This approach thus ensures that our observed pattern of results, particularly given our relatively small sample size, cannot be solely attributed to random variations in the sample we tested. Relative to traditional analyses of variance, LMMs are also more robust to unbalanced or missing data points and violations of compound symmetry (for detailed discussion of LMMs see, e.g., Gelman and Hill, 2006; Baayen et al., 2008; Magezi, 2015).

In light of the right skew of the RT data (skewness = 1.63), RTs from all 90 participants were first log-transformed, then regressed onto all main effects and interactions of stimulation condition (anode, sham, cathode), intensity level (1.0, 1.5, 2.0 mA) and trial type (congruent vs. incongruent). All results reported below hold without this transformation. The model also included the fullest random effects structure that allowed the model to converge: a random intercept for participant and a by-participant random slope for trial type. This random effect structure enabled us

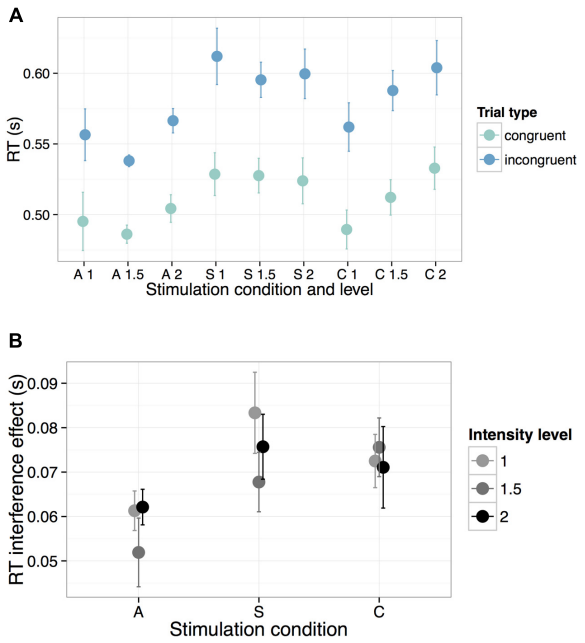

FIGURE 3 | Behavioral performance on the Flanker task across all experimental manipulations (A = Anode, S = Sham, C = Cathode). To illustrate the general speed-up in RTs during A-tDCS, we show in **(A)** response times across all stimulation parameters for both congruent (teal) and incongruent (blue) trials. In **(B)**, we highlight the reduced interference effect during A-tDCS, plotting the mathematical difference in RTs between the incongruent and congruent trials across all levels of intensity. Error bars represent one standard error of the mean.

to account for inter-individual variation in overall speed of RT as well as magnitude of the interference effect. Predictors were contrast coded with a zero mean in order to reduce multicollinearity between fixed effects ($rs < 0.6$). Specifically, the condition predictor was simple coded so as to compare cathode vs. sham stimulation and anode vs. sham stimulation and the intensity predictor was reverse-helmert coded to reflect the *a priori* hypothesis that the effect of stimulation intensity would increase across levels. Because the trial type predictor includes only two levels (congruent vs. incongruent), they were directly compared to one another. All models were fit using a Restricted Maximum Likelihood procedure, which has been shown to yield unbiased variance estimates. Finally, as no-go trials required the suppression of a motor response, they could not be included in subsequent analyses.

RESULTS

Examining the Effects of Current Polarity and Intensity on Flanker Performance

Results are summarized in **Table 2**. For the anode relative to the sham contrast, we found a significant main effect of condition ($\beta = -0.069$, $t = -3.37$, $p = 0.001$): overall RTs were faster during A-tDCS, regardless of trial type. Unsurprisingly, we also obtained a significant main effect of trial type: RTs were faster for the congruent relative to the incongruent trials ($\beta = -0.063$, $t = -31.85$, $p < 0.0001$), regardless of stimulation condition. Crucially, we found only one significant interaction: for anode relative to sham stimulation, the effect of trial type was reduced ($\beta = 0.010$, $t = 2.10$, $p = 0.04$). In other words, the RT penalty associated with incongruent trials was smaller during anodal stimulation (i.e., there was a smaller interference effect, **Figure 3**). As further highlighted by a simple effects analysis, the effect of trial type in the sham condition ($\beta = -0.067$, $t = -19.45$, $p < 0.0001$) was of a greater magnitude than for the A-tDCS condition ($\beta = -0.057$, $t = -16.52$, $p < 0.0001$). No reliable effect of stimulation intensity was observed, and we found no evidence that Flanker RT performance was impeded by cathodal stimulation.

However, inspection of **Figure 3** (top panel) revealed a striking qualitative pattern: an apparent linear increase in the effect of intensity level on RTs for the cathodal condition, independent of trial type. To probe the significance of this trend *post hoc*, intensity level was contrast-coded to test for a linear effect on the response variable within the cathodal condition. Similar to the full model detailed above, log-transformed RTs from the C-tDCS condition were regressed onto all main effects and interactions of intensity level and trial type, including a random intercept for participant and a by-participant random slope for the latter. Results revealed a significant linear increase in RTs associated with stimulation intensity ($\beta = 0.053$, $t = 2.06$, $p = 0.049$). Importantly, this trend did not differ between trial types (i.e., the interaction between intensity and trial type was not significant:

TABLE 2 | Coefficients (and corresponding *t*-values and *p*-values) for each predictor in a model examining the effect of stimulation condition (anode, sham, and cathode), intensity level (1–2 mA), and trial type (congruent vs. incongruent) on log-transformed RTs from the Eriksen Flanker.

Predictor	Coefficient	*T*-value	*P*-value
Condition (C vs. S)	–0.027	–1.35	0.18
Condition (A vs. S)	**–0.069**	**–3.37**	**0.001**
Level (1.5 vs. 1)	0.002	0.16	0.88
Level (2 vs. 1/1.5)	0.008	1.42	0.16
Trial type (con vs. incon)	**–0.063**	**–31.85**	**<0.0001**
Condition (C vs. S) *Level (1.5 vs. 1)	0.028	1.14	0.26
Condition (A vs. S)*Level (1.5 vs. 1)	–0.005	–0.18	0.85
Condition (C vs. S) *Level (2 vs. 1/1.5)	0.021	1.44	0.15
Condition (A vs. S) *Level (2 vs. 1/1.5)	0.014	0.95	0.35
Condition (C vs. S)*Trial type	0.001	0.19	0.85
Condition (A vs. S)*Trial type	**0.010**	**2.10**	**0.04**
Level (C vs. S)*Trial type	0.003	1.32	0.19
Level (A vs. S) *Trial type	0.0002	0.15	0.89
Condition (C vs. S) Level (1.5 vs. 1)* Trial type	–0.006	–0.95	0.35
Condition (A vs. S)*Level (1.5 vs. 1)* Trial type	–0.002	–0.37	0.72
Condition (C vs. S) Level (2 vs. 1/1.5)* Trial type	0.003	0.79	0.43
Condition (A vs. S) Level (2 vs. 1/1.5)* Trial type	–0.00004	–0.01	0.99

Significant values (determined using the Sattherwaite approximation and corresponding to $p < 0.05$) are bolded.

$\beta = 0.004$, $t = 0.73$, $p = 0.47$). Thus, while the intensity of current for the cathodal condition had dose-dependent effects on *general* motor response time, this parameter had no unique effect on cognitive control performance.

Examining the Effects of Physical Sensation on Flanker Performance

While no participant reported explicit awareness of the stimulation condition, we investigated whether the physical sensations experienced by participants might differ by current polarity (anode, sham, cathode). From the debriefing questionnaire, we calculated an average rating of physical sensation per participant and submitted these scores to a Mann–Whitney *U* test. Data from the debriefing questionnaire were not obtained for 8 of the 90 participants (S-tDCS: $n = 2$; C-tDCS: $n = 3$; A-tDCS: $n = 3$). Although it is widely reported that participants cannot distinguish active stimulation from sham (e.g., in double-blind sham controlled studies; Gandiga et al., 2006), our analyses revealed that anodal stimulation (mean rating = 2.88, $SE = 0.26$) was experienced differently from sham (mean rating = 1.60, $SE = 0.25$; Mann–Whitney *U* test: $Z = 3.34$, $p = 0.0008$): No such difference was found for cathodal stimulation (mean rating = 1.99, $SE = 0.28$) relative to sham ($Z = 1.05$, $p = 0.29$).

In light of this finding, we next examined whether performance on the Flanker task might be affected by individual differences in the strength of physical sensation experienced by the participants. If a significant effect of physical sensation was observed, particularly an interaction between physical sensation and trial type, then any observed variations in RT could be attributed to participants' experience of A-tDCS, not necessarily to changes in cortical excitability. Using the same random effects structure described above, log-transformed RTs from the remaining 82 participants were regressed onto all main effects and interactions of stimulation condition (anode, sham, cathode), intensity level (1.0, 1.5, 2.0 mA), trial type (congruent vs. incongruent), and physical sensation ratings, mean-centered across participants. Crucially, we observed no significant main effect of physical sensation ($\beta = -0.008$, $t = -1.23$, $p = 0.22$) nor any significant interactions involving this predictor. Moreover, the original main effects of condition (anode vs. sham: $\beta = -0.073$, $t = -2.98$, $p = 0.004$) and trial type (congruent vs. incongruent: $\beta = -0.064$, $t = -26.98$, $p < 0.0001$) were maintained. Notably, the interaction between stimulation condition (anode vs. sham) and trial type was rendered marginally significant ($\beta = 0.009$, $t = 1.49$, $p = 0.14$), suggesting that some of the variance associated with that interaction was shared with the physical sensation predictor. Without the sensation predictor, we maintained the pattern of significant results described in the original model, even with the reduced number of participants (82 vs. 90).

DISCUSSION

Here, we systematically probed the effects of current polarity and stimulation intensity on participants' ability to perform a task of inhibitory cognitive control. Results indicated nearly at-ceiling levels of accuracy on the Eriksen Flanker across stimulation parameters. Statistical modeling of RT data clearly showed an effect of current polarity for the anodal condition relative to sham (i.e., an overall greater speed up of RTs). Most compellingly, we have demonstrated that A-tDCS to left prefrontal cortex (via the F3-RSO electrode montage) facilitated the deployment of cognitive control resources when applied concurrently with task. This evidence was clear from the reduced difference in RTs between congruent and incongruent trials (i.e., a smaller interference effect).

Nonetheless, it is important to note that we observed significant differences in the physical sensations experienced during anodal and sham stimulation. This finding runs contrary to the bulk of the tDCS literature, which overwhelmingly reports no difference in physical perception between stimulation conditions. While it is possible that differences in physical sensation, not cortical excitability, account for observed effects in behavior, including this variable in our statistical models did not on the whole dramatically alter our results. We suggest here that participants experiencing A-tDCS may have reported increased sensitivity to stimulation because they were devoting fewer cognitive resources to perform the task required. A related possibility is that overall enhanced attentional capacity during A-tDCS may have induced learners to attend more to their physical environment. Indeed, challenging cognitive control tasks have been shown to attenuate pain intensity (Bantick et al., 2002; Valet et al., 2004; Buhle and Wager, 2010). Consonant with our findings, pain reduction in one study was shown in low working memory capacity but not high working memory capacity individuals, suggesting that attenuation of pain scales with individual differences in cognitive control (Nakae et al., 2013).

While it is best to be cautious in interpreting null effects, it is also useful to review the experimental manipulations that showed *no* effect on cognitive control. First, we observed no significant interaction between stimulation intensity (1–2 mA) and trial type (congruent vs. incongruent). In other words, cognitive control capacities were not influenced in a dose-dependent manner. A *post hoc* analysis did reveal a dose-dependent increase in *overall* RTs for the cathodal condition, but this trend did not apply to the RT difference between trial types. Most strikingly, we found no evidence that cathodal stimulation differed reliably from sham, either in significantly improving or impeding Flanker performance. While such results suggest weaker reliability of cathodal stimulation, we stress that the relatively small sample size of the current study precludes us from making definitive claims about its efficacy (Minarik et al., 2016).

Nonetheless, previous studies contextualize this null finding. Specifically, Zmigrod et al. (2016) demonstrated a significantly increased Flanker interference effect (reduced cognitive control) during cathodal stimulation of *right* prefrontal cortex (electrode montage: F4-RSO; current intensity: 2 mA), but no such effect on Simon task performance (demonstrating specificity of right PFC to stimulus-stimulus rather than stimulus–response conflict). Similar to the present findings, Nozari et al. (2014) found no evidence from either accuracy or RT measures that C-tDCS

to left prefrontal cortex mediated the strength of the Flanker interference effect (electrode montage: F7-right mastoid; current intensity: 1.5 mA). Thus, it appears that cathodal stimulation of right but not left DLPFC stimulation may impede Flanker performance, but precisely why this behavioral modulation is specific to these particular stimulation conditions (C-tDCS to the right hemisphere) remains an open question. One possibility is that the Flanker task more strongly recruits right relative to left prefrontal cortex (Hazeltine et al., 2000). Indeed, recent evidence suggests that patients with right prefrontal damage showed greater Flanker interference effects than those with similar damage in the left hemisphere (Geddes et al., 2014). However, other neuroimaging studies point to more diffuse, bilateral prefrontal involvement during the Flanker (Ullsperger and von Cramon, 2001; Bunge et al., 2002; Durston et al., 2003), suggesting that the left hemisphere does assume a processing burden during tasks of inhibitory control.

In general, our findings concur with the observation that, within the broader cognitive domain, the consequences of cathodal stimulation are more varied compared to anodal stimulation (Jacobson et al., 2012). It is worth stressing that this general pattern might be traced to the observation that high-level cognitive tasks are likely to engage diffuse swathes of the brain. For example (and as indicated above), fMRI recordings of brain activation during the Flanker task have implicated widespread frontal and posterior parietal regions that are often bilaterally distributed (e.g., the middle frontal gyrus, the precentral gyrus, inferior frontal gyrus, precuneus, superior parietal lobule, etc., Zhu et al., 2010). Thus, while a stimulation-induced increase in activity in one of these areas might be enough to improve behavioral performance, suppression of an area might have unpredictable effects (likely due to compensatory recruitment of other regions). Second, whereas both A-tDCS and C-tDCS involve NMDA-receptor mediated effects, anodal stimulation effects also require sodium channel function in motor cortex (Liebetanz et al., 2002). The extent to which receptor mediated effects generalize to cognition remain to be seen. Genetically mediated individual differences in response to C-tDCS may offer a third explanation for the unreliable effects of C-tDCS. Nieratschker et al. (2015) showed that a genetic polymorphism associated with prefrontal dopamine levels predicted individual differences in behavioral response to C-tDCS. Specifically, cathodal stimulation was found to reduce cognitive control abilities in COMT 166 Val–Val homozygotes but not in Met-allele carriers (Nieratschker et al., 2015). To be clear, Plewnia et al. (2013) also showed that Met–Met homozygotes under anodal stimulation were impaired in their set-shifting abilities; however, a smaller percentage of the population are Met-allele carriers (Auton et al., 2015). Pinpointing the underlying sources of varied responses to C-tDCS, including relevant genetic determinants, is an exciting and imperative area of future research.

In sum, we have begun to disentangle the contribution of two key stimulation parameters: current polarity and intensity. Using a behavioral task that demanded the suppression of prepotent responses, we offer convincing evidence that the former, current polarity, is a robust predictor of inhibitory control abilities but that the latter, current intensity, is not. Intriguingly, this effect was specific to anodal stimulation of left prefrontal cortex, which induced a boost in cognitive control. Thus, our initial hypotheses were only partially confirmed: current polarity indeed influenced performance on a task of cognitive control. However, contrary to our expectations, this effect was specific to the anodal stimulation condition and RT interference effects did not unfold in a dose-dependent manner.

While our efforts to probe the stimulation parameter space represent an important step forward, we stress that the present approach was by no means exhaustive. Nonetheless, by providing a template for how the stimulation parameter space *might* be mapped, we open up the possibility for future research to build substantially on the findings reported here. Particularly in light of the null effects observed during cathodal stimulation, one clear next step is to examine whether these results would be overturned with a much larger sample size (i.e., perhaps C-tDCS of prefrontal cortex has a weaker, but significant behavioral impact). One might also ask whether current polarity is influenced by stimulation timing or precise electrode placement. Through increased understanding of the impact of parameter selection, a more consistent picture may emerge across cognitive tasks, and only then will truly generalizable inferences be forthcoming.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Pennsylvania Institutional Review Board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the IRB.

AUTHOR CONTRIBUTIONS

EK, ZB, RH, and ST-S formulated the experiment. EK and ZB implemented the experiment, supervised data collection and performed data analysis. RH, JM, NT, and ST-S provided input on stimulus materials and data analysis. EK and ZB wrote the original draft of the paper, with revisions and additional content contributions from RH, JM, NT, and ST-S.

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frontiers in Human Neuroscience

MINI REVIEW
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Using Transcranial Direct Current Stimulation to Enhance Creative Cognition: Interactions between Task, Polarity, and Stimulation Site

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Creative cognition is frequently described as involving two primary processes, idea generation and idea selection. A growing body of research has used transcranial direct current stimulation (tDCS) to examine the neural mechanisms implicated in each of these processes. This literature has yielded a diverse set of findings that vary depending on the location and type (anodal, cathodal, or both) of electrical stimulation employed, as well as the task's reliance on idea generation or idea selection. As a result, understanding the interactions between stimulation site, polarity and task demands is required to evaluate the potential of tDCS to enhance creative performance. Here, we review tDCS designs that have elicited reliable and dissociable enhancements for creative cognition. Cathodal stimulation over the left inferior frontotemporal cortex has been associated with improvements on tasks that rely primarily on idea generation, whereas anodal tDCS over left dorsolateral prefrontal cortex (DLPFC) and frontopolar cortex has been shown to augment performance on tasks that impose high demands on creative idea selection. These results highlight the functional selectivity of tDCS for different components of creative thinking and confirm the dissociable contributions of left dorsal and inferior lateral frontotemporal cortex for different creativity tasks. We discuss promising avenues for future research that can advance our understanding of the effectiveness of tDCS as a method to enhance creative cognition.

Keywords: creative cognition, transcranial direct current stimulation, idea generation, idea selection, frontotemporal cortex, dorsolateral prefrontal cortex

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INTRODUCTION

Creative cognition—cognition manifesting in ideas that are both novel and useful (Barron, 1955; Runco and Jaeger, 2012)—comprises two primary processes: (1) idea generation; and (2) idea selection (Christoff et al., 2001; Smallwood, 2014; Beaty et al., 2016; Chrysikou, in press). Assessments of creativity sometimes examine elements of both of these processes, yet several creativity tasks rely more heavily on one process over the other. Tasks that rely primarily on idea generation involve production of original or unusual responses to presented stimuli. These responses are then assessed on fluency, flexibility and originality (Guilford, 1950). In contrast, tasks that rely primarily on idea selection concern the integration of seemingly remote concepts or pieces of information to discover or identify something novel.

The neuroscientific exploration of creative cognition has focused on brain regions that support creative idea generation and selection using functional neuroimaging and electrophysiological measures. Recent inquiries have also used transcranial direct current stimulation (tDCS) to provide causal evidence for the role of specific brain areas in each of these processes. tDCS is the application of a constant, low-level electrical current to the cortex through surface electrodes positioned on the scalp to modulate the excitability of neurons within a region of interest (Nitsche et al., 2008; Stagg and Nitsche, 2011). tDCS studies may use anodal stimulation (generally intended to increase regional cortical excitability), cathodal stimulation (generally intended to decrease regional cortical excitability), or a combination of the two. Most studies also include a "sham" condition in which electrodes are placed on the scalp but without the application of sustained electrical current. If a cortical target plays a role in creative processing, then modulating activity in that region via tDCS should influence the form of creative thought it supports.

The examination of creative cognition through tDCS has yielded a diverse set of findings that vary depending on the task's reliance on idea generation or idea selection, as well as the stimulation location and type (anodal, cathodal, or both). Thus, understanding the relationship between task demands and stimulation montages is required to evaluate the potential of tDCS to enhance creative performance. Here, we survey the effects of tDCS on creative cognition, drawing particular distinctions between the generative and selective processes and the corresponding stimulation designs under which enhancements in creative performance can be achieved.

CREATIVE IDEA GENERATION

Recent theoretical proposals on the neurocognitive mechanisms of creative thinking have suggested that creative idea generation may depend on the availability of unfiltered, low-level perceptual information (e.g., Thompson-Schill et al., 2009; Chrysikou et al., 2014; Chrysikou, 2017). That is, the potential for creative generation is highest when a wider array of possible ideas and solutions to a situation are considered. From this perspective, an effective tDCS design would produce a cognitive mindset that is less inhibited, with a weaker reliance on past routines and representations, allowing for the consideration of information that may have been otherwise prematurely rejected. Researchers have investigated enhancements on forms of creative thought that depend on idea generation by *reducing* cortical excitability of left inferior frontotemporal cortex (a set of regions involved in inhibitory control and semantic knowledge, including the inferior frontal gyrus [IFG], anterior temporal lobe [ATL] and middle temporal gyrus [MTG]) through cathodal tDCS (Chi and Snyder, 2011, 2012; Chrysikou et al., 2013; Mayseless and Shamay-Tsoory, 2015).

Chi and Snyder (2011) used bilateral tDCS to target the ATL—a region associated with the storage of mental templates and contexts. They hypothesized that reducing cortical excitability of the left ATL may bring about less reliance on past strategies. Subjects completed challenging insight problems ("matchstick arithmetic", in which participants are tasked with correcting false statements composed of Roman numerals and symbols formed from matchsticks by moving a stick from one position to another; Ollinger et al., 2008) after solving structurally analogous but conceptually different ones during a pre-testing phase. Such prior exposure has been shown to impair performance on subsequent flexible thinking tasks, likely due to functional fixedness on a routine that was formerly effective but not applicable for the problem participants are currently attempting to solve (e.g., Ollinger et al., 2008). Cathodal stimulation of the left ATL (half way between T7 and FT7 according to the 10/20 electroencephalography (EEG) electrode placement system; **Figure 1**), with anodal stimulation of the homologous area on the right hemisphere, improved subjects' performance on the test problems. A follow up study (Chi and Snyder, 2012) produced similar results on the challenging 9-Dot Problem, which requires "thinking outside the box" to connect dots with lines that extend outside the ostensible boundaries of a square array (Maier, 1930); cathodal tDCS over the left ATL with anodal tDCS over the right ATL dramatically improved solution rates for this problem, whereas the opposite stimulation montage did not (Chi and Snyder, 2012). The authors suggested that

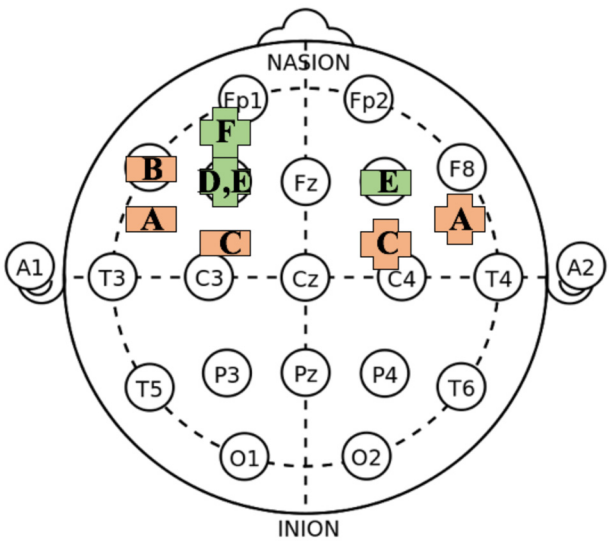

FIGURE 1 | Approximate transcranial direct current stimulation (tDCS) montage arrangements on International 10–20 system for electroencephalography (EEG) recording associated with increased creative cognition. (https://commons.wikimedia.org/wiki/File:21_electrodes_of_International_10-20_system_for_EEG.svg); public domain. The figure is a simplification and does not account for differences in montage size/type or duration of stimulation. Plus-symbol = anodal; Horizontal bar = cathodal; Orange = primarily generative tasks; Green = tasks with additional selectivity demands. A = Chi and Snyder (2011, 2012); B = Chrysikou et al. (2013); C = Mayseless and Shamay-Tsoory (2015); D = Cerruti and Schlaug (2009); E = Zmigrod et al. (2015) and Colombo et al. (2015); F = Green et al. (2017).

reducing the excitability of the left ATL might have allowed participants to consider novel approaches as opposed to familiar strategies to solve this problem (see also Goel et al., 2015).

Idea generation has also been successfully augmented through cathodal stimulation of left lateral prefrontal cortex (PFC; Chrysikou et al., 2013). Subjects performed a kind of alternative use task in which they were asked to generate either common (non-creative) or uncommon (creative) uses for a set of everyday objects. Subjects in the uncommon use condition who received cathodal tDCS over left PFC (area F7 on the 10–20 system) generated uses significantly faster and omitted significantly fewer responses than those undergoing cathodal stimulation over the right PFC or sham stimulation. Effects on latencies and omissions were not observed for common uses. These results suggest that a hypofrontal state in which an individual applies less top-down filtering may improve performance on creative generative tasks that rely on unfiltered, bottom-up processing (i.e., generating uncommon uses), but not for tasks that require access to well-rehearsed knowledge (i.e., generating common uses). In line with these findings, Mayseless and Shamay-Tsoory (2015) found that cathodal stimulation of the left IFG with concurrent anodal stimulation of the right IFG significantly improved fluency and flexibility (but not originality) measures on the Alternative Uses Task (AUT) relative to sham stimulation. The reverse montage did not elicit the same effect. A follow up experiment further failed to show significant effects of unilateral cathodal tDCS over left IFG or unilateral anodal tDCS over the right IFG. Thus, in that study, only concurrent cathodal tDCS over the left IFG with anodal tDCS over the right IFG was effective in modulating ideational fluency and flexibility.

Overall, the results of these studies show that reducing the excitability of regions of cortex involved in inhibitory control and the retention of previous experiences and contexts may improve one's ability to come up with creative ideas or problem solutions. Whether these positive effects on creative cognition also require concurrent excitation of homologous regions in the right hemisphere is likely determined by the nature of the creative task. Although the tasks reported in the current literature primarily involve the generation of creative ideas, they vary with regards to the type of problem solving (i.e., visual, verbal) required or their reliance on the retrieval of semantic information. For example, establishing and breaking a mental set in problems involving visual reasoning was a primary component of the studies by Chi and Snyder (2011, 2012), but was not an element of the experiments by Chrysikou et al. (2013) or Mayseless and Shamay-Tsoory (2015), whose tasks largely relied on verbal semantic memory retrieval. Similarly, the creativity measures (reaction times and omissions) employed by Chrysikou et al. (2013), who inhibited inferior PFC unilaterally, differed from those (fluency, flexibility) used by Mayseless and Shamay-Tsoory (2015), who inhibited left inferior PFC while concurrently exciting right inferior PFC. Lastly, tasks that rely on distancing oneself from current context or an established task mindset may benefit by stimulating temporal cortex (e.g., Chi and Snyder, 2011, 2012), whereas tasks that rely on flexibility in cognitive control (e.g., for memory retrieval) may benefit from stimulating inferior frontal cortex (e.g., Chrysikou et al., 2013; Mayseless and Shamay-Tsoory, 2015). Thus, the effectiveness of particular tDCS montages (e.g., unilateral vs. bilateral; stimulation of temporal vs. inferior frontal cortex) in modulating creative cognition appears to depend on the precise nature of the creativity task used. Despite this variability in the reported effects, overall, these studies support the conclusion that cathodal tDCS over the left inferior frontotemporal cortex can effectively boost performance on creativity tasks that contain a generative component, but have limited—at least not explicit—selection demands.

CREATIVE IDEA SELECTION

Contrary to creative idea generation, creative idea selection requires task-directed thoughts and integration of semantically distant concepts. When approaching a creative problem, one must be able to effectively direct their thoughts towards a specific goal and evaluate the suitability of potential solutions before choosing the optimal one depending on context and task demands. One appealing neural target for creative thinking that relies on such selective processes is dorsolateral PFC (DLPFC), which has been widely linked to executive function, including promotion of task-relevant thoughts and suppression of inappropriate ones (Bunge et al., 2001; Metzuyanim-Gorlick and Mashal, 2016). The first study to examine the effects of tDCS on creative cognition applied anodal, cathodal and sham stimulation to the left and right DLPFC (F3/F4 on the 10–20 system **Figure 1**; Cerruti and Schlaug, 2009). The authors assessed creativity via the Remote Associates Test (RAT; Mednick, 1962) in which subjects are presented with three "problem words" and are tasked with identifying the "target word" that links them together (e.g., "Fish, Mine, Rush" → "Gold"). The RAT contains a generative component (subjects must produce a remotely associated word given the three problem words), but its focus on appropriateness places an additional high demand on selectivity (a number of possible solutions connect two of the three problem words, but only one strings together all three; Bowden and Jung-Beeman, 2003; Gonen-Yaacovi et al., 2013). Results indicated that anodal stimulation of left, but not right, DLPFC selectively improved RAT scores without affecting solution latencies. Although additional research is required to better understand the lateralized effects, the results are consistent with the well-established role of DLPFC in guiding task-appropriate thoughts—a cognitive process that is relevant for idea selection. Increasing regional excitability of left DLPFC produced gains on a task that required not only generation, but also selection of creative ideas. The non-significant outcome of cathodal tDCS to the same area further supports this conclusion; boosts following a *reduction* of excitability of left DLPFC would have been antithetical to theories that implicate this region in creative idea selection. Critically, enhancements did not extend to a separate verbal fluency task, a measure of creativity that is primarily generative. Increased DLPFC activity may not be enough to induce changes

in performance on tasks that rely more heavily on idea generation, suggesting that other regions (e.g., inferior PFC) have a more critical role in highly generative forms of creative thought.

The Thinking Cap Effect

Research has revealed that humans are able to deliberately think more creatively when prompted by explicit instructions to do so (Harrington, 1975; Chen et al., 2005; O'Hara and Sternberg, 2011; Green et al., 2012a; Nusbaum et al., 2014; Weinberger et al., 2016). These findings suggest that—beyond being a stable *trait* that differs among individuals—creativity is also a *state* that can vary acutely over time. Functional neuroimaging has shown that enhancement of this creative state is associated with increased activation and altered functional connectivity of left frontopolar cortex during creative verbal relational thinking (Green et al., 2010, 2012b, 2015; Prabhakaran et al., 2013). Furthermore, the formation of more creative analogies has been associated with greater activation of the same region (Green et al., 2012a; Prabhakaran et al., 2013). For tasks of creative relational thinking, creativity of responses is typically assessed by "semantic distance"—a measurement of similarity/difference between the English-language context usages of terms that form analogies (more creative analogies cover a greater semantic distance; Green, 2016). Frontopolar cortex is also a good candidate to support creative idea selection because of its well-established role in more broad cognitive processes; following the rostro-caudal hierarchy of prefrontal cognitive architecture, frontopolar cortex is likely engaged in combining abstract pieces of information (Badre and D'Esposito, 2009). Additionally, neurons in frontopolar cortex are highly arborized, suggesting a key role in integrating abstract representations (Ramnani and Owen, 2004; Knowlton et al., 2012). As such, potentiating this area with anodal tDCS should produce gains on one's ability to combine and evaluate semantically distant information during analogical reasoning, thus improving performance on creativity tasks that require idea selection. To explore this prediction, Green et al. (2017) recently used anodal tDCS to target the region of peak activation of left frontopolar cortex observed in the foregoing neuroimaging studies (AF3 on the 10–20 system). Following stimulation, participants completed: (1) a task in which they were presented with word pairs (i.e., Helmet: Head) and were explicitly cued to think creatively as they selected additional word pairs from a large matrix to form valid and creative analogies (Atmosphere: Earth); and (2) a verb generation task in which they saw noun prompts onscreen and generated verbs that were related to the nouns (i.e., see: "arrow" → say: "shoot"), with a cue to think creatively given on half of the trials (Green et al., 2017). Anodal stimulation of left frontopolar cortex relative to sham lead to significantly improved creative performance on the matrix search task (as measured by semantic distance between word pairs), and a tDCS × Creativity Cue interaction yielded maximal creative performance on the verb generation task. These results are consistent with past literature on other aspects of cognition for which the combined effects of stimulation and behavioral interventions (i.e., cuing, priming) that engage the same structure targeted by tDCS have yielded larger effect sizes compared to tDCS alone (e.g., Jacobson et al., 2012).

In the absence of a creativity cue, the analogy matrix and the verb generation tasks depend on both creative processes, although the former task likely places a greater demand on selection (participants, quite literally, select appropriate creative word pairs), whereas the latter task more strongly taxes the generative resources. However, instructing participants to think creatively introduces additional selectivity demands—particularly for the verb generation task. When participants were asked to think creatively, they needed to inhibit more common, prepotent responses and select more semantically distant options. With this greater focus on idea selection, potentiating left frontopolar cortex produced greater enhancements compared to the uncued—and less selective—conditions. Our study showed that, without a cue to think creatively, anodal tDCS to left frontopolar cortex was not associated with enhanced performance on the otherwise non-selective verb generation task (see also Brunye et al., 2015). Thus, only after emphasizing selectivity explicitly did potentiating left frontopolar cortex boost performance, suggesting support for the region's contributions to creative idea selection.

Similarly, anodal stimulation to left DLPFC, paired with cathodal stimulation to right DLPFC, can improve remote association performance compared to the reverse stimulation montage or no stimulation; yet the same montage did enhance performance on the AUT, a largely generative measure as discussed above (Zmigrod et al., 2015). However, pairing the same stimulation design with explicit instructions to visualize using an object in an unusual, relative to its typical, way significantly elevated AUT total creativity scores (Colombo et al., 2015). In line with the findings of Green et al. (2017), these results demonstrate that when participants deliberately search for more creative or unusual responses the need for selectivity is amplified. Critically, anodal tDCS over regions implicated in directing one's thoughts towards a specific goal led to enhanced creativity after increased selection demands.

Taken together, this emerging literature suggests that anodal tDCS over cortical areas involved in promoting relevant thoughts and integrating discrete pieces of information (DLPFC and frontopolar cortex, respectively) can augment creative idea selection. These results support the effectiveness of this particular study design in which stimulation type (anodal) and location (left DLPFC, left frontopolar cortex) interact with task context (increased demands on selectivity) to produce significant behavioral gains for creativity performance.

CONCLUSION

Creative cognition likely relies on two primary operations, idea generation and idea selection. Although most measures of creative thought involve—to an extent—both of these processes, the growing literature on tDCS interventions to promote creative thinking suggests that creative idea generation and idea selection involve inherently different mechanisms with distinct neural

bases. This review article outlined tDCS designs that have elicited dissociable creative enhancements on each of these processes. Cathodal stimulation over the left inferior frontotemporal cortex, a region implicated in inhibitory control and the maintenance of mental templates, has been associated with improvements on tasks that rely primarily on idea generation, without significantly changing performance on tasks that rely primarily on idea selection. In contrast, anodal tDCS over left DLPFC and frontopolar cortex—brain regions that likely contribute to goal-directed thought and informational integration—can augment performance on tasks that impose high demands on creative idea selection, without significant consequences for tasks that rely primarily on creative idea generation.

tDCS effects on creative cognition as a function of the interactions between task, polarity and stimulation site highlight a critical aspect of the *in vivo* neurobiological mechanisms of tDCS: the effects of tDCS may be functionally specific, because the stimulation may affect mechanisms that are already undergoing neural plasticity (Reato et al., 2010; Rahman et al., 2015). As the contributions of left dorsal and inferior lateral frontotemporal cortex vary by the nature of the creative task (i.e., generative vs. selective), so does the effectiveness of excitatory or inhibitory stimulation over these regions. Based on the current literature, the particular montages detailed above are anticipated to elicit positive effects on creative performance depending on the generation or selection emphasis of the creative task. Nevertheless, several questions still remain. What are the neurochemical mechanisms underlying tDCS effects for creative thinking? How do individual differences due to expertise or individual genetic variability influence the effectiveness of electrical stimulation? Under which circumstances does bilateral stimulation benefit performance in creativity tasks? Extensive examination of these and other questions in future research will advance our understanding of the effectiveness of tDCS as an intervention that can reliably augment creative cognition.

AUTHOR CONTRIBUTIONS

ABW, AEG and EGC co-designed the project; wrote the manuscript. AEG and EGC provided conceptual guidance on the manuscript.

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Genetic Modulation of Transcranial Direct Current Stimulation Effects on Cognition

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High inter-individual variability substantially challenges the explanatory power of studies on the modulation of cognitive functions with transcranial direct current stimulation (tDCS). These differences in responsivity have been linked with a critical state-dependency of stimulation effects. In general, genetic diversity is a decisive biological basis of variations in neuronal network functioning. Therefore, it is most likely that inter-individual variability of tDCS-induced changes in cognitive functions is due to specific interactions between genetically determined network properties and the specific type of stimulation. In this context, predominantly the brain-derived neurotrophic factor (BDNF) Val66Met and the catechol-O-methyltransferase (COMT) Val108/158Met polymorphisms have been investigated. The studies on the interaction between the BDNF Val66Met polymorphism and the effect of brain stimulation indicate a critical but yet heterogeneous interaction. But up to now, data on the interplay between this polymorphism and tDCS on cognitive functioning are not available. However, recently, the functional Val(108/158)Met polymorphism in the COMT gene, that is particularly involved in the regulation of executive functions by means of the dopaminergic tone in frontal brain areas, has been demonstrated to specifically predict the effect of tDCS on cognitive control. Following an inverted U-shaped function, the high dopaminergic activity in Met allele homozygous individuals has been shown to be associated with a reduction of executive functioning by anodal tDCS to the prefrontal cortex. Consistently, Val homozygous individuals with lower dopaminergic tone show a clear reduction of response inhibition with cathodal tDCS. These findings exemplify the notion of a complex but neurophysiologically consistent interaction between genetically determined variations of neuronal activity and tDCS, particularly in the cognitive domain. Consequently, a systematic analysis and consideration of genetic modulators of tDCS effects will be helpful to improve the efficacy of brain stimulation and particularly tDCS in the investigation and treatment of cognitive functions.

Keywords: brain stimulation, cognition, BDNF, COMT, dopamine, neuroplasticity, stimulation genetics, tDCS

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INTRODUCTION

Targeted modulation of cortical areas by means of magnetic impulses or electric stimulation can modify brain functioning and the associated cognitive processes (Parkin et al., 2015; Plewnia et al., 2015). Transcranial direct current stimulation (tDCS) is a well-established neurostimulation technique. With using this method, a weak constant current is applied via scalp electrodes causing a subthreshold alteration of the resting membrane potential and, consequently, a modulation of cortical excitability (Nitsche et al., 2008). Typically, anodal stimulation increases excitability, whereas cathodal stimulation decreases it (Nitsche and Paulus, 2000). This transient modulation of neuronal activity with tDCS can induce specific facilitatory or inhibitory behavioral effects, respectively. However, it is important to note that the simple dichotomy of anodal enhancement and cathodal impairment is not always applicable within the complexity of neurocognitive functioning (Jacobson et al., 2012; Schroeder et al., 2016). Moreover, the neuromodulatory effects are critically affected by the current state of the system, that is they depend on the present activity of the stimulated brain region. This state dependency causes tDCS effects to be task- and activity-specific (Miniussi et al., 2013; Zwissler et al., 2014). Although research in tDCS effects gained increased attention over the past two decades, high variability of effects and sometimes even contradictory results are reported (Horvath et al., 2014). In addition to anatomical (Kim et al., 2014) and psychological differences (Sarkar et al., 2014) the genetic makeup (Witte et al., 2012) of an individual has a major contribution to this interindividual variability. Therefore, to approach this question, the following review focuses on current findings on the genetic factors influencing the malleability of cognitive processes by tDCS and gives a brief outlook on the perspectives of genetically informed, individualized brain stimulation research and treatment.

TDCS IN COGNITION

The first experiments involving tDCS were exploring the effects of motor cortex stimulation (e.g., Fuortes, 1954; Hern et al., 1962; Priori et al., 1998; Nitsche and Paulus, 2000) but over the past years, more attention has been paid to the modulation of cognitive processes (Kuo and Nitsche, 2012). Especially executive functions, often associated with dorsolateral prefrontal cortex (dlPFC) activity, are targeted by different study designs. Corresponding functions like planning ability, cognitive flexibility and working memory are essential to establish goal-directed behavior and to cope with daily life challenges. The modification of activity in the dlPFC by anodal stimulation has often been associated with improved cognitive functions, for instance, better working memory performance (Brunoni and Vanderhasselt, 2014), improved cognitive control (Plewnia et al., 2015) and enhanced planning abilities (Dockery et al., 2009). However, some findings are inconsistent with this association (e.g., Marshall et al., 2005) and, in fact, the effects of cathodal stimulation on cognition are even more diverse (Jacobson et al., 2012; Zwissler et al., 2014; Schroeder et al., 2016).

To address this variability, the influence of genetic factors on stimulation effects has already been investigated in several studies (Li et al., 2015). For this purpose, mainly genes with an established role in the regulation of neuroplasticity (Chhabra et al., 2016), particularly the brain-derived neurotrophic factor (BDNF) Val66Met and the catechol-O-methyltransferase (COMT) Val108/158Met polymorphisms have been investigated.

TDCS AND THE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

Brain-Derived Neurotrophic Factor belongs to the family of neurotrophins, which promote cell survival and development (Huang and Reichardt, 2001). It is expressed as a precursor peptide, proBDNF, which is proteolytically cleaved to generate the mature protein (Seidah et al., 1996). Binding of BDNF either to the tropomyosin-related kinase (Trk) B receptor or the p75 receptor activates different intracellular signaling cascades (Patapoutian and Reichardt, 2001). It seems to play an important regulatory role in the neurophysiological processes underlying cognitive functions. For instance, hippocampal-dependent learning paradigms rely on BDNF/Trk signaling (Tyler et al., 2002). Furthermore, BDNF has been shown to be involved in synaptic plasticity (Lu, 2003) as well as in long-term potentiation and depression (Aicardi et al., 2004).

There are several single nucleotide polymorphisms in the gene encoding BDNF (Liu et al., 2005). One of them causes a substitution in the prodomain of BDNF at position 66 of valine to methionine (Val66Met), which impacts BDNF expression and secretion (Mallei et al., 2015). In cultured hippocampal neurons it has been shown that viral transfection with the BDNF Met allele causes less depolarization induced secretion than Val allele transfection (Egan et al., 2003). On the behavioral level, this polymorphism has been associated with impaired executive functions (e.g., Hariri et al., 2003). This renders BDNF as an excellent candidate gene having an impact on the effects of brain stimulation (**Table 1**). It has been shown that the BDNF polymorphism interacts with training-dependent increases in the amplitude of motor-evoked potentials and motor map reorganization, as Val66Met individuals show reduced plasticity relative to Val66Val individuals (Kleim et al., 2006). These findings have also been replicated for plasticity-inducing TMS protocols, to which only Val66Val homozygous individuals showed a neuroplastic response (Cheeran et al., 2008). Furthermore, the investigation of this interaction was extended to transcranial random noise stimulation (tRNS) and tDCS. Only for tDCS protocols heterozygous Val66Met allele carriers displayed an enhanced cortical excitability following anodal stimulation and a more pronounced cortical inhibition after cathodal stimulation as measured by motor evoked potentials. For tRNS there was no group difference observed

TABLE 1 | Overview of previous studies investigating the interaction of the common BDNF Val66Met Polymorphism with brain stimulation effects.

BDNF allele	Effect	Stimulation Target	Method	Population	Study
Met carrier	⇓ Plasticity	Motor cortex	Motor training/TMS	Healthy subjects	Kleim et al., 2006
Met carrier	⇓ Plasticity	Motor cortex	Repetitive TMS	Healthy subjects	Cheeran et al., 2008
Val homozygous	⇑ Plasticity	Motor cortex	Repetitive TMS	Healthy subjects	Antal et al., 2010
Met heterozygous	⇑ Plasticity	Motor cortex	Anodal and cathodal tDCS	Healthy subjects	Antal et al., 2010
Met carrier	⇑ Plasticity	Motor cortex	Anodal tDCS	Older healthy subjects	Puri et al., 2015
Val homozygous	⇓ Plasticity	Motor cortex	Anodal tDCS	Healthy subjects/patients with schizophrenia	Strube et al., 2015
	⇓ Inhibition	Motor cortex	Cathodal tDCS	Patients with schizophrenia	Strube et al., 2015
Met heterozygous	⇑ Inhibition	Motor cortex	Cathodal tDCS	Healthy subjects	Strube et al., 2015
Val homozygous	⇑ Plasticity	Motor cortex	motor training/anodal tDCS	Healthy subjects	Fritsch et al., 2010
Val66Met	No effect	Antidepressant response (DLPFC)	Bifrontal stimulation	Patients with depression	Brunoni et al., 2013

(Antal et al., 2010). A more recent study investigated an interaction of the Val66Met polymorphism and stimulation duration in older adults on the modulating effects of anodal tDCS on motor cortex plasticity. After 20 min but not after 10 min of anodal stimulation Met allele carriers experienced enhanced corticospinal excitability compared to individuals homozygous for the Val allele (Puri et al., 2015). Furthermore, Strube et al. (2015) demonstrated increased facilitatory effects of anodal stimulation on cortical plasticity in patients suffering from schizophrenia as well as in healthy controls for heterozygous compared to Val allele homozygous individuals. In contrast, cathodal stimulation caused reduced cortical inhibition in heterozygous schizophrenia patients but enhanced inhibitory effect in healthy heterozygotes indicating an interaction of interindividual differences. Another animal study showed that anodal tDCS combined with low-frequency direct synaptic stimulation applied to the motor cortex causes long-lasting synaptic potentiation most likely mediated by the BDNF Val66Met polymorphism as the effect was absent in mice with an inhibited TrkB activity, which is influenced by the BDNF Val66Met polymorphism. Specifically, individuals homozygous for the Val allele demonstrated greater motor skill improvement under anodal tDCS than Met allele carriers (Fritsch et al., 2010). Aiming at a prediction of therapeutic tDCS effects, Brunoni et al. (2013) have examined the interaction of two genetic variants, the BDNF Val66Met and the 5-HTTLPR polymorphism, with the antidepressant effect of tDCS. The latter one describes an insertion/deletion of 44 bp, which regulates the activity of the serotonine transporter (5-HTT) and is a potential susceptibility gene for affective disorders (Collier et al., 1996). Interestingly, they did not find an impact of the BDNF genotype but of the 5-HTTLPR polymorphism on the antidepressant response of tDCS. Specifically, there was no effect of tDCS in homozygous short allele carriers, whereas the number of long alleles appeared to correlate with the stimulation effect. In sum, studies on the interaction between the BDNF Val66Met polymorphism and the effect of brain stimulation on neuronal and behavioral functioning indicate a critical but yet heterogeneous interaction with predominant evidence for a reduced susceptibility of the Met allele carrier. However, findings from clinical trials do not provide support for the notion that the BDNF polymorphism is suitable to predict the efficacy of tDCS as a treatment of depression. To our knowledge, evidence for an association between BDNF polymorphisms and tDCS on cognitive functions is not yet available.

TDCS AND THE CATECHOL-O-METHYLTRANSFERASE (COMT)

Another gene, discussed to be involved in cognitive processes and potentially influencing stimulation outcome, is the COMT gene. The COMT enzyme plays a critical role in the degradation of catecholamines, e.g., dopamine by transferring a methyl-group of *S*-adenosylmethionine to the 3-hydroxy group of the catechol (Axelrod and Tomchick, 1958). A functional polymorphism at position 108/158 causing an amino acid exchange from valine to methionine (Val108/158Met) impacts the enzyme's thermostability as well as its activity. The Met allele results in a more thermolabile and less active COMT phenotype (Lotta et al., 1995; Lachman et al., 1996; Chen et al., 2004). Especially, in the prefrontal cortex, where the expression of dopamine transporters is low, the COMT enzyme plays an important role in regulating dopamine levels (Sesack et al., 1998; Käenmäki et al., 2010). This is also reflected in the fact that the Val108/158Met polymorphism is affecting cognitive functions being associated with prefrontal cortex activity. In patients suffering from schizophrenia as well as unaffected siblings and healthy controls it has been demonstrated that the number of Met alleles positively correlates with prefrontal executive functions and working memory performance assessed by the Wisconsin Card Sorting Test (Egan et al., 2001). This might result from the lower dopamine degradation rate caused by the Met allele. Furthermore, they identified the Val allele as a risk factor for schizophrenia. Although many studies replicated these findings, there were also contradictory results and a meta-analysis concluded that the interaction of the COMT Val108/158Met polymorphism with cognitive performance is questionable (Barnett et al., 2008). However

several neuroimaging studies linked differences in prefrontal cortex activity to COMT Val108/158Met genotype. Specifically, Met allele carriers show increased prefrontal activity indicating lower cortical efficiency during emotion processing tasks, whereas Val allele carriers exhibit higher prefrontal activity during cognitive processes (Mier et al., 2010). For optimal cognitive functioning a physiological prefrontal dopamine concentration is required (Goldman-Rakic et al., 2000). The inverted-U shape hypothesis describes a non-linear relationship between cognitive performance and dopamine concentrations. Accordingly, both too high as well as too low concentrations of dopamine are associated with suboptimal cognitive processing (Cools and D'Esposito, 2011). In parallel, the tDCS effects also depend on dopaminergic activity. Administration of L-Dopa has been shown to extend the inhibitory effects of cathodal stimulation and invert the excitatory effects of anodal stimulation to inhibition (Kuo et al., 2008). Of note, this modulatory influence of dopamine turned out to be strongly dose-related with both high and low activation of dopamine receptors preventing plasticity induction with tDCS (Monte-Silva et al., 2010; Fresnoza et al., 2014). These findings point toward a non-linear, inverted U-shaped relationship between dopaminergic activity and neuroplastic changes by tDCS.

Therefore, a behaviorally relevant interaction of tDCS effects with the individual COMT Val108/158Met polymorphism, which is regulating the prefrontal dopamine concentration, must be taken into account and might open new options to integrate the individually variable dispositions to tDCS in the planning and interpretation of brain stimulation studies. In the clinical domain, one study investigated the influence of this polymorphism on the antidepressant response in a TMS protocol. Although no effect of the COMT polymorphism was found, the 5-HT1A serotonergic receptor promoter region polymorphism predicted the treatment outcome (Malaguti et al., 2011). In the context of another clinical application, Shivakumar et al. (2015) reported a better reduction of auditory hallucinations in schizophrenic patients by tDCS treatment in COMT Val allele homozygous individuals compared to Met allele carriers.

In healthy subjects, two recent studies have demonstrated a specific interaction of the COMT polymorphism with both anodal as well as cathodal tDCS during cognitive tests (Plewnia et al., 2013; Nieratschker et al., 2015). They investigated executive functioning using a Parametric Go/No-Go (PGNG) task. This task comprises three levels tapping different aspects of executive functioning: sustained attention, response inhibition and set-shifting abilities (Langenecker et al., 2007). In both experiments tDCS (1mA) was applied during task performance and targeted to the left dlPFC. In the first study, an effect of anodal stimulation was only observed when including genotype information of the COMT Val108/158Met polymorphism. Specifically, the stimulation impaired set-shifting abilities indicated a deterioration of cognitive flexibility in homozygous Met allele carriers but not in Val allele carriers. In the three levels of the PGNG task, no baseline differences were found. The tasks measuring sustained attention and response inhibition were not affected by adding anodal stimulation (Plewnia et al., 2013). Correspondingly, in the second experiment an interaction of stimulation and genotype information has been found for cathodal tDCS. This time an interference of stimulation with response inhibition was found for the overall group but including genotype as a between subjects factor showed that this effect was specific to individuals homozygous for the Val allele. These researchers showed a deterioration of response inhibition specifically under cathodal stimulation (Nieratschker et al., 2015). These complementary studies clearly indicate the decisive influence of the individual genetic profile on the malleability of executive functions by tDCS and particularly highlight the task specificity of this interaction.

These results can be put in context of the inverted-U shape hypothesis in which both excessively high and low dopaminergic activity is associated with impairment (Schacht, 2016). Subjects homozygous for the Val allele have lower dopaminergic signaling and, therefore, are located more to the left on the inverted-U shape curve than homozygous Met allele carriers who have higher dopaminergic signaling. As **Figure 1** illustrates, this hypothesis suggests that the performance level of COMT Val108/158Val homozygous individuals is on the ascending side of the curve, whereas that of the Met108/158Met homozygous individuals is on the descending part. Based on this model, anodal tDCS might increase dopaminergic activity in Val108/158Val individuals in the range of optimal performance, which is why anodal stimulation does not have an effect on performance. In contrast, cathodal stimulation decreases the activity of dopaminergic neurons and shifts Val108/158Val individuals to lower performance levels. In turn, consistent with this model, the further increase of dopaminergic activity in Met108/158Met individuals by anodal stimulation leads to a deterioration of cognitive flexibility, as their dopaminergic tone is already relatively high. However, the cathodal decrease of excitability does not yield behavioral effects in these subjects with an already high dopaminergic activity.

Although these results fit well into this concept of an inverted-U shape relationship, many open questions remain. First, it will be necessary to disentangle the role of COMT Val108/158Met heterozygous individuals. In the two reported studies only individuals homozygous for either the Met or Val allele are significantly affected by anodal or cathodal stimulation, respectively. However, it is not clear if the stimulation actually has an intermediate effect on the heterozygous subjects. Second, it is of interest to further investigate the task specificity and state-dependency of the interaction between brain stimulation and genotype. The fact that in each study only one out of three executive functions showed a significant genotype-dependent modulation of performance is consistent with a differential influence of frontal dopamine concentrations on executive functioning. In this regard the influence of the COMT Val108/158Met polymorphism on changes in cognitive stability and flexibility after a tDCS-enhanced working memory training was recently investigated. However, no effects were found most likely due to a different study design targeting lasting transfer effects and/or a rather small sample size (Stephens and Berryhill, 2016). Another study related effects

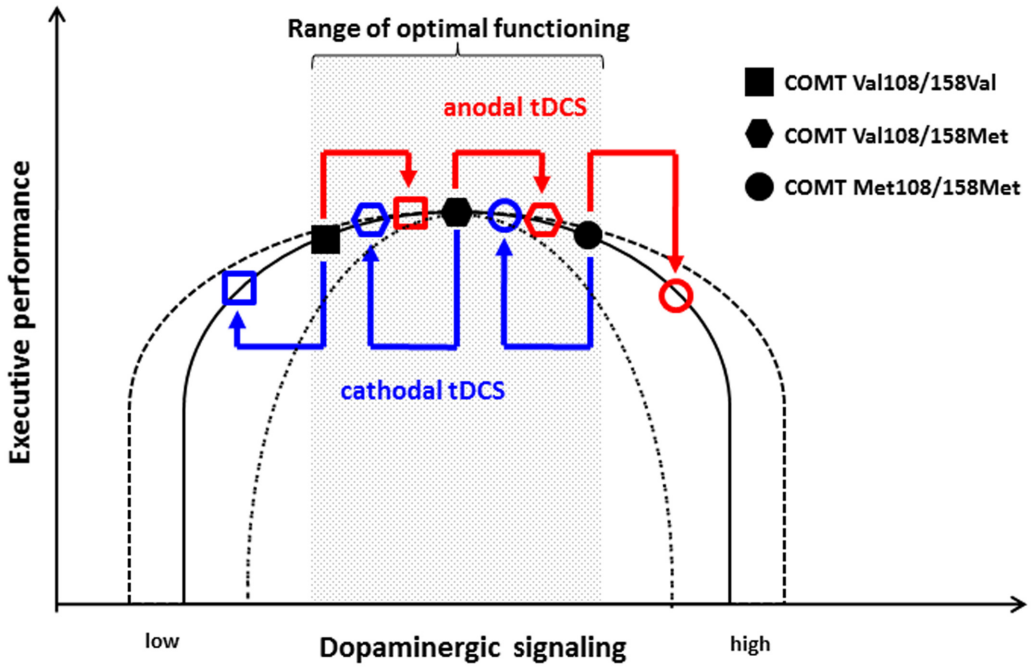

FIGURE 1 | Model of the effect of tDCS on the non-linear association between dopaminergic signaling and executive performance with regard to COMT Val108/158Met genotype. Homozygous COMT Val108/158Val individuals are located on the ascending part of the curve. Therefore, anodal tDCS does not significantly impact their executive functioning, whereas cathodal stimulation causes deterioration. In contrast, homozygous COMT Met108/158Met individuals are located on the descending part. Consequently, their performance is not substantially affected by cathodal stimulation, whereas anodal stimulation leads to impaired cognitive functioning. According to this model, heterozygous COMT Val108/158Met individuals remain unaffected by both anodal and cathodal tDCS. The inverted-U shape curve might be highly variable between individuals and different tasks as indicated by the dashed line.

of tDCS over the right dlPFC on response inhibition to psychopathic traits like coldheartedness, since there is an association between psychopathic personality traits and impaired response inhibition. Here, a positive correlation between the score rating the participants' coldheartedness and an improvement due to cathodal tDCS in their performance was found in the PGNG task measuring response inhibition (Weidacker et al., 2016). This is particularly remarkable in the context of the studies indicating an interaction between the COMT Val108/158Met polymorphism and tDCS (Plewnia et al., 2013; Nieratschker et al., 2015). Variability in executive functioning (Wishart et al., 2010) as well as antisocial behavior (Langley et al., 2010) have been linked with this gene. Therefore, the particular findings of this study might be based on a similar genetic profile particularly with respect to the COMT Val108/158Met polymorphism. However, the stimulation protocols used differed as Weidacker et al. (2016) applied stimulation to the right dlPFC before task completion, whereas Nieratschker et al. (2015) stimulated the left dlPFC during the task. Third, it will be important to also include genotype information from other polymorphisms. For instance, an interaction of the BDNF and the COMT polymorphisms has been demonstrated in a paired associative stimulation protocol inducing cortical plasticity (Witte et al., 2012). While no single polymorphism caused interindividual variability on its own it was shown that subjects homozygous for the BDNF Val allele, who were homozygous for the COMT Met allele at the same time, exhibited higher cortical plasticity. These results indicate a complex influence of the individual genetic makeup on the interaction between stimulation and cognition. Finally, epigenetic variability could also contribute to different tDCS responses. There is evidence from an animal study suggesting that long-lasting stimulation effects might be caused by epigenetic alterations of BDNF regulatory sequences increasing BDNF expression levels (Podda et al., 2016). Although epigenetic modifications are dynamic, certain baseline differences as well as variability in the epigenetic alterations potentially induced by tDCS could affect stimulation outcome.

To conclude, several studies indicate that genetic factors contribute to the interindividual variability of tDCS effects on cognition. Particularly, the COMT Val108/158Met polymorphism has been already demonstrated to shape the effects of tDCS on executive functions. Yet, the number of studies examining this interaction is still very small. Therefore, more research is needed to test the reliability of the existing data and to investigate the differential interactions of genetic disposition with specific cognitive processes and stimulation parameters. In addition, the complexity of this challenge is even increased by the critical interaction of different polymorphisms. However, for future brain-stimulation research the inclusion of genetic information in the design and analysis of brain

stimulation studies, will essentially contribute to reduce the variability and allow for the development of more individualized stimulation protocols in basic and clinical research.

AUTHOR CONTRIBUTIONS

AW drafted the manuscript. VN and CP revised the article. All authors gave final approval of the version to be published.

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Individual Differences and State-Dependent Responses in Transcranial Direct Current Stimulation

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Transcranial direct current stimulation (tDCS) has been extensively used to examine whether neural activities can be selectively increased or decreased with manipulations of current polarity. Recently, the field has reevaluated the traditional anodal-increase and cathodal-decrease assumption due to the growing number of mixed findings that report the effects of the opposite directions. Therefore, the directionality of tDCS polarities and how it affects each individual still remain unclear. In this study, we used a visual working memory (VWM) paradigm and systematically manipulated tDCS polarities, types of different independent baseline measures, and task difficulty to investigate how these factors interact to determine the outcome effect of tDCS. We observed that only low-performers, as defined by their no-tDCS corsi block tapping (CBT) performance, persistently showed a decrement in VWM performance after anodal stimulation, whereas no tDCS effect was found when participants were divided by their performance in digit span. In addition, only the optimal level of task difficulty revealed any significant tDCS effect. All these findings were consistent across different blocks, suggesting that the tDCS effect was stable across a short period of time. Lastly, there was a high degree of intra-individual consistency in one's responsiveness to tDCS, namely that participants who showed positive or negative effect to anodal stimulation are also more likely to show the same direction of effects for cathodal stimulation. Together, these findings imply that tDCS effect is interactive and state dependent: task difficulty and consistent individual differences modulate one's responsiveness to tDCS, while researchers' choices of independent behavioral baseline measures can also critically affect how the effect of tDCS is evaluated. These factors together are likely the key contributors to the wide range of "noises" in tDCS effects between individuals, between stimulation protocols, and between different studies in the literature. Future studies using tDCS, and possibly tACS, should take such state-dependent condition in tDCS responsiveness into account.

Keywords: non-invasive brain stimulation, transcranial direct current stimulation (tDCS), visual working memory (VWM), state-dependence, right posterior parietal cortex (rPPC)

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INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique, and its therapeutic and neuronal-based enhancing potential has attracted interest from basic scientists and clinicians alike. By applying a weak electric current over the scalp, where cortical neuronal activities beneath the stimulated area would change with the direction of current flow, tDCS can modulate cortical excitability and, consequently, various cognitive performances. Early animal studies have reported a bi-directional effect of tDCS in modulating neural activities, where anodal tDCS was associated with the depolarization of neurons, and cathodal tDCS was associated with the hyperpolarization of neurons (Creutzfeldt et al., 1962; Bindman et al., 1964; Purpura and McMurtry, 1965). Similar effects were also observed in humans' motor cortex excitability (Nitsche and Paulus, 2000; Stagg and Nitsche, 2011; Pellicciari et al., 2013), where anodal and cathodal stimulation increased and decreased MEP amplitudes, respectively. This suggests that, consistent with previous studies done on animals, the excitability of cortico-motor neurons was modulated by the current direction of tDCS (Antal et al., 2007; Miyaguchi et al., 2013; Chew et al., 2015). The assumption of bipolarity with opposite neuronal and cognitive effects has since been adopted in many of the earlier cognitive work (for a review, see Paulus, 2011; Vallar and Bolognini, 2011; Jacobson et al., 2012; Horvath et al., 2015a,b). For example, anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) increased the number of correct responses in a 3-back working memory (WM) task (Fregni et al., 2005). Along the same line, anodal stimulation over the left DLPFC also improved WM performance (Zaehle et al., 2011) and decreased reaction times (Mulquiney et al., 2011) whereas no improvement/decrement on memory performance was observed after cathodal stimulation on the same brain area (Fregni et al., 2005; Ohn et al., 2008; Andrews et al., 2011; Zaehle et al., 2011). Additionally, tDCS has also revealed its great potential in treatment. Improvement in major depression (Fregni et al., 2006; Brunoni et al., 2011), memory deficit in Parkinson disease (Boggio et al., 2006a,b), aphasia (Baker et al., 2010; Kang and Paik, 2011; You et al., 2011) and recovery from stroke patients (Fregni et al., 2005; Miniussi et al., 2008; Jo et al., 2009; Kang et al., 2009; Bolognini et al., 2011; Bueno et al., 2011) all suggest that neuromodulation is able to critically affect patients' cognitive functions.

Recently, despite the simple anodal-increase and cathodal-decrease rules of thumb, many studies have observed that, beyond tDCS polarity, stimulation parameters such as duration, intensity, frequency, electrode position and control settings can also modulate the final outcome of the tDCS effect (Teo et al., 2011; Jacobson et al., 2012; Batsikadze et al., 2013; Brunoni et al., 2013; Hoy et al., 2013; Benwell et al., 2015; Horvath et al., 2015a,b). In addition, inter- and intra-individual differences, including genetics, age, gender, physiological differences and baseline task performances, all imply the importance of "neural state" that may determine the modulating effect through its interaction with tDCS (Mattay et al., 2003; Cheeran et al., 2008; Krause and Cohen Kadosh, 2014; Veniero et al., 2016). Supporting evidence from pharmacologic studies showed that L-dopa-induced learning and memory formation can interact with tDCS-induced neuroplasticity (Monte-Silva et al., 2010). When L-dopa was applied alone, the dosage of dopamine and cognitive functions displayed an inverted U-shaped relationship: mainly, when dosage of L-dopa was low or high, the corresponding plasticity was inhibited, whereas a medium dosage facilitated neural plasticity. When tDCS was applied concurrently with medium dosage of L-dopa, tDCS turned facilitatory plasticity into inhibitory, suggesting that tDCS induced plasticity changes in a similar fashion as L-dopa. Also, this possibly suggests that tDCS might have placed an additive/subtractive effect to the medium dosage of L-dopa, which turned median dosage into low/high dosage to induce such inhibitory effect.

The non-linear state-dependence of the tDCS effect was not only found in pharmacological studies, but also in cognitive performances (Learmonth et al., 2015). In the field of visual working memory (VWM), previous fMRI studies have reported that the BOLD signal of the posterior parietal cortex (PPC) would increase with memory capacity until reaching a neural and behavioral plateau (Todd and Marois, 2004; Vogel et al., 2005; Xu and Chun, 2006). According to the anodal-increase and cathodal-decrease rules of thumb, anodal stimulation over PPC should increase neural activities and memory performance, and vice versa for the cathodal stimulation. However, the observed effect of tDCS was much more complicated. Our previous studies reported that, despite identical stimulation parameters and proper counterbalancing, the effect of tDCS was not equal for all participants: it altered with participants' baseline performance. When we lined up the participants based on their natural performances from the sham-tDCS condition, only low performers showed a boost in neural activities and behavioral WM performance with right PPC (rPPC) anodal stimulation, but not the high performers (Tseng et al., 2012). Evidence from behavioral, event-related potentials, and alpha oscillation all supported the finding that memory capacity in low performers was selectively enhanced by rPPC anodal stimulation (Tseng et al., 2012; Hsu et al., 2014). The same pattern was also observed when we used AC stimulation in combination with a similar VWM task (Tseng et al., 2016). These findings suggest that the baseline state of each individual is different and that the tDCS effect, or one's receptivity to the tDCS effect, changes with his or her baseline performance. Together, this observation is also consistent with the transcranial magnetic stimulation (TMS) literature, suggesting that the effect of tDCS is associated with the neural state of the stimulated individuals (Dockery et al., 2009; Berryhill and Jones, 2012; Tseng et al., 2012; Hsu et al., 2014; Benwell et al., 2015; Learmonth et al., 2015).

Given the growing number of studies reporting varied effects of tDCS with different baseline performances (Gözenman and Berryhill, 2016; Heinen et al., 2016; Looi et al., 2016), it is important for studies to choose an appropriate baseline on which to evaluate the effect of tDCS. The studies mentioned above have mostly adopted participants' behavioral performances from the sham condition to serve as a baseline to split the participants into different groups (Tseng et al., 2012, 2016; Hsu et al., 2014).

Alternatively, one important study by Jones and Berryhill (2012) adopted the digit span task as an independent measure, rather than using VWM performance from the sham condition, to split the participants into low and high performers. The authors found that anodal stimulation increased memory performance. More importantly, they also found that the tDCS effect varied with participants' baseline digit span performance: only the high WM capacity group enjoyed an improvement after stimulation but not the low WM capacity group. Recently, Heinen et al. (2016) also provided another evidence of tDCS effect varying with participants' baseline performance. They showed that only cathodal stimulation enhanced WM precision, especially for those participants whose baseline performance was low. Together, although these studies are not entirely consistent with one another, they do point out one thing in common: the importance of baseline memory performance on which to evaluate tDCS effect.

In addition to baseline performance, task difficulty is also another likely contributor to the state-dependent nature of the effects of tDCS. In a cognitive control task, the effect of tDCS was observed in the easy and medium difficulty conditions, but not the most difficult condition. In the context of VWM, Jones and Berryhill (2012) found that only the high performers showed improved memory performance with tDCS as task difficulty increased. Using another VWM paradigm, Wu et al. (2014) also found that the most difficult memory condition is usually the one that participants show a significant amount of tDCS-induced improvement. However, without using the same memory paradigm, it is difficult to equate or properly compare task difficulties across studies.

Based on the mixed findings reviewed above, the present study aims to investigate the interaction between tDCS polarity, task difficulty, and individual differences by systematically varying different parameters of task difficulty and tDCS polarity, while testing them on the same set of individuals that include a mixture of low and high performers. We continued to use a VWM change detection task since VWM has been extensively investigated with tDCS, thus better relevance with the existing literature. For a better understanding of the influence of baseline performance on tDCS effects, we also revisited the issue of splitting participants by using the digit span task and another visuospatial WM variant—the corsi block tapping (CBT) task. CBT is a well-studied task, and is widely used in the clinical population to evaluate their VWM performance (e.g., Kessels et al., 2000). Furthermore, it has been shown to be sensitive to anodal tDCS both in the healthy (Wu et al., 2014) and neurological (Wu et al., 2016) populations. In the present study, participants performed digit span and CBT, in counterbalanced order, on a separate day prior to their participation in the formal session, which included sham, anodal and cathodal tDCS on three different days (separated by a week) in counterbalanced order. Finally, we analyzed participants' change detection performance, the main dependent measure of this experiment, in two different ways. We approached this by splitting the participants either based on their CBT or digit span performance. Levels of task difficulty were also included to investigate whether the effects of tDCS would change with task difficulty.

MATERIALS AND METHODS

Ethical Standards

This study has received the human study approval (101-1930A3) from the Institutional Review Board, Linkou Chang Gung Memorial Hospital, Taoyuan County. It has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Participants

Eighteen right-handed participants (mean age 22.7 years, range of 20–27; 11 females and 7 males) were recruited in this experiment. All had normal or corrected-to-normal visual acuity, and reported no neurological history. All participants signed informed consent prior to their participation in the experiment and they received monetary reimbursement upon completion of all four sessions (one behavioral pre-session and three tDCS sessions).

Apparatus

Stimuli were presented on a 19-inch CRT screen using a video resolution of 1024 × 768 pixels and a vertical refresh rate of 100 Hz. Subjects sat 57 cm in front of the screen, which was positioned at eye level. Stimuli were generated and delivered in MATLAB (MathWorks) using Psychtoolbox (Brainard, 1997; Pelli, 1997), which controlled the presentation of the stimuli and recorded participants' responses.

tDCS was delivered with a Magstim Eldith DC-stimulator and a pair of electrodes housed in 4 cm × 4 cm saline-soaked sponge coverings. The center of the stimulation electrode was placed over the target site, P4 according to the international 10-20 system for EEG electrode placement. P4 was chosen because of its importance in the task used in the present study (Vogel et al., 2005; for a review, see Juan et al., in press), and also because of our goal of comparing against previous tDCS studies that have investigated the effects of tDCS in change detection performances (Jones and Berryhill, 2012; Tseng et al., 2012; Hsu et al., 2014). The other electrode was placed over the left cheek. In the tDCS conditions the current was applied for 15 min with an intensity of 1.5 mA (Berryhill et al., 2010; Jones and Berryhill, 2012; Tseng et al., 2012; Hsu et al., 2014). The sham tDCS condition followed an identical procedure, including electrode placements, but only ramp-up and ramp-down for a total of 30 s and no electric stimulation for 15 min.

Design and Procedure

The entire experiment consisted of four separate sessions: the behavioral pre-session, sham tDCS, anodal tDCS and cathodal tDCS. The behavioral pre-session always took place on the first day, while the order of the three tDCS sessions were counterbalanced across participants. Each tDCS session was separated for at least 1 week apart to control for any unanticipated carry-over effects. On the day of the behavioral pre-session, participants completed a block of digit span and CBT in counterbalanced order. On the remaining 3 days, participants first completed

36 practice trials of the change detection task, then went through 15 min of tDCS, and finally completed 576 more trials of change detection task over the course of eight blocks.

Each participant was to complete a computer-based version of CBT task (Corsi, 1972; Bo et al., 2011; Brunetti et al., 2014) to measure their baseline performance in visuospatial WM. The task requirement was that participants had to reproduce a given flash sequence by mouse-clicking on the corresponding blocks. There were nine blue colored patches on each array. Only one of them flashed with yellow color on each array for 200 ms. The experiment started with sequences of two flashes, which constituted as the easiest trial. The length of the sequence was gradually increased by one item when the participants correctly recalled the sequences on two consecutive trials. In contrast, the task ended if the participant could not reproduce the given sequences in two consecutive trials. The length of the sequence in the very last trial would serve as an index of that person's visuospatial WM span. Participants also performed a computer-based version of forward digit span on the same day. Each digit was presented by voice with a 1 s interval between each digit. After each sequence, participants were to repeat the sequence by pressing the corresponding number keys on a keyboard. The cutoff procedure for digit span is identical to the CBT, where two consecutive correct trials would lead to a one-digit span increase, and two consecutive error trials would end the task and determine participant's verbal WM capacity.

The experimental design included within-subjects factors of a set size (4, 6, 8), tDCS (anodal, cathodal, sham), and a between-subjects factor of groups (low performer, high performer). In the change detection task, each trial began with 1000–1500 ms fixation, followed by a 500 ms cue array, a 500 ms memory array, a 1000 ms retention interval, and a 2000 ms test array. Participants were to click the left button on the mouse with their right index finger when there was a change or click right button on the mouse with their right middle finger for no change. The task was modified from the Vogel and Machizawa (2004) study. All the stimuli were presented within two 5° × 12° rectangular regions placed 1° away from a central fixation cross on a gray background. Each memory array consisted of 4, 6, or 8 colored squares (0.4° × 0.4°) in each hemifield. The color of each square on memory array was randomly selected from a set of colors (red, green, blue, yellow, dark gray, pink, purple, cyan and white). Stimulus positioning was randomized on each trial. In 50% of trials, one of the colored squares in the test array would differ from the memory array (also known as change trials), with the remaining 50% of trials being no-change trials. Before the memory array, a central arrow cue would instruct the participants to remember the items in either the left or right hemifield.

Data Analyses

Two measures were used to index participants' performance: d' and Pashler's K. The value of d' is a common measure of sensitivity derived from the signal detection theory (Macmillan and Creelman, 1991). The d' is estimated by the difference of standardized hit rate and false alarm rate (1). Larger d' means higher sensitivity whereas d' near zero means chance-level performance. Pashler (1988) K is a formula used in estimating how many items are held in one's memory (2). The rationale is that if an individual can hold K number of items in memory from an array out of S items, then K could be estimated via set size and correct response rate to change trials. To correct for guessing and interference from the test array, false alarm rate is also taken into account in the formula (Rouder et al., 2011).

$$d' = z\,(\text{Hit rate}) - z\,(\text{False alarm rate})\,; \tag{1}$$

$$K = \frac{\text{Set Size} * (\text{Hit rate} - \text{False alarm rate})}{(1 - \text{False alarm rate})} \tag{2}$$

RESULTS

Individual Differences in Responsiveness to tDCS

As other studies have previously documented (Chew et al., 2015), there was a wide range of individual differences even at set size 4 where the difficulty level is optimal (see our analysis in the sections below). However, although differences existed between different individuals (**Figure 2**, left chart), the directions of tDCS effect seemed quite consistent within each individual. That is, when we computed the anodal-sham and cathodal-sham contrasts for each participant, most of the participants had the same direction of tDCS effect for both anodal and cathodal stimulation. In summary, there were seven participants who showed improvement in both anodal and cathodal sessions, five participants who showed consistent impairment regardless of tDCS polarity, and five participants whose tDCS performance followed the traditional anodal-increase and cathodal-decrease assumption (**Figure 2**, lower right pie chart). Only one participant showed a cathodal-increase and anodal-decrease pattern that is less consistent with the literature.

At the group level, from the assumption of anodal-increase and cathodal-decrease, a negative correlation between anodal-increased performance and cathodal-decreased performance would be expected. To investigate whether this assumption also applies to the current study, a correlation analysis was conducted on signal detection performance between anodal-sham and cathodal-sham contrasts. However, a positive correlation between anodal-sham and cathodal-sham was found, $r_{(18)} = 0.692$, $p = 0.001$, which is not supporting the anodal-increase and cathodal-decrease assumption. In addition, Pearson's chi-square test was conducted to examine whether the tDCS effect on each individual was coming from the same distribution or not. The tDCS effect was relabeled according to the size of contrast scores. When the contrast scores are smaller or equal to ±0.5, they are relabeled as ±1. When

the contrast scores larger than ±0.5, which is quite large in terms of d', the contrast scores are relabeled as ±2. The result showed that the tDCS effect on each individual was coming from different distributions, $\chi^2_{(9,\ N=18)} = 24.05$, $p = 0.004$. This can potentially be explained by the high intra-subject consistency between anodal and cathodal tDCS described above.

Splitting Participants into Low- and High-Performing Groups Using Forward Digit Span Task

Participants were split into two groups according to their digit span score. Independent sample *t*-test showed a significant group differences, $t_{(16)} = -4.24$, $p = 0.001$. The digit span score was significantly higher in the high-performing group ($M = 10.11$) than the low-performing group ($M = 7.88$). To check whether our statistical power was undermined by limited sample size, we conducted *post hoc* power analyses using GPower (Faul and Erdfelder, 1992; for a full description, see Erdfelder et al., 1996) with effect size $d = 2.006$, power $(1 - \beta)$ set at 0.95 and $\alpha = 0.05$, two-tailed. The analysis showed that power reaches 0.963 when sample sizes are 8 and 8 for group 1 and 2 for group differences to reach statistical significance at the 0.05 level. Thus, our sample sizes even after dividing participants into subgroups do not seem to compromise statistical power too much. This "group" factor also was integrated into subsequence analysis. Three-way mixed effect ANOVA was conducted to investigate the effects of groups (low vs. high), tDCS (anodal, cathodal, sham) and set size (4, 6, 8) on the behavioral indexes: d' and K. The d' data showed significant main effects of set size, $F_{(2,32)} = 118.63$, $p = 0.000$, $\eta_p^2 = 0.881$. No other main effects or interactions reached significance ($p > 0.05$).

Regarding K values, the main effect of tDCS, $F_{(2,32)} = 0.737$, $p = 0.487$, $\eta_p^2 = 0.044$, and set size, $F_{(2,32)} = 0.639$, $p = 0.534$, $\eta_p^2 = 0.038$, both did not reach statistical significance. Only the interaction between set size and group did, $F_{(2,32)} = 3.879$, $p = 0.031$, $\eta_p^2 = 0.195$, because K values in set size 6 was significantly higher than those in size set 8 ($p = 0.008$). No other comparisons showed any significant difference. These results suggest that perhaps digit span is not an optimal measure to divide participants' visuospatial WM performance. Participants who had high digit span scores did not have high change detection performance, and vice versa for low performers, suggesting that digit span is probably not tapping into the same mechanisms used by VWM.

Splitting Participants into Low- and High-Performing Groups Using CBT Task

We also divided participants into low and high performers based on their CBT performance. Independent sample *t*-test showed significant group differences, $t_{(16)} = -5.030$, $p = 0.000$, where the high performers ($M = 7.55$) significantly outperformed low performers ($M = 5.88$). We again conducted *post hoc* power analyses using GPower (Faul and Erdfelder, 1992; for a full description, see Erdfelder et al., 1996) with effect size $d = 2.507$, power $(1 - \beta)$ set at 0.95 and $\alpha = 0.05$, two-tailed. The analysis showed that power reaches 0.973 when sample sizes are 6 and 6 for group 1 and 2 for group differences to reach statistical significance at the 0.05 level. This "group" factor was also integrated into subsequence analysis. Three-way mixed effect ANOVA was conducted to investigate the effects of groups (low vs. high), tDCS (anodal, cathodal, sham) and set size (4, 6, 8) on the behavioral indexes: d' and K. The d' data showed significant main effects of set size, $F_{(2,32)} = 158.366$, $p = 0.000$, $\eta_p^2 = 0.908$, along with a significant interaction between set size and group, $F_{(2,32)} = 5.379$, $p = 0.010$, $\eta_p^2 = 0.252$. The d' scores in set size 4 condition were significantly higher than those under set size 6, which in turn was higher than set size 8 ($ps < 0.01$). Participants' performance significantly decreased with increasing set sizes. The interaction arose because low performers' d' was significantly lower than high performers under set size 4 ($p = 0.040$), with no group difference for set size 6 or 8 ($ps > 0.05$), suggesting low and high performers showed different target detection abilities only under relatively-easy condition. No other main effects or interactions reached statistical significance ($p > 0.05$).

Regarding K values, the main effect of tDCS, $F_{(2,32)} = 0.852$, $p = 0.436$, $\eta_p^2 = 0.051$, and set size, $F_{(2,32)} = 0.514$, $p = 0.603$, $\eta_p^2 = 0.031$, were not significant. A marginally-significant interaction between tDCS and group was observed, $F_{(2,32)} = 3.066$, $p = 0.061$, $\eta_p^2 = 0.161$. The simple main effect showed that K values for low performers in the anodal condition was significantly lower than those in the sham condition ($p = 0.01$), and marginally lower than those in the cathodal condition ($p = 0.069$). A significant interaction between tDCS, set size, and group was observed, $F_{(4,64)} = 2.502$, $p = 0.050$, $\eta_p^2 = 0.135$. The interaction arose because K value in the anodal condition was lower than those in the sham condition under set size 6 ($p = 0.032$) and 8 ($p = 0.045$) within low performers, but not high performers, indicating that anodal stimulation selectively interfered low performers' memory performance in the more difficult conditions (**Figure 3**). Other comparisons were not statistically significant.

To further investigate the stability of tDCS effect across time in low performers, another three-way repeated measure ANOVA was conducted to examine the effect of tDCS, set size, blocks. A significant main effect of tDCS was observed, $F_{(2,16)} = 4.354$, $p = 0.031$, $\eta_p^2 = 0.352$. *Post hoc* analysis showed that K values in the anodal condition was lower than those in sham ($p = 0.029$) and cathodal ($p = 0.073$) conditions across time, indicating that anodal stimulation constantly affected VWM performance across different blocks, rather than being modulated by extreme cases.

Given these results in set size 4, we conducted another correlation analysis to see whether there was any correlation between the different choices of independent baseline measure and the dependent measure. There was a significant correlation between CBT and K, $\rho_{(18)} = 0.606$, $p = 0.008$. In contrast, no significant correlation was observed between digit span scores and K under the same condition, $\rho_{(18)} = 0.051$, $p = 0.841$. These suggest that the processing of digit span and change detection likely relies on different mechanisms (**Figure 1**) and highlights the fact that an independent VWM measure can dissociate high

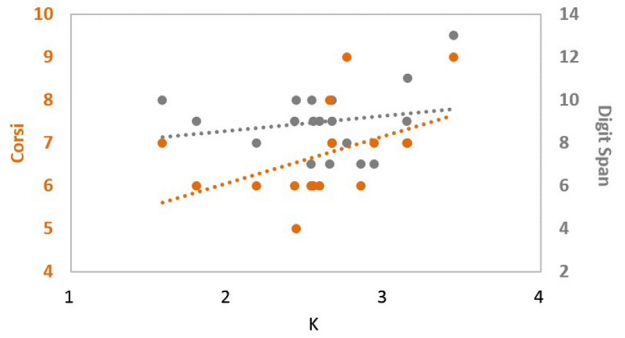

FIGURE 1 | Correlation between change detection performance and different independent measures. corsi block tapping (CBT) scores (orange) showed a significant positive correlation with participants' change detection performance (*X*-axis), while digit span (gray) did not, suggesting that CBT and digit span tasks are most likely probing different mechanisms of memory.

and low performing groups on a near-transfer VWM task better than an independent far-transfer verbal WM measure.

GENERAL DISCUSSION

The aim of the present study was to investigate the interaction between different choices of independent baseline measures, task difficulty, individual differences and tDCS polarity. Here is a brief summary of our findings regarding each factor. In terms of independent baseline measures, when we divided participants using CBT, we observed an impairment effect from anodal tDCS only in the low performers, while high performers' WM capacity remained unaltered. No significant results were observed if we used digit span to separate participants. Therefore, choices of independent behavioral measures are indeed critical to the interpretation and analysis of the effects of tDCS. In terms of task difficulty, we found that set size 4, where participants are properly challenged but have not hit floor performance, is the optimal level of difficulty for the effect of tDCS to show through. Regarding individual differences and tDCS polarity, there was a high degree of intra-subject consistency in the direction of tDCS effects, and one-thirds of participants who showed anodal-increase/cathodal-decrease trends that are consistent with the literature, suggesting that the traditional assumption may perhaps be valid, but only applies to a subset of participants, where most of the participants respond the same way to both anodal and cathodal stimulation. We discuss each of these points in more details below.

Implications for Choosing Independent Behavioral Baseline Tasks for tDCS Studies

We obtained similar results as previous findings on alternating VWM performance through tDCS (Jones and Berryhill, 2012; Tseng et al., 2012; Berryhill et al., 2014; Hsu et al., 2014). Participants were split by their performance in sham condition (Tseng et al., 2012; Hsu et al., 2014) or by independent CBT task, and both approaches showed a tDCS effect in elevating low performers' memory performance. There was no correlation between digit span and change detection performance, thus digit span may be probing different neural and cognitive mechanisms from VWM. Together, these results suggest that, regardless of using the sham baseline or another independent measure such as the CBT, as long as the baseline is something similar to the dependent task measures (evidenced by significant positive correlation), the effect of tDCS can be quite evident and it is usually the low performers that are more responsive to such effect. This pattern cannot be explained by regression to the mean because no VWM studies to date have reported a declining effect in the high performers. Thus the responsiveness to tDCS in low performers seems quite specific. Similarly, the effective polarity also seems quite specific: previous students and the current experiment have all shown effective stimulation via anodal tDCS, and no effect was found with cathodal stimulation in both low and high performers. This helps rule out the factor of poor motivation (Berryhill et al., 2014), which would predict an equal, or randomly distributed, improvement effect that is not specific to anodal tDCS only.

tDCS, rPPC and Visual WM

One notable difference between the present and previous studies is the direction of the effect of anodal tDCS on VWM. Previous studies (Tseng et al., 2012; Hsu et al., 2014) have consistently reported that anodal stimulation improved low performers' VWM performance, and Tseng et al. (2012) proposed that this may be due to the fact that low performers had room for increased activities (neural) and improvement (cognitive), whereas the high performers do not. In the current study, however, we found an impairing effect of anodal stimulation on the low performers, even though our low performers also had plenty of room for improvement. There are several possible explanations for this. The most notable change in the current paradigm is the addition of a directional cue that instructs participants to remember one side of stimuli while inhibiting the opposite side. This manipulation increased the role of visual attention, orienting and distractor inhibition, which is has been associated with frontal areas such as the frontal eye fields or DLPFC (e.g., Wu et al., 2014). As such, stimulating and improving one's memory abilities non-selectively (for a similar finding in non-selective memory, see Tseng and Bridgeman, 2011) may be helpful in a conventional change detection paradigm where every stimulus is a potential target with no obvious distractors to be inhibited (Tseng et al., 2012; Hsu et al., 2014), this non-selective memory mechanism is detrimental in the current paradigm because it doubles one's memory load when it is clearly optimal not to.

The complexity and divergent functions of any brain region obviously increases the difficulty in defining anatomical specificity for tDCS (Peterchev et al., 2012; Bikson and Rahman, 2013). Studies applying tDCS over rPPC have shown that, even with identical montage and setup, the positive effects of tDCS on cognitive functions such as WM

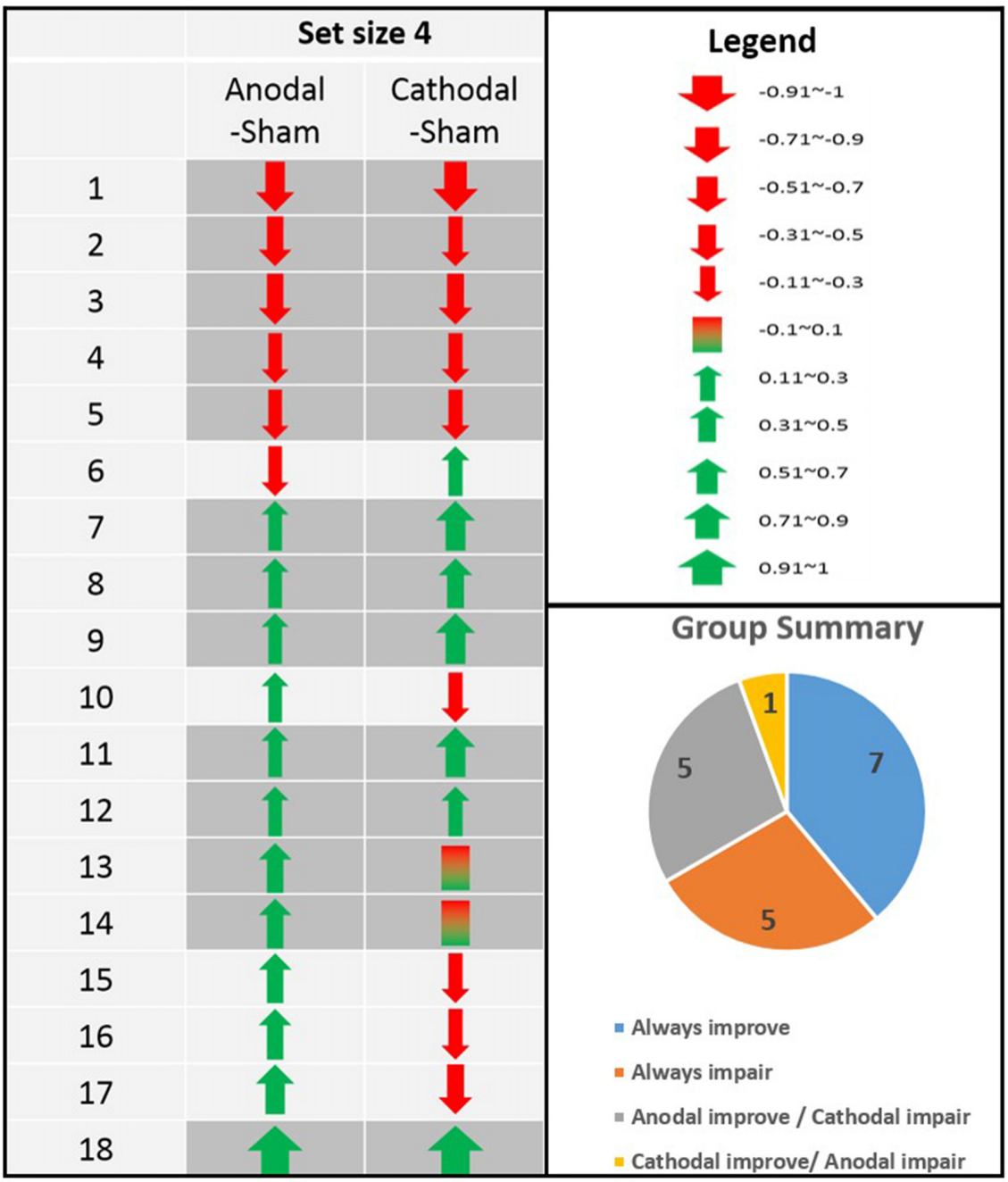

FIGURE 2 | Individual differences in the directions of tDCS effects in 18 participants (Anodal-sham and Cathodal-sham contrasts). Even in set size 4 where the level of difficulty is optimal, there is still a wide range of individual differences. Interestingly, although differences exists between different individuals (left chart), the directions of tDCS effect is quite consistent within each individual (lower right pie chart).

and spatial attention (Tseng et al., 2012; Hsu et al., 2014; Wu et al., 2014, 2016; Juan et al., in press) can vary quite a bit, depending on the participants' current task set and cognitive context. Under the sliding-scale concept (Bikson and Rahman, 2013), anodal stimulation may enhance either the subgroup of neurons for WM or spatial attention, though excitation of multiple subgroups may lead to mutual inhibition, thus impairing WM and spatial attention. This would also be consistent with the state-dependency/signal-to-noise ratio account (Silvanto et al., 2007, 2008; Miniussi et al., 2010, 2013; Ruzzoli et al., 2010; Benwell et al., 2015), which proposes that the relative balance between task relevant ("signal") and irrelevant ("noise") neurons at baseline has a strong impact on tDCS outcomes. However, when both subgroups of neurons

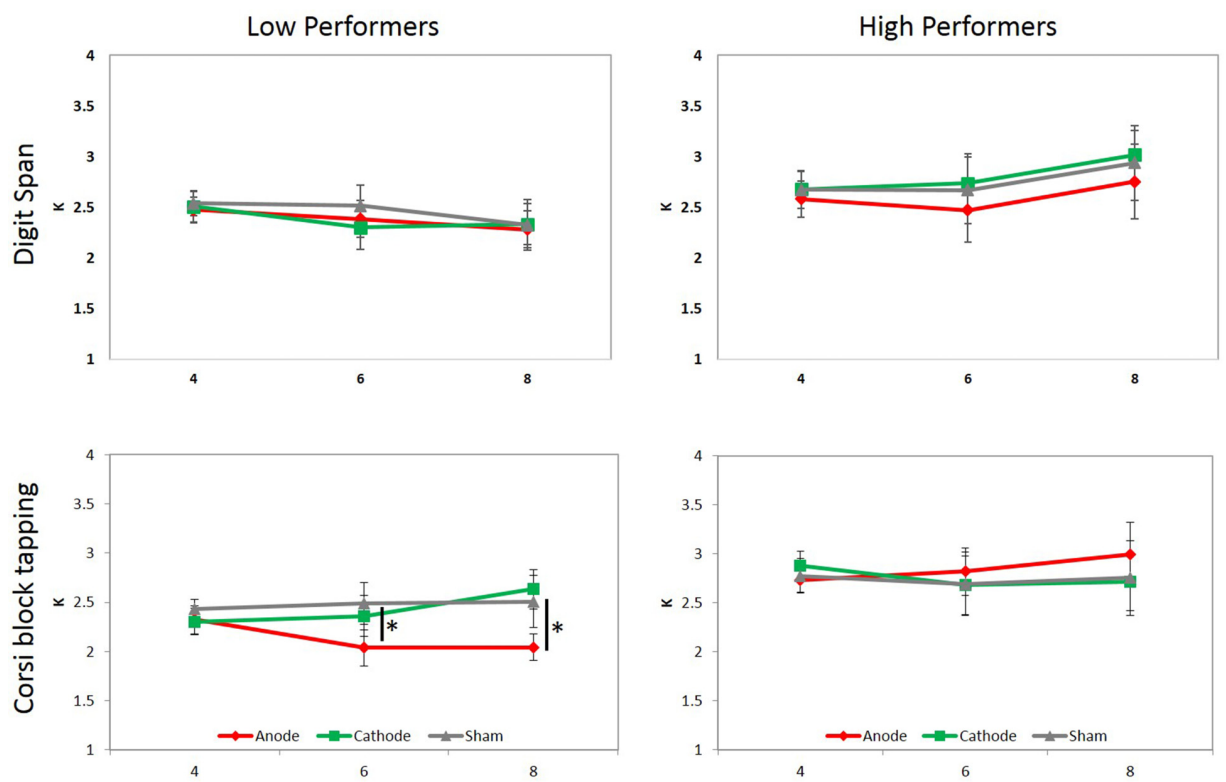

FIGURE 3 | Mean *K* values under manipulations of tDCS and set size. Participants were divided into low and high performers by either digit span (top panel) or CBT (bottom panel) scores, and two separate three-way ANOVAs were conducted for each. A significant interaction between tDCS, set size and group was only observed when participants were divided based on their CBT performance, which was driven by lower *K* values in the anodal tDCS condition than sham and cathodal conditions under set size 6 and 8 in low performers. Asterisks denote $p < 0.05$, and error bars denote standard error of the mean.

are boosted simultaneously by anodal stimulation, these two subgroups of neurons may compete with each other through mutual inhibition and lead to poor performance. Lastly, another possibility is that anodal stimulation may have kept active neurons from declining, thus leading to poor performance. This trend is evident from the L-dopa study (Monte-Silva et al., 2010), where optimal cognitive functions can only be observed at medium dosage of L-dopa. Increasing the amount of L-dopa actually resulted in a decline in cognitive functioning, suggesting that extremely high or low neuronal activity is associated with poor performance. In this light, anodal stimulation may elevate PPC's activities beyond the optimal point. However, these two speculations are beyond the scope of the current study.

Recently, one study by Heinen et al. (2016) found that cathodal stimulation over rPPC can selectively enhanced memory performance by reducing the number of misbinding errors. In addition, this was found in low-performers but not high-performers. The authors provided comprehensive details and suggested that cathodal stimulation over the PPC may enhance VWM performance by boosting the attentional selection mechanism via preventing feature-misbinding and protecting the memory trace. In contrast to our studies, these authors have consistently found improved memory performance using cathodal stimulation over rPPC (Heimrath et al., 2012; Heinen et al., 2016), with an interesting difference that our studies applied tDCS before the task while Heinen et al. (2016) applied tDCS during the task. This suggests that even the timing of tDCS application can have profound impact on the traditional assumption of tDCS polarity and its effects on cognitive functioning. When tDCS is applied before the task, all task-relevant or irrelevant neural activities are non-selectively increased until the first stimulus is finally introduced, which gave participants the proper cognitive task set that would define which stimulus to be relevant and useful for the next hour or so. This timing is obviously different in the concurrent stimulation paradigm, where the balance between task-relevant and irrelevant activities is well established at the start, which would create a different neuronal state that would interact differently with tDCS. However, the poor focality of the conventional tDCS pads is likely to result in diffused electrical current across adjacent areas of the target region (Datta et al., 2009). From one study by Datta et al. (2009), the highest electric field/current density was estimated and found in the frontal regions rather than the area beneath the stimulated site. Our montage is similar to that of Datta et al. (2009) with the exception that one patch was placed over the right instead of left parietal region. With this rationale, one potential

factor is that tDCS may excite unintended frontal regions that then lead to the different findings across studies. Additionally, the asymmetrical nature of tDCS effect has been documented by many studies (e.g., Ellison et al., 2014). Here we also did not observe any cathodal-induced performance changes. The underlying mechanism behind such asymmetry still requires further investigation.

tDCS and Task Difficulty

We have previously reported an anodal tDCS effect that improves VWM performance in low performers. In contrast, Jones and Berryhill (2012) observed an improved effect in the high performers after anodal or cathodal stimulations. In addition, in the present study we observed an impairment effect in low performers after anodal stimulation. However, note that in Jones and Berryhill's study, participants' mean digit span scores for each group were 10.8 for low and 14.10 for high performers, which is quite different from 7.88 and 10.11 in the current study. These numbers highlight the importance of individual differences in baseline performance as they may determine the final tDCS outcome.

Regarding task difficulty, one consistent finding across several studies (Jones and Berryhill, 2012; Wu et al., 2014, 2016) is that tDCS effect usually emerges in difficult task settings that is challenging for the participants. Indeed, across these studies, no tDCS effect was observed under set size 4 in both low or high performers. Therefore, future studies can perhaps focus on the optimal level of task difficulty, knowing that it is the most likely level at which the effect of tDCS will emerge. In terms of neural activations, it is likely that when tasks are easy, the overall activation of task-relevant and irrelevant neurons is limited such that a small tip of the balance via tDCS is hard measure. As task difficulty increases, any tiny changes to the signal-to-noise ratio would then lead to observable behavioral outcomes.

Lastly, in the present study we observed that the effect of tDCS was stable across different blocks. This suggests that the aftereffect of offline anodal tDCS over PPC can be quite persistent for at least 60–90 min or so. Furthermore, the fact that tDCS was stably observed across different blocks suggests that the tDCS effect was not caused by a specific block. Thus, the effect of tDCS may consistently affect memory performance within a given period of time.

Individual Differences in Response to tDCS Polarity

One observation from the present study that is worth noting is the range of individual differences in the aftereffects of tDCS. Out of the 18 participants, there were seven participants who showed improvement in both anodal and cathodal sessions, five participants who showed consistent impairment regardless of tDCS polarity, and five participants whose tDCS performance followed the traditional anodal-increase and cathodal-decrease assumption (**Figure 2**, lower right pie chart), with one participant showing a cathodal-increase and anodal-decrease pattern that is less consistent with the literature. Therefore, although there is considerable *inter*-subject differences in the directions of tDCS effect, within each participant there also seems to be a high degree of *intra*-subject consistency. Twelve out of 18 participants either always showed improved performance or impaired performance following stimulation regardless of tDCS polarity. Therefore, two-thirds of our participants seemed to be insensitive to polarity manipulation. Of the remaining one-third, five out of six participants showed a tDCS pattern that is consistent with the traditional anodal-increase and cathodal-decrease prediction, with only one participant going the other way. Therefore, perhaps the traditional anodal-increase and cathodal-decrease assumption is valid, but it applies only to a subset of participants (one-third in our case), whereas other participants (two-thirds in our case) are less sensitive to the changes in polarity. But why does the anodal-increase and cathodal-decrease rule of thumb work on these people but not others? So far there is no measurement that can tell them apart. However, it is important to note that the anodal-increase and cathodal-decrease idea was first proposed by studies done on the motor cortex because it is easy to measure and relatively easy to set a resting baseline in participants. We think the latter may be the key to explaining the diverse individual differences when tDCS is combined with a complex cognitive task; namely that a neuronal resting baseline for regions other than the motor cortex is hard to do and to monitor. As such, it is easier to tell participants to sit still and relax their muscles (and get cleaner data), it is harder to do the same with other cortical regions. Therefore, an objective way to get all participants' task set and concentration standardized may be a useful approach to explaining different sub-categorical population differences, and possibly resolve much of the controversies and inconsistent findings in the literature. Future tDCS studies should examine each individual's data more closely, and this issue of different subgroups reacting differently to tDCS polarity, as well the mechanisms behind such differences, require further research.

In sum, in this study we found that visuospatial WM performance is impaired by anodal tDCS in low performers but not high performers. This pattern only holds true in the set size 6 and 8 condition, and only when participants were categorized into low and high performing group based on their CBT performance, while division based on digit span scores failed to show any systematic effects. Together, these results highlight the influence of adopting different independent baseline measures, as well as task difficulty, have on the expression of the effects of tDCS. Based on these results, future studies should: (1) choose an independent baseline measure that is within the same cognitive domain and tapping into the same neural mechanisms as the experimental dependent measure; and (2) use a medium-to-difficult level of task difficulty that is sensitive enough for any effect of tDCS to show through.

AUTHOR CONTRIBUTIONS

T-YH designed and performed experiment, analyzed data and wrote the article; C-HJ designed experiment and wrote the article; and PT designed experiment, analyzed data and wrote the article.

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Anodal tDCS to Right Dorsolateral Prefrontal Cortex Facilitates Performance for Novice Jazz Improvisers but Hinders Experts

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Research on creative cognition reveals a fundamental disagreement about the nature of creative thought, specifically, whether it is primarily based on automatic, associative (Type-1) or executive, controlled (Type-2) processes. We hypothesized that Type-1 and Type-2 processes make differential contributions to creative production that depend on domain expertise. We tested this hypothesis with jazz pianists whose expertise was indexed by the number of public performances given. Previous fMRI studies of musical improvisation have reported that domain expertise is characterized by deactivation of the right-dorsolateral prefrontal cortex (r-DLPFC), a brain area associated with Type-2 executive processing. We used anodal, cathodal, and sham transcranial direct current stimulation (tDCS) applied over r-DLPFC with the reference electrode on the contralateral mastoid (1.5 mA for 15 min, except for sham) to modulate the quality of the pianists' performances while they improvised over chords with drum and bass accompaniment. Jazz experts rated each improvisation for creativity, esthetic appeal, and technical proficiency. There was no main effect of anodal or cathodal stimulation on ratings compared to sham; however, a significant interaction between anodal tDCS and expertise emerged such that stimulation benefitted musicians with less experience but hindered those with more experience. We interpret these results as evidence for a dual-process model of creativity in which novices and experts differentially engage Type-1 and Type-2 processes during creative production.

Keywords: creativity, expertise, tDCS, jazz improvisation, dual-process model, neuroplasticity

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INTRODUCTION

The study of improvisation is pertinent to any domain that requires adaptation, problem solving, and innovation. The ability to generate, execute, and evaluate choices in real-time can be seen in a range of scenarios from friends having a conversation, to surgeons operating in an emergency room, to musicians performing in a jazz club. In jazz, as in other domains, creative improvisation

is developed through rigorous training and experience over many years. Research has begun to offer insights into the structural and functional neural changes that occur as this expertise is acquired (Beaty, 2015).

In the present study, we tested a dual-process model for understanding creativity (Rosen et al., in press) and jazz improvisation (Pressing, 1988; Johnson-Laird, 2002) by using transcranial direct current stimulation (tDCS) to modulate the quality of jazz pianists' improvisations. Based on our previous work (Rosen et al., in press), we hypothesized that musical improvisation involves a mixture of deliberate and unconscious processes and that the contributions of these two types of processes depend on the expertise of the performer. Our results show that tDCS can produce different effects on musical improvisation that depend on the performer's level of accumulated expertise, thereby supporting our dual-process model of creativity.

LITERATURE REVIEW

Musical Improvisation

Musical improvisation is sometimes cited as an ecologically valid creative task that does not benefit from increased cognitive control in contrast to standardized laboratory assessments of creativity (see Beaty, 2015 for a review). fMRI studies of musical improvisation suggest that widespread frontal-lobe deactivation, particularly in the right hemisphere, is characteristic of expert-level jazz musicians and that the magnitude of these deactivations is predicted by musicians' number of hours spent improvising (Pinho et al., 2014). Thus, expert jazz improvisation contradicts the view that creativity is primarily supported by top-down control, analytical processing (Nijstad et al., 2010; Baas et al., 2013), and executive function (Nusbaum and Silvia, 2011; De Dreu et al., 2012). Instead, neuroimaging studies of expert-level jazz improvisation suggest decreased activation of prefrontal and parietal cortices, increased activation of the default-mode network (posterior cingulate, medial prefrontal cortex, angular gyrus, etc.), and enhanced connectivity among prefrontal, premotor, motor, and default mode regions (Limb and Braun, 2008; Pinho et al., 2014, 2016). These activation and deactivation patterns are thought to represent a shift from top-down control to more automatic, bottom-up, implicit processing, which facilitates creative performance (Yang, 2015), not only for expert improvisers, but also in other creative domains and tasks (Jung et al., 2013; Chrysikou et al., 2014).

In a behavioral study of jazz improvisation, Rosen et al. (in press) reported that engaging more executive processing and cognitive control via explicit instructions to "be creative" significantly increased improvisation ratings for less experienced jazz musicians; however, more experienced jazz musicians did not show similar improvement. They interpreted these results as evidence for a dual-process model of creativity in which both unconscious, associative (Type-1) and deliberate, controlled (Type-2) processes can contribute to creative thought (e.g., Nijstad et al., 2010; Sowden et al., 2015) with the mixture of these types of processes determined by individual differences (e.g., expertise and personality) and context (e.g., instructions).

While improvising, one must manage rapid chord changes, note choices, appropriate rhythmic execution, and so forth. Type-2 processes activated by instructions (Green et al., 2015) facilitate performance for less experienced musicians by redirecting their attention to a goal of creative expression, recruiting strategies likely to yield a highly creative product and by avoiding the cognitive fixation (Howard-Jones, 2002) that can result from limited domain knowledge and proficiency. However, ramping up Type-2 processes does not improve creative performance for more experienced jazz musicians because experts rely more heavily on Type-1, implicit processes. Due to their extensive training and experience, experts develop enhanced domain-related functional connectivity (Pinho et al., 2014) reflecting a dominance of Type-1 processes or a near-optimal balance between Type-1 and Type-2 processes. Therefore, triggering additional Type-2 processing via creativity instructions does not significantly benefit experts' improvisations, as rated by expert judges (Rosen et al., in press).

tDCS and Creativity

tDCS is another cognitive modulation technique which may enhance creative performance. This technique applies a weak direct current to the scalp using two saline-soaked sponge electrodes. The electrical current is thought to alter neuronal membrane potentials, affecting the excitability of a targeted brain region (Zheng et al., 2011). It has been reported that anodal stimulation increases cortical excitability, and cathodal stimulation decreases cortical excitability (Nitsche and Paulus, 2001). In this study, we sought to extend findings of enhancement of cognitive (Coffman et al., 2014; Nelson et al., 2014) and creative production (Chrysikou et al., 2013; Mayseless and Shamay-Tsoory, 2015; Green et al., 2016) via tDCS to the domain of creative musical performance. It has been suggested that tDCS stimulation can differentially impact individuals depending on their baseline abilities and degree of expertise (Kadosh et al., 2010; Turkeltaub et al., 2012; Mayseless and Shamay-Tsoory, 2015). We therefore examined the effects of stimulation to right dorsolateral prefrontal cortex (rDLPFC) on the creativity of jazz improvisations in a sample of jazz pianists who had different levels of expertise.

Although several studies have examined the effects of tDCS on creativity and insight, the literature offers little clear evidence for its effectiveness as an enhancer of these abilities. Nevertheless, this small body of work has yielded some intriguing preliminary results. One of the earliest of these studies showed that participants were three times as likely to correctly solve an insight problem with concurrent bilateral stimulation to the anterior temporal lobes (ATL) when the cathode was over left ATL and the anode was over right ATL (Chi and Snyder, 2011). However, the stimulation was reliable only compared to sham—the effect was not significant when reversing the stimulation polarity (anode—left ATL, cathode—right ATL). Furthermore, the study did not determine whether participants' solutions really resulted from insight or whether they resulted from analytical thinking. (This was also a limitation of the study by Cerruti and Schlaug, 2009).

Other tDCS creativity research asked participants to generate a common or uncommon use for objects in pictures. Chrysikou

et al. (2013) stimulated left or right inferior frontal gyrus (l-IFG, r-IFG) unilaterally with cathodal stimulation (the anode was placed on the contralateral mastoid) along with a sham condition. While not testing creativity directly, the authors reported that cognitive flexibility improved only with cathodal stimulation to the l-PFC in the uncommon uses condition such that reaction times and response omissions significantly decreased. Here, cathodal stimulation may have inhibited linguistic left-hemispheric dominance and induced hypofrontality of the l-PFC. This finding may be similar to those from neuroimaging studies of jazz improvisation that suggest that deactivation of PFC may benefit creative cognition by facilitating a flow state (Limb and Braun, 2008), characterized as feeling energized focus, complete engagement, and enjoyment in the process of the activity (Csikszentmihalyi, 1990).

Other studies have not been able to reproduce the beneficial effects of unilateral stimulation on creative tasks. Mayseless and Shamay-Tsoory (2015) found that bilateral stimulation with anodal tDCS over right inferior frontal gyrus (r-IFG) and cathodal tDCS over left inferior frontal gyrus (l-IFG) significantly increased flexibility and fluency in a verbal divergent thinking task. The opposite pattern of stimulation yielded no effect. Interestingly, in a second experiment, separately targeting l-IFG with cathodal stimulation or r-IFG with anodal stimulation did not impact divergent thinking scores. The authors hypothesized that the lack of an effect of unilateral cathodal stimulation to l-IFG, similar to Chrysikou et al. (2013), was potentially due to a difference in stimuli—pictures of objects may initially recruit more right-hemisphere brain areas (Corballis, 2003) while verbal stimuli initially engage a left-hemisphere network (Binder et al., 1997). It is also possible that the disparity in the measures of creativity make the comparison between these results problematic.

A recent study by Green et al. (2016) found that anodal high-definition tDCS administered to left frontopolar cortex, compared to sham, increased the likelihood of successfully validating analogy pairs whose words had a greater semantic distance. Here, the authors used semantic distance as a measure of creativity because a higher semantic distance indicates that the words are uncommonly paired, requiring participants to cast a broader search between terms to correctly identify their relationship. Thus, semantic distance may offer a glimpse into one type of verbal creativity, as it satisfies the common creativity definition "unusual and appropriate" (Sternberg, 1988). For the same stimulation paradigm in a verb-generation task, tDCS did not increase semantic distance; however, when combined with a cue to be creative, there was a significant interaction with tDCS increasing semantic distance of verb responses to a noun stimulus. With the creativity cue, there was evidence of increased activation of frontopolar cortex and other brain areas (Green et al., 2015). These researchers proposed that the neural intervention induced a creative state that enhanced participants' ability to generate semantically distant responses. However, the linguistic nature of the task promotes left-hemisphere dominance and may not generalize to other creative domains such as music.

tDCS and Music Performance

Few studies have examined the effects of tDCS on creative performance. Even fewer have studied the impact of tDCS on creative performance in artistic domains. Though none of these investigations have examined musical creativity directly, two studies examined the effects of targeting motor cortex (C3 and C4) with tDCS on trained and untrained pianists' finger dexterity and fine motor control (Furuya et al., 2013, 2014). In the first study, concurrent bilateral tDCS to motor cortex improved keystrokes for untrained musicians but did not improve performance for professionals. Interestingly, some professional pianists who began training at a later age did show improvement for some movement features, indicating that the age at which pianists started training was positively correlated with the amount of finger-movement improvement from tDCS.

In the other study, Furuya et al. (2014) replicated these findings, displaying a ceiling effect on skilled musicians' improvement in fine motor control due to tDCS. As before, the untrained control participants demonstrated improvements in both the left and right hands when receiving concurrent bilateral brain stimulation to motor cortex in both conditions (anode—C3, cathode—C4; anode—C4, cathode—C3). Furthermore, placing the anode over the contralateral cortex and cathode over the ipsilateral cortex (relative to the hand one was performing with) degraded performance for professional pianists compared to the sham condition. These results provide further evidence for the expertise-dependent functional networks and organization, specifically within motor cortex. In contrast, for the control participants, either montage of bilateral stimulation to motor cortex improved motor control.

Evidently, tDCS can disrupt the optimized neural architecture of highly-trained musicians. Together, these studies suggest expert musicians' functional networks may be resistant to, or even hindered by, modulation by tDCS, especially anodal tDCS.

In the current experiment, we hypothesized that anodal stimulation of r-DLPFC during musical improvisation would enhance the performances of non-expert musicians while yielding neutral or negative effects for experts; however, we predicted that the inhibitory effects of cathodal tDCS would have the opposite effect, as deactivation of frontal cortex should disinhibit experts' optimized Type-1 performance networks.

METHODS

Participants

Jazz pianists from local collegiate music departments, seminaries, bands, and jazz associations in the Philadelphia, PA region were recruited for this study. Due to the highly specialized nature of the sample population, we pursued subject recruitment for 6 months, stopping after we could find no more musicians who met our criteria for participation. Due to the within-subject design of this study, pianists were required to attend three experimental sessions each of which featured a different stimulation-type (anodal, cathodal, or sham). Of the 23 musicians recruited, 4 were not able to complete the study due to scheduling conflicts; 1 participant decided not to complete the study; 1 subject's data were not included due to an apparent, unreported,

neurological problem. The remaining jazz pianists ($N = 17$) were free of neurological or psychiatric issues and were not taking any neurological or psychiatric medications. They also met the musical requirements: having improvised in a live jazz setting at least 3 times and having at least 10 years of musical training.

Four jazz experts were recruited to judge the improvisations after all of the experimental sessions were complete. These judges included a director of a collegiate jazz program, two jazz faculty members, and a professional jazz pianist and instructor. All jazz faculty worked at different universities in the Philadelphia area. All raters had more than 25 years of professional performance experience. Musicians and judges were given monetary compensation for their time.

Experimental Procedure

Participants were tested individually and completed the experiment in 3 sessions. Each session lasted approximately 1 h and was conducted at the Laboratory for Cognition and Neural Stimulation (LCNS) at The University of Pennsylvania in Philadelphia, PA. This study was approved by the University of Pennsylvania's Institutional Review Board. At the beginning of the first session, participants signed informed consent, 2 questionnaires as part of a separate study, a handedness inventory, and a mood survey. Upon completion of these surveys, participants were told that they were taking part in a study to examine the effects of tDCS on jazz improvisation without any mention of creativity or expertise. Each participant was given a brief overview of the tDCS equipment, electrodes, and setup while their heads were measured. Once the measurements were complete, participants were fitted with the tDCS electrodes.

At this point in each session, an M-Audio Keystation 88 USB MIDI Controller Keyboard (M-Audio, Cumberland, RI), sustain pedal, music stand, studio quality headphones, and a binder containing task instructions and jazz lead sheets (a visual representation of the chords of a song) were provided for the improvisation task. The experiment's improvisation and recording setup can be viewed in **Figure 1**. Instructions emphasized that pianists "should improvise as they would in a jazz setting." Headphones were worn by the musicians for all improvisation "takes," so that only the musician was able to hear the output of their improvisation, which was not audible in the room with the experimenter present. We did this to decrease the likelihood of self-consciousness among subjects that could occur if the researcher could hear the improvisations as they were performed. Musicians improvised over a 2-min "Dominant 7ths" exercise during inactive tDCS (electrodes worn but machine turned off) to ensure comfort in the recording environment and to allow for any volume adjustments between their piano and the backing tracks. Apple's *Logic Pro 9* v.9.1.8 (Cupertino, CA) music software recorded the improvisations, collected MIDI performance data, and provided musicians with a bass and drums audio accompaniment. Accompaniments were created through *iReal b* for Mac OS X v.2.8 (New York, NY), a practice tool with a full rhythm section for any properly formatted jazz chart (**Figure 2**).

Musicians were randomly assigned to one of six groups which determined stimulation order in their three sessions.

FIGURE 1 | Experimental setup.

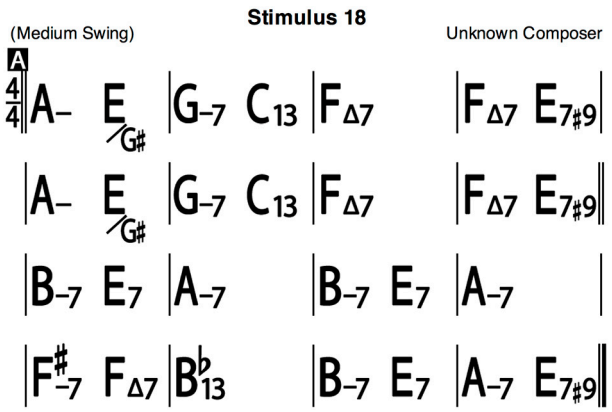

FIGURE 2 | Sample jazz lead sheet.

The stimulation order was nearly counterbalanced, except for the sham/cathodal/anodal sequence which had one less subject. Musicians were instructed to sit quietly with eyes open while gazing at a fixation cross during the first 6 min of stimulation. The researcher presented the first lead sheet and reminded participants they were now going to improvise to 6, 16-bar jazz songs. Each song included 4 chord cycles and lasted approximately 2 min. The improvisation audio stimulus began with a 4-click count-in, and there were intervals of 15–20 s between stimuli. Musicians improvised with online tDCS for the first 4 takes and offline tDCS for the last 2 in each session. Only the final two offline takes from each session were rated and used in the subsequent analyses. Cognitive demands during online tDCS can influence offline, post-stimulation performance (Gill et al., 2015); therefore, the choice to only assess the final 2 takes was done in pursuit of maximal, task-specific, long-lasting tDCS effects.

After the improvisations were complete, the electrodes were removed, and musicians noted which performance they thought was their best. They were then presented with two creativity tasks: a Verb Generation Task (Prabhakaran et al., 2014) and a Compound Remote Associates test (Bowden et al., 2005) followed

by a number Stroop test (Windes, 1968). Data from these tests have not yet been analyzed and are not included in the present report. Also, a post-tDCS survey was collected as part of another ongoing project to better understand how participants perceive the effects of brain stimulation (Kessler et al., 2012). A personality inventory and demographic survey, which included questions about participants' musical backgrounds, were administered during the final session. **Figure 3** provides an overview of the study design.

Upon completion of data collection, the jazz improvisations ($n = 102$) recorded during sham ($n = 34$), anodal ($n = 34$), and cathodal ($n = 34$) stimulation were normalized to ensure the piano and accompaniment had the same relative volume levels across all takes (see Supplemental Materials for sample jazz improvisations). The order of the performances was pseudo-randomized for judging with the constraints that the same musician could not be heard consecutively or more than twice within a single judging block. Judging blocks began with an improvisation from an expert and novice improviser from 1 of the first 4 takes in the sham condition. These ratings were not included in the analysis. They were included as a reference point for raters, so they could familiarize themselves with the range of quality of the performances. To determine expert and novice clip selection, we split the participants into quartiles and randomly selected an improvisation from the top (200 or more live performances) and bottom (15 or less live performances) quartiles. Each judge rated the 102 improvisations and 10 baseline takes in 5 blocks of 22–23 improvisations each; however, only the final two, offline takes from each session were included in the analysis. Judging time for each block was approximately 45 min.

Measures and Instruments

Judges scored improvisations on creativity (CR), technical proficiency (TP), and esthetic appeal (AA) on a 7-point Likert scale according to the Consensual Assessment Technique (CAT) (Amabile, 1982). This technique has been used in hundreds of creativity studies and is based on the idea that evaluating a real product is not dependent on any single theory of creativity. Instead, this mode of assessment mirrors how creativity is determined in real-world domains (Baer, 2010). Critically, the CAT tasks experts in a domain to rate creative products relative to one another rather than against an absolute standard (e.g., a Miles Davis solo). This method has been used to assess the creativity of musical improvisation with high interrater reliability (De Dreu et al., 2012; Beaty et al., 2013).

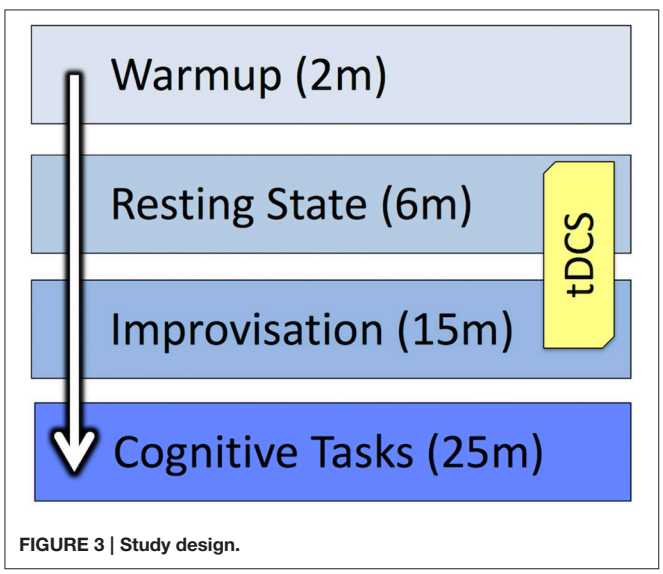

FIGURE 3 | Study design.

The demographic musician questionnaire asked basic questions about participants' musical backgrounds and perceptions of the study improvisation task. This included: age; years of music and jazz training; primary performance genre (10 jazz, 2 rock, 2 classical, 1 folk/bluegrass, 1 electronica, 1 other); number of gigs; degree of comfort improvising jazz ($M = 3.82$, $sd = 1.29$); difficulty of the improvisation task ($M = 2.41$, $sd = 1.18$); ecological validity of the task ($M = 2.41$, $sd = 0.94$); individual practice routines; and experiences improvising in other genres. Values presented here are on a 5-point Likert scale. In the present report, we focus on age and the expertise variables.

Transcranial Direct Current Stimulation

A battery-powered constant DC stimulator (neuroConn DC-Stimulator Plus, neuroConn, Ilmenau, Germany) was used to deliver the stimulation current. Thin, saline-soaked sponges were used to interface the 5 × 5 cm rubber electrodes with the scalp. Electrode placement locations were determined using the International 10–20 System. The target-site electrode was placed on the F4 site, approximately overlaying r-DLPFC (Homan et al., 1987). The return electrode (Nasseri et al., 2015) was placed over the contralateral mastoid process. Though we targeted r-DLPFC, we acknowledge that other brain areas may have been directly or indirectly stimulated (Stagg et al., 2013). Additionally, changes in functional connectivity with tDCS have been shown with various imaging techniques including EEG, fMRI, and graph-theoretical approaches (Polanía et al., 2011a,b).

Unilateral monopolar stimulation ramped gradually to its final intensity of 1.5 mA over the course of 30 s. Stimulation began 360 s prior to the first improvisation to allow for stimulation to take effect prior to the experimental trials (Nitsche and Paulus, 2000). Stimulation continued for an additional 9 min while musicians continued to improvise (total time under stimulation = 15 min). Ramp-down to no stimulation was 30 s. In the sham stimulation condition, subjects received 30 s of stimulation before ramp-down. The anode/cathode placement was counterbalanced in the sham condition. Stimulation ended after the fourth trial in each session, and the final 2 trials were completed offline. Improvisation during stimulation was done to maximize tDCS effects on the offline performances (Gill et al., 2015), and stimulation length was decided based on previous reports that tDCS of 10 min or longer can have lasting effects for up to 1 h (Nitsche et al., 2008).

Statistical Analyses

We analyzed the impact of tDCS and expertise on jazz improvisation ratings using linear mixed-effects (LME)

hierarchical regression models (Baayen et al., 2008) as implemented in the *lme4* software package (Bates et al., 2012) in R (Vienna, Austria). LME models simultaneously assess group-level and individual-level patterns within a single analysis, taking into consideration fixed (tDCS, expertise) and random-effect parameters. We included random intercepts for each subject and each stimulus ($n = 6$) to account for inter-individual variation and inter-item variation (Baayen et al., 2008; Mirman, 2016). Models included maximal random-effect structures that allowed the model to converge (Barr et al., 2013).

ANOVA model comparisons were used to determine the parameters that best predicted the improvisation ratings. That is, we first computed the model with only the intercept term followed by "session #" to test for practice effects across sessions. We then computed the model with each potential expertise parameter, age, music training, jazz training, and number of jazz gigs, keeping jazz gigs in the model as it was significantly predictive of improvisation ratings. Stimulation condition was included as an additional fixed effect and as an interaction term with expertise, testing our main hypothesis that tDCS would have differential effects based on expertise. Models were compared using the log-likelihood (LL) goodness-of-fit measure. Changes in -2LL are distributed as χ^2 with degrees of freedom equal to the number of parameters added. For all model comparisons, the random effects structures were identical.

TABLE 1 | Chi-square difference tests for model comparisons.

Model parameters	Log-likelihood	Chi-squared (χ^2)	Degrees of freedom (*df*)	*P*-Value
Baseline	−109.45	NA	NA	
Session #	−108.76	1.39	2	0.498
Age	−107.71	3.49	1	0.062
Music Training (years)	−108.13	2.65	1	0.104
Jazz Training (years)	−108.10	2.71	1	0.099
Expertise	−99.08	20.74	1	<0.001***
Expertise + tDCS	−98.74	0.68	2	0.713
Expertise x tDCS	−94.16	9.84	4	0.043*

*Significance codes: *p < 0.05, ***p < 0.001. Each model was tested against the Baseline model until Expertise significantly improved model fit. Then, the tDCS fixed-effect and interaction models were compared to Expertise. The best performing model included the interaction term, Expertise x tDCS, predicting quality scores significantly better than only Expertise.*

RESULTS

Musician Demographics and Expertise Analysis

The musicians were 19–34 years of age ($M = 24.2$, $sd = 4.0$), and participants were predominantly male (2 females). Expertise data was collected for years of music training ($M = 17.17$, $sd = 4.26$), years of jazz training ($M = 7.29$, $sd = 4.57$), and number of live jazz gigs performed ($M = 108.53$, $sd = 125.26$). The number of gigs covered a large range that spanned 2 orders of magnitude (3–400) and were skewed (skew = 1.95). The number of live jazz performances is an accurate descriptor of a musician's improvisational experience and expertise (Rosen et al., in press), and previous work has shown that the number of hours of improvisational experience is predictive of distinct brain-activation patterns beyond years of music training or age (Pinho et al., 2014). Because estimates of time spent improvising can be imprecise, we use the number of gigs as our expertise parameter, and we show that this measure significantly predicts pianists' improvisation ratings better than age, musical training, and even jazz training (see **Table 1**).

We applied a natural logarithmic transformation to the number of jazz gigs. The power law of practice posits that skill increases logarithmically. Empirical evidence shows that improvement with practice is linear in a log-log space (Newell and Rosenbloom, 1981). For example, a musician's second performance gives them twice as much experience over the first, but the 401st performance is only a slight increase beyond the 400th. A secondary motivation for the logarithmic transformation was to improve model fit optimization for wide ranges of data with substantial skew (Zumel et al., 2014). Thus, when we reference "expertise parameter," it is the natural logarithmic transformation of the number of live jazz gigs.

Interrater Reliability

The intraclass correlation coefficient (ICC) measured interrater reliability (IRR) for judges' ratings of CR, AA, and TP. Reliability was calculated such that values were computed for consistency where systematic differences between raters are considered to be irrelevant (McGraw and Wong, 1996). IRR was calculated for creativity ($ICC = 0.81$, $N = 4$), technical proficiency ($ICC = 0.77$, $N = 4$), and esthetic appeal ($ICC = 0.84$, $N = 4$). All scales had high reliability, as an $ICC > 0.75$ is excellent 0.40 to 0.74 is adequate to good, and <0.40 is poor (Fleiss, 1986).

Scale-Type Correlations

The 3 scale types had highly significant positive correlations after averaging the four judges' ratings for each improvisation: CR and AA [$r_{(100)} = 0.96$, $p < 0.01$], CR and TP [$r_{(100)} = 0.91$, $p < 0.01$], AA and TP [$r_{(100)} = 0.93$, $p < 0.01$]. These high correlations between scale types may represent the interconnectedness of these three performance features, such that one is needed to express the others in a technically demanding domain like jazz improvisation. Thus, the individual CR, AA, and TP scale-type ratings were averaged to form a single "quality" rating for each improvisation. For further analyses and mixed-effect regression models, the quality rating composite score across judges and scales was the dependent measure for each improvisation.

Descriptive Statistics

Each musician performed 2 takes x 3 conditions (anodal, cathodal, sham); an overall quality rating was calculated for each take ($M = 3.85$, $sd = 1.33$). Quality ratings were approximately normally distributed (skew = 0.04), though displaying less peakedness and shorter tails due to negative kurtosis (kurtosis = −1.06). Scores ranged from 1.58 to 6.33, covering almost the entire range of the 7–point Likert scale. No single improvisation received the top score from all judges on all scales, indicating that scores were not clustered at the top

or bottom end of the range, avoiding ceiling or floor effects. Although scale-type was not included in the LME regression analyses due to the extremely high correlations between scores on different scales, ratings on the CR scale ($M = 4.04$, $sd = 1.34$) were the highest, followed by TP ($M = 4.00$, $sd = 1.28$) and AA ($M = 3.50$, $sd = 1.45$).

LME Regression Model Comparisons

Table 1 displays the results of the model comparison difference tests. Variables thought to contribute to the model were tested against a baseline model. Session was the initial fixed effect, yielding no evidence of practice effects across sessions. For the domain-expertise parameters, age, years of music training, and years of jazz training failed to significantly predict improvisation quality. Expertise based on the number of live jazz performances, did significantly improve model fit. Keeping expertise in our model, we then tested the stimulation conditions' predictive abilities, which did not improve model fit beyond expertise (see **Table 1**). To test our hypothesis that tDCS would have differential effects for jazz musicians with varying levels of expertise, we tested the interaction between expertise and tDCS, which revealed a significant increase in the model fit. To estimate tDCS effects at the high end of the expertise scale, the same model was also refitted with Expertise rescaled so that the maximal number of gigs was 0 and fewer gigs were represented as negative numbers. The model below displays the parameters with the best fit after all comparisons (terms in parentheses are random effects):

$$\textit{Quality Rating} = \text{Expertise} + \text{tDCS} + \text{Expertise} \times \text{tDCS} + (1|\text{Subject}) + (1|\text{Stimulus})$$

Fixed-Effect Parameters

As expected, expertise significantly increased improvisation ratings in the sham stimulation condition (*Estimate* = 0.80, $SE = 0.11$, $p < 0.001$). Thus, in the sham condition, there was an 0.80 increase in ratings per unit increase in expertise. Anodal and cathodal tDCS compared to sham did not affect the quality of performance for the sample as a whole (see **Table 1**); however, anodal tDCS significantly interacted with expertise-level. The significant negative interaction between tDCS and expertise reflects that quality ratings increase with anodal tDCS compared to sham for novices and significantly decrease for the experts (*Estimate* = −0.24, $SE = 0.08$, $p = 0.002$). **Figure 4** displays this interaction. Furthermore, those musicians with the least experience benefited from anodal stimulation (*Estimate* = 0.91, $SE = 0.32$, $p = 0.004$), and those musicians with the most experience were hindered (*Estimate* = −0.54, $SE = 0.20$, $p = 0.007$). Here, ratings of our least experienced participants improved by almost a point when they had anodal stimulation, and the ratings of our most experienced participants decreased by about half a point when they had anodal stimulation compared to sham. The interaction between cathodal tDCS and expertise trended in the same direction but was not significant (*Estimate* = −0.14, $SE = 0.08$, $p = 0.08$). There was also a trend for cathodal stimulation to increase ratings for the least experienced musicians (*Estimate* = 0.60, $SE = 0.32$, $p = 0.06$), but experts' ratings were not affected (*Estimate* = −0.22, $SE = 0.20$, $p = 0.28$).

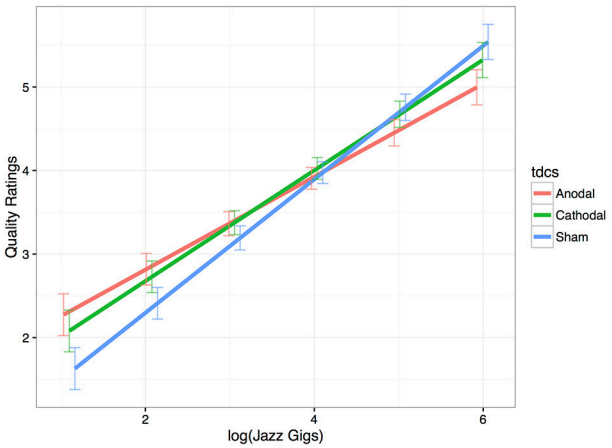

FIGURE 4 | Improvisation quality ratings as a function of Expertise × tDCS. This model-based estimation displays musicians with less performance experience (left side of the x-axis) received higher ratings with anodal tDCS (red) compared to sham (blue). For the most experienced musicians, anodal stimulation decreased quality ratings compared to sham. Cathodal stimulation (green) did not significantly affect ratings. Error bars are displaying standard error.

DISCUSSION

Understanding the tDCS × Expertise Interaction

Neuroimaging studies of creativity and music improvisation report contradictory results with regard to the role of DLPFC. However, as new studies seek to tease apart this paradox, there is evidence that the DLPFC may have various functional roles dependent upon the creative task, goals, and individual-difference factors such as expertise (Pinho et al., 2014). It has been theorized that baseline abilities may differentially affect tDCS stimulation effects (Mayseless and Shamay-Tsoory, 2015), and that increased cognitive control is only advantageous in certain creative domains and situations (Chrysikou et al., 2014). In this study, we implemented a novel approach to examining the interaction between tDCS and jazz pianists' degree of domain-expertise with regard to the quality of their improvisations. We hypothesized that anodal tDCS to r-DLPFC would facilitate less-experienced musicians' performances, as novices display higher activity in frontoparietal executive systems (Pinho et al., 2014), relying on more explicit, conscious, Type-2 processes (Rosen et al., in press) compared to experts. In the cathodal stimulation condition, we predicted tDCS to amplify the benefits of hypofrontality to creativity (Chrysikou et al., 2013), jazz improvisation (Limb and Braun, 2008), and implicit, automatized, Type-1 processes acquired through expertise (Rosen et al., in press). Yet, we did not expect cathodal stimulation to improve novice performance because they rely more on top-down cognitive control and focused attention. Without engaging executive systems, less-experienced musicians

would "presumably produce less adequate responses that are either too simplistic or esthetically inappropriate" (Pinho et al., 2016).

As an initial attempt to test these hypotheses about creative cognition in the ecologically valid domain of jazz improvisation, we applied unilateral tDCS to r-DLPFC as jazz pianists of various levels improvised to a series of chord changes across 3 sessions. As predicted, the musicians with the most professional experience received the highest improvisation ratings, consistent with data from past jazz improvisation studies (Beaty et al., 2013; Rosen et al., in press). These benefits of expertise align with theories of creative cognition in the performing arts in which musicians draw from a hierarchical structure of learned and novel ideas, form associative links between choices, and select and retrieve ideas activated in associative memory (Clarke, 1988). Thus, more experience develops finely-tuned, robust, functional neural networks.

There was no significant main effect of stimulation on the quality of jazz improvisations for the sample of jazz pianists; however, a highly-significant interaction between expertise and tDCS emerged in the anodal condition compared to sham, providing evidence for different modes of creative thought for experts and novices. Anodal tDCS improved performance for the least-experienced musicians relative to sham stimulation, and the opposite effect was obtained for the most-experienced musicians such that their performance was hindered relative to the sham condition.

These results suggest that anodal stimulation may increase the efficacy of r-DLPFC processes that are recruited during improvisation, allowing explicit top-down control and action selection (Nijstad et al., 2010) when novices' associative processes, knowledge structures and memory systems are insufficient for high-level, automatized performance (Pinho et al., 2016). De Dreu et al. (2012) reported that working memory (WM) in cellists predicted improvisation ratings over time, such that higher WM led to increased scores on subsequent takes. Thus, one explanation for these findings is that Type-2, executive processes that are critical to domain-general creativity such as working memory (Fregni et al., 2005; Boggio et al., 2006), attention (Coffman et al., 2014), inhibitory control (Javadi and Walsh, 2012), and visuospatial memory (Jeon and Han, 2012) are improved when anodal tDCS targets r-DLPFC. Still, the most recent meta-reviews do not provide evidence for benefits to working memory in healthy adults with anodal tDCS targeting r-DLPFC (Mancuso et al., 2016). It should be noted that the plethora of cognitive functions associated with DLPFC cannot be individually targeted with tDCS; therefore, we cannot ascertain how each executive process contributes to the modulation of novice jazz improvisation performance without combining tDCS with other techniques.

Another possibility is that the network of distant brain areas that are functionally connected to the stimulation area during improvisation are also affected by tDCS (Polanía et al., 2011a; Stagg et al., 2013). These downstream effects are likely to amplify the functional connectivity (Green et al., 2015) between prefrontal, premotor, and motor areas, potentially strengthening these networks to a point where they appear similar to more-experienced musicians. However, using this logic, we should have seen comparable improvement among experts. Furthermore, anodal tDCS may synchronize several brain regions that comprise a functional network if they are connected to the stimulation site (Kunze et al., 2016). This has been displayed through increased theta coherence between frontal and parietal lobes (Polanía et al., 2011a; Notturno et al., 2014). Interestingly, Gruzelier (2014) reports that neurofeedback training aimed to increase theta coherence, benefits musicians' creative performance such that training was associated with improvement in 9 of 13 performance criteria including interpretative imagination, expressive range, stylistic accuracy, technical security, rhythmic accuracy, tonal quality, and spectrum, deportment, emotional commitment and conviction, and the ability to cope with situational stress. It is thought that the role of theta coherence integrates widely distributed neural networks that underlie creativity (Gruzelier, 2009). This is another possible mechanism underlying the increases in improvisation scores for less-experienced musicians with anodal tDCS.

Based on the literature, we did not expect prefrontal anodal stimulation to assist the experts because the executive processes that they instigate are no more effective than, and may be inferior to, experts' typical emphasis on Type-1 processes associated with frontal-lobe deactivation (Limb and Braun, 2008; Liu et al., 2012; Pinho et al., 2014). Once enough domain expertise is gained, disinhibition and decreased cognitive control is an effective approach toward improvisation proficiency (Pinho et al., 2016). Thus, the anodal stimulation disrupted the trained neural networks of the most-experienced musicians. tDCS may have facilitated the recruitment of explicit processes that are normally inhibited, similar to what happens when one attends to the components of a well-learned skill, causing performance decrements (Beilock et al., 2002) and "choking" (Gray, 2004).

The interaction between expertise and cathodal tDCS was not significant, though there was a trend in the same direction as in the anodal stimulation condition, facilitating novice and hindering expert performance. Furthermore, we expected any impact of cathodal stimulation to have reverse effects of anodal stimulation with beneficial effects for the more-experienced jazz musicians, amplifying deactivations of prefrontal cortices that occurs as one gains expertise. There are a few reasons why we may not have seen the expected effect. First, cathodal stimulation does not reliably produce inhibitory behavioral effects (Jacobson et al., 2012). Compensation from other brain areas within functional networks may occur in some cognitive domains, masking the inhibitory behavioral effects of applying the cathode to one node of a network. We posit that improvisation performance gains via increased activation of compensatory networks are expertise-dependent. This would explain the trend for increases in quality ratings for less-experienced musicians but not experts. We propose a very different mechanism underlying the facilitation of performance with cathodal stimulation compared to similar improvements with anodal stimulation for novices. While anodal stimulation increased the efficacy of DLPFC's executive processes which novices routinely engage, we hypothesize that cathodal stimulation caused less experienced musicians to lessen their

prefrontal dominance and cognitive control and recruit other brain areas within their functional networks (dorsal premotor cortex, medial prefrontal cortex, supplementary motor area), more so than normal. Thus, it is possible that cathodal stimulation allows novices to perform using a more bottom-up approach through downstream activations of this compensatory network. With regard to experts, past studies have shown that during improvisation musicians with more experience show greater deactivations of DLPFC (Pinho et al., 2014). Although we had hypothesized that cathodal tDCS would amplify these effects, it appears that cathodal stimulation does not further downregulate executive systems in such a way that would alter the optimal functional networks engaged by expert musicians.

Lastly, we did not find that cathodal stimulation facilitated expert-level jazz improvisatory performance. Of course, the question regarding the inhibitory effects of cathodal stimulation is a relevant one here, as well. Although motor studies consistently see inhibition of brain areas beneath the cathode, such evidence is rare for non-motoric cognitive studies. As mentioned, Jacobson et al. (2012) theorized that the lack of cognitive inhibition may reflect the complexity of cognition in that other brain areas in a rich neural network may serve as a buffer against potential disruption. Beyond that, one possibility is that expertise produces robust functional networks that are resistant to change from modulation techniques such as tDCS or explicit instructions (Rosen et al., in press). However, anodal stimulation did significantly impair expert performance. Unfortunately, with only 17 musicians, we were not able to determine whether the differences between stimulation conditions at each expertise-level were significant. Still, we report significant differential effects of tDCS on the quality of jazz improvisations for musicians with the highest and lowest degrees of expertise.

Another possible explanation for the lack of a significant positive impact of cathodal tDCS on seasoned jazz musicians may be analogous to studies examining pianists' finger dexterity and motor control (Furuya et al., 2013, 2014). In these studies, only untrained control participants and players that commenced training at an older age saw gains in finger dexterity with stimulation to motor cortex. These results "indicate robustness of the motor system of pianists against the tDCS intervention, being likely to reflect an early optimization of neuroplasticity" (Furuya et al., 2013). This would be a case in which previous experience results in an optimized system that imposes a ceiling effect that tDCS cannot improve upon. In the present study, this optimized system would consist of Type-1 improvisation mechanisms that develop over decades of jazz improvisation. If, for experts, deactivation of r-DLPFC is a critical component of this network, it follows that cathodal stimulation would not further inhibit this region in a way that would enhance expert performance.

While we do not present these results as the definitive evidence of the impact of tDCS on jazz improvisation and musical creativity, they are important for understanding the processes engaged by novices and experts in pursuit of creativity in real-world domains. To date, brain stimulation studies of creativity have relied too heavily on standardized assessments such as the Alternate Uses Test or the Remote Associates Test. The development of practical methods for enhancing creativity depends on further research in ecologically valid studies, for example, math (Kadosh et al., 2010; Hauser et al., 2013), reading (Turkeltaub et al., 2012), and music and the arts. In particular, such work could have powerful implications for music education and the enhancement of musical creativity as instructors can leverage knowledge about music cognition in their training programs and curricula.

Limitations

This study has some limitations that future research will need to address. First, the neurological and psychological requirements of tDCS participants, multiple test sessions, and the highly specialized population led to our relatively small sample size: only 17 jazz pianists completed all three sessions. Nevertheless, each musician contributed 6 improvisations rated by expert judges, two with cathodal, anodal, and sham stimulation, for a total of 102 rated improvisations. In spite of the relatively small sample, the interaction effect between tDCS and expertise still led to highly significant results partly due to the within-subject stimulation design. Still, it is important to note that this is the first evidence of tDCS influencing the quality of music performance, and this effect requires replication, especially because lack of power (due to small samples) can lead to over-estimation of effect sizes (Button et al., 2013).

In addition, our sample of jazz pianists included only a moderate range of age and expertise because recruitment was limited by age (older adults producing different responses to tDCS; Fujiyama et al., 2014). Although jazz musicians ranged from college undergraduates with under 10 gigs to professional adults with 400 gigs, the experiment did not include the most seasoned jazz professionals who have been performing over the course of decades—the masters. Therefore, it is unclear how the present results may extrapolate to the most experienced musicians, though there is no evidence that the inclusion of such experts would have altered the results.

In this experiment, as in many tDCS studies, localization of the tDCS current is a concern as the pattern of current flow can influence various cortical regions contingent upon individual differences in the geometry of the sulci and gyri (De Berker et al., 2013) and characteristics of soft tissue and bone mass (Datta et al., 2009). However, in the present study, even if the electrode montage we employed stimulated additional or other brain areas that were not considered, our central finding that brain stimulation differentially affected the performances of musicians with greater and lesser experience still holds. The basic implications for a dual-process model of creativity would still apply. In addition, one could question our decision to only include the offline improvisations in the analysis. The decision to exclude the online takes was done a priori based on work by Gill et al. (2015) which reports that effects of offline tDCS are enhanced when the online and offline tasks require the same cognitive processes. When tDCS began, there was a resting-state period lasting 6 min. During this time, it is impossible to determine what kind of processes, thoughts, or mental-states had been occurring, altering the initial impact of

tDCS. Thus, in this experiment, we wanted to give musicians plenty of time to engage the cognitive processes used during improvisation with tDCS, in hopes of maximizing the effects of stimulation offline and on the subsequent cognitive tasks. To date, there are no reports comparing the effects of tDCS for online and offline performance. We plan to examine these differences and the time-course of the effects of stimulation in future research.

Although we examined performance in the real-world musical domain of jazz improvisation, the ecological validity of this study may have been somewhat lessened by the stimuli and setting. The chord sequences were loosely based on 16-measure segments of jazz standards, often shifting keys to make them more novel to the performers. While a melody is typically provided on a jazz lead sheet, we did not include a written melody, or "head," as we did not want sight-reading skills to interfere with one's ability to improvise. While attempting to limit confounding variables, it is unknown how the omission of melodies may have altered the underlying improvisation processes. Additionally, the computer-generated accompaniment did not respond to musicians and had a static tempo; therefore, the soloist could not have the interactions that they would have had in a live jazz setting (Monson, 2009).

CONCLUSIONS

The present study is a first attempt to explore the effects of tDCS on jazz improvisation, a demanding, ecologically valid form of creative expression. Here, we report that brain stimulation differentially influences the ratings of musicians' improvisations dependent upon their degree of expertise. Anodal stimulation to r-DLPFC significantly increased performance quality for the less-experienced pianists while hindering it for those with the most experience. These results provide evidence supporting a dual-process creativity model in which the recruitment of Type-1 and Type-2 processes differs for experts and non-experts. This provides an insight into the neuroplasticity associated with expertise in musical improvisation which may extend to other domains, both artistic and non-artistic.

AUTHOR CONTRIBUTIONS

DR, BE, YK, RH, and JK contributed to the conception and design of this work. DR and BE, collected all data. Data analysis and interpretation was conducted by DR, BE, DM, RH, and JK. DR drafted the article, and DM, RH, YK and JK provided critical revisions of the article. Final approval of the version to be published was given by DR, BE, YK, DM, RH, and JK.

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frontiers in Human Neuroscience

ORIGINAL RESEARCH
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Baseline Performance Predicts tDCS-Mediated Improvements in Language Symptoms in Primary Progressive Aphasia

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Primary Progressive Aphasia (PPA) is a neurodegenerative condition characterized by insidious irreversible loss of language abilities. Prior studies suggest that transcranial direct current stimulation (tDCS) directed toward language areas of the brain may help to ameliorate symptoms of PPA. In the present sham-controlled study, we examined whether tDCS could be used to enhance language abilities (e.g., picture naming) in individuals with PPA variants primarily characterized by difficulties with speech production (non-fluent and logopenic). Participants were recruited from the Penn Frontotemporal Dementia Center to receive 10 days of both real and sham tDCS (counter-balanced, full-crossover design; participants were naïve to stimulation condition). A battery of language tests was administered at baseline, immediately post-tDCS (real and sham), and 6 weeks and 12 weeks following stimulation. When we accounted for individuals' baseline performance, our analyses demonstrated a stratification of tDCS effects. Individuals who performed worse at baseline showed tDCS-related improvements in global language performance, grammatical comprehension and semantic processing. Individuals who performed better at baseline showed a slight tDCS-related benefit on our speech repetition metric. Real tDCS may improve language performance in some individuals with PPA. Severity of deficits at baseline may be an important factor in predicting which patients will respond positively to language-targeted tDCS therapies.

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INTRODUCTION

Primary Progressive Aphasia (PPA) is a neurodegenerative disorder characterized by gradual and initially isolated deterioration of language function (Mesulam, 2001). There are currently three recognized variants of PPA; semantic, non-fluent/agrammatic and logopenic. Semantic variant PPA (svPPA) involves anomia, reduction of expressive vocabulary and a severe single-word comprehension deficit, and involves atrophy of the anterior and ventral temporal lobe (Hodges and Patterson, 2007; Gorno-Tempini et al., 2011; Grossman, 2012). Non-fluent/agrammatic (nfvPPA) and logopenic variant PPA (lvPPA) are both characterized by more prominent

difficulties with language production; naPPA typically involves grammatical simplification, effortful speech and motor speech impairment, and involves atrophy of the left inferior frontal lobe and insula (Ogar et al., 2007; Gorno-Tempini et al., 2011; Grossman, 2012), while individuals with lvPPA have trouble with word retrieval and repetition, and show atrophy of the left temporal and parietal lobes (Gorno-Tempini et al., 2011; Grossman, 2012). There are currently no effective treatments for PPA. Traditional speech and language therapies used in rehabilitation of post-stroke aphasia (e.g., Brady et al., 2012; Otal et al., 2015), have yielded limited benefits for PPA patients. However, recent research in the field of noninvasive brain stimulation shows promise for the development of symptom-oriented therapies (Wang et al., 2013).

Transcranial direct current stimulation (tDCS) is a type of noninvasive brain stimulation that modulates the resting excitability of neuronal populations, thereby altering patterns of brain activity in potentially behaviorally relevant ways (Stagg and Nitsche, 2011). The technique involves the application of low-intensity electrical current through electrodes placed on the scalp. A commonly invoked, but highly oversimplified, convention is that the application of anodal tDCS produces excitatory effects in underlying brain regions, and that cathodal stimulation is associated with inhibitory neural effects (Creutzfeldt et al., 1962; Nitsche and Paulus, 2000; Nitsche et al., 2008). However, some studies have highlighted that this traditional claim may not be entirely consistent depending on individual study parameters (Vallar and Bolognini, 2011; Batsikadze et al., 2013).

TDCS has been used to examine causal relationships between brain regions or networks and a variety of cognitive functions, including language processing (Nitsche and Paulus, 2000; Wiener et al., 2010; Turkeltaub et al., 2012; Chrysikou et al., 2013; Filmer et al., 2014; Price et al., 2015). A variety of language mechanisms have been interrogated with tDCS, such as word learning (Flöel et al., 2008; Fiori et al., 2011) and semantic verbal fluency (Cattaneo et al., 2011; Meinzer et al., 2012; Vannorsdall et al., 2012; Penolazzi et al., 2013). A recent meta-analysis of language processing in healthy adults found significant effects of single-session tDCS compared to sham across 11 studies (Price et al., 2015).

A number of left-hemispheric, anodal tDCS studies in patients suffering from post-stroke aphasia have shown promising effects of tDCS in language recovery (Flöel et al., 2008; Fridriksson et al., 2011; Cotelli et al., 2014; Wu et al., 2015). Anodal tDCS over the left frontal cortex of stroke patients with aphasia led to significant improvement in naming accuracy lasting 1 week following stimulation (Baker et al., 2010). However, therapeutic outcomes of tDCS studies across different studies are variable. Polanowska et al. (2013) found no statistically significant differences between anodal and sham tDCS over Broca's area in naming accuracy or response time in post-stroke, non-fluent aphasic patients.

The use of tDCS in treating symptoms of neurodegenerative disorders has been studied to a lesser degree, with mixed findings for the efficacy of tDCS in these populations (see Elder and Taylor, 2014 for meta-analysis). Only a handful of studies have investigated the utility of tDCS for PPA symptoms specifically. Cotelli et al. (2014) found that 10 sessions of anodal tDCS over the left dorsolateral prefrontal cortex in combination with individualized speech therapy led to significant improvement in picture-naming (action and object naming) that lasted up to 12 weeks post-stimulation. However, the authors also reported significant performance gains in individuals who received only sham tDCS lasting the same amount of time, though these gains were smaller following sham relative to real tDCS. These results suggest that tDCS may enhance the outcome of intensive, targeted speech therapies, but do not indicate that tDCS on its own may be an effective intervention.

A recent case study of an individual with nfvPPA demonstrated improvements in auditory word-picture identification, picture naming, oral world reading and word repetition in the absence of speech therapy after 5 days of twice-daily anodal tDCS over the left posterior peri-Sylvian region (in the morning) and the left inferior frontal gyrus (in the afternoon; Wang et al., 2013). However, these improvements were modest and were not assessed at time-points following the conclusion of stimulation sessions.

Tsapkini et al. (2014) found that tDCS applied to the left inferior frontal gyrus paired with spelling therapy showed improvements in spelling lasting up to 2-months post-stimulation on untrained items compared to a sham control in six individuals with nfvPPA (n = 2) and lvPPA (n = 4). A double-blind, sham-controlled counterbalanced cross-over design study involving 12 patients with svPPA and 15 healthy subjects found that left-excitatory (anodal) and right-inhibitory (cathodal) tDCS to the temporal poles improved semantic accuracy in verbal modality among individuals with svPPA (Teichmann et al., 2016). Finally, a recent open-label study from our study team has demonstrated that 10 consecutive (5 weekdays for 2 weeks, with no stimulation on weekend days) sessions of anodal tDCS led to improvements in speech production, grammatical comprehension and semantic processing in patients with nfvPPA, some of which lasted up to 12 weeks post-stimulation (Gervits et al., 2016).

The main objective of the current study was to determine if tDCS, unpaired with individualized language therapy, can be used as a therapeutic tool to improve language impairments in patients with nfvPPA and lvPPA. We pursued this question using a blinded, sham-controlled crossover design in which participants were naïve to stimulation type and served as their own control. Additionally, we aimed to assess whether there are specific individual difference factors that may help to account for variability and possible tDCS-related improvements in language function in order to help determine whether and when tDCS may be appropriate to employ as a language therapy in PPA. One factor that we were specifically interested in exploring was baseline severity. Limited data from cohorts

of healthy subjects suggest that performance on baseline assessment can be an important determinant of tDCS effects; individuals with weaker baseline performance have exhibited more consistent improvement than subjects with better baseline performance in several studies (Turkeltaub et al., 2012; Sarkar et al., 2014; Benwell et al., 2015). We hypothesized that real tDCS would be associated with improved language performance relative to sham, and that these improvements may be more or less pronounced depending on individual differences in baseline language performance.

MATERIALS AND METHODS

Participants

Fifteen patients with a diagnosis of either nfvPPA or lvPPA were recruited from a large cohort of research participants at the Frontotemporal Degeneration Center at the University of Pennsylvania. All participants had been evaluated by a neurologist at the University of Pennsylvania and had received clinical diagnoses of PPA. Patients were excluded who were non-native English speakers, or who had a history of small vessel ischemic disease, seizures, other neurological conditions, unexplained loss of consciousness, or surgical breach of the skull. Patients who scored below 15 on the Mini-Mental State Exam (MMSE) were also excluded due to concern with global impairments precluding adequate comprehension and execution of task instructions. The study was approved by the Institutional Review Board at the University of Pennsylvania and all participants provided informed consent prior to participation.

Of the 15 participants recruited, seven are included in the present analyses (**Figure 1**). Four participants withdrew prior to completing the protocol (two due to medical events unrelated to tDCS; one due to decline and unfeasibility of travel; one due to dislike of tDCS sensation). One participant was lost to follow-up prior to the final language assessment. Two participants received a change of diagnosis during or after completion of the study. Finally, one participant was excluded for being a non-native English speaker.

Our final sample for analysis consisted of five females and two males with a mean age of 68.71 years (Range = 58–79 years, *SD* = 6.97 years) and mean education of 13.86 years (Range = 10–18 years, *SD* = 2.73 years; see also **Table 1**). Our sample included patients with nfvPPA and lvPPA, although it was biased in favor of non-fluent/agrammatic PPA (six nfvPPA; one lvPPA)[1]. Patients reported varying time since the onset of their symptoms (*M* = 4.29 years, *SD* = 1.89 years). Four participants were randomized to receive real tDCS first and three received sham first.

TABLE 1 | Demographic information.

# Males/Females	2/5
Age	68.71 ± 6.97
Years of education	13.86 ± 2.73
MMSE score at screening	24.40 ± 4.77
Diagnosis (lvPPA/nfPPA)	1/6
Disease duration at baseline (years)	4.29 ± 1.89
tDCS order (real first/sham first)	4/3

Study Design

Overview

This was a blinded, randomized, sham-controlled tDCS study. Subjects received 10 daily sessions of real or sham tDCS (Monday–Friday × 2 weeks), employing the stimulation parameters detailed below. Neuropsychological evaluation was administered at baseline (T0) and immediately following the final stimulation session (T1). Follow-up assessments were conducted at 6 weeks (T2) and 12 weeks (T3) post-stimulation. The T3 assessment also served as a second baseline measure for participants as they crossed over into the next arm of the study. This was done for two reasons: first, it allows for examination of the time-course of any tDCS effects in arm 1; and second, it allows us to account for possible carry-over effects of stimulation in examining performance during and following tDCS in arm 2. Immediately after the T3 assessment, participants began a second 10-day round of tDCS. If they had received real stimulation first, they crossed over into the sham condition; if they received sham first, they crossed over into the real condition. Additional assessments were administered immediately post-stimulation (T4), as well as 6 weeks (T5) and 12 weeks (T6) post-stimulation (see also **Figure 2**).

tDCS Procedures

tDCS was administered using a battery-driven Magstim Eldith machine. 5 × 5 cm electrodes were placed in saline-soaked pads and secured to the scalp with a rubber headband. Stimulation was delivered at 1.5 mA (current density = 0.06 mA/cm^2) over a period of 20 min per session, with additional 30-s ramp-up and ramp-down periods at the start and end of stimulation, respectively. The anode was placed over the left prefrontal region (F7 in the International EEG 10–20 system; Homan et al., 1987), and the cathode was placed over the left occipital region (O1). This montage was identical to that used in Gervits et al. (2016). Since it is not possible to focally target specific brain regions with tDCS, this montage was selected for its capacity to influence activity broadly within the left hemisphere in order to target the left-lateralized language network (see **Figure 3** for a theoretical model of current distribution in the brain associated with this electrode montage). Sham stimulation was delivered for 30 s with built-in ramp-up and ramp-down periods proportional to the total stimulation time, in this case approximately 11 s.

[1]Given the imbalance in diagnosis of participants included in this sample, we visually examined individual subjects' raw scores across all metrics within the language battery. There were no apparent systematic differences in the pattern of outcomes for lvPPA vs. nfvPPA. To confirm this statistically, an exploratory analysis of Global Performance excluding this participant showed no change in statistical outcomes. Therefore, we have chosen not to exclude our lvPPA patient from these analyses.

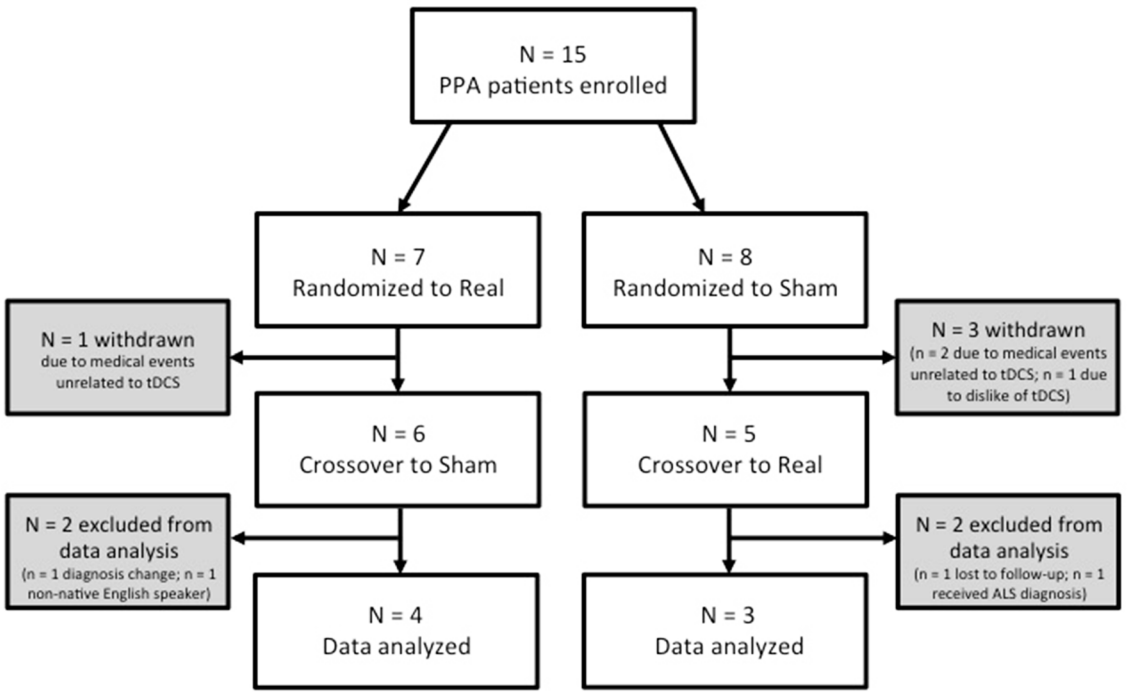

FIGURE 1 | Recruitment and attrition information.

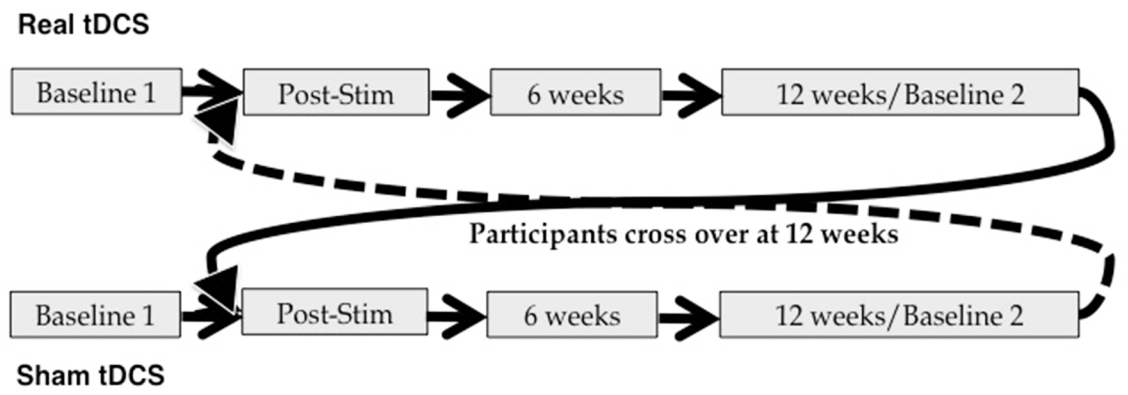

FIGURE 2 | Study design. Participants were randomized to begin in either the real or sham arm of the study, and crossed over at 12 weeks post-stimulation.

Because we were interested in whether tDCS can be used to improve speech production in PPA and to control the activity performed during stimulation across patients, we employed an unstructured language task during stimulation in which patients were asked to verbally narrate wordless children's books during each stimulation session (real and sham). This task was not intended to serve as a therapeutic intervention in and of itself, simply to engage the language network during tDCS. Evidence indicates that cognitive activities pursued during stimulation can strongly influence the kinds of performance changes induced by stimulation (Andrews et al., 2011; Gill et al., 2015). A different book was used in each session and participants engaged in unstructured narration throughout each 20-min period of real or sham stimulation. Sessions were recorded to allow for the possibility of exploratory offline scoring, though we have no specific hypotheses regarding changes in narration ability during stimulation in the real or sham conditions.

Language Battery

A battery of linguistic assessments designed to evaluate a wide range of language abilities was administered to each participant

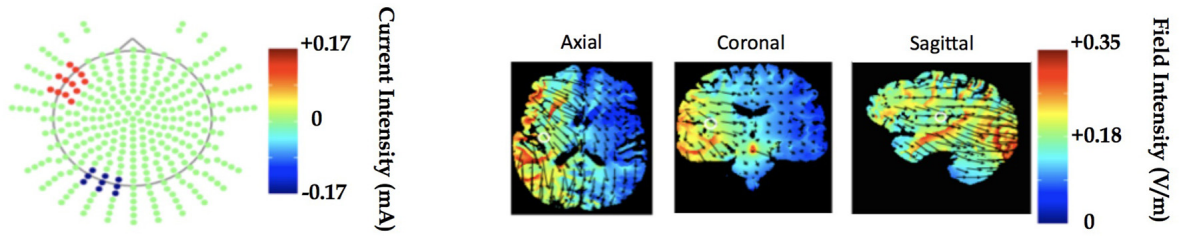

FIGURE 3 | Electrode montage and underlying left hemisphere cortical regions to be stimulated modeled in Soterix transcranial direct current stimulation (tDCS)-Explore™. The model demonstrates current delivery to the F7 and O1 locations results in field intensity increase in regions associated with language processing.

by testers trained in the administration of psychometric assessments (FG, NW)[2]. All sessions were digitally audio-recorded for offline analysis by a coder blinded to time-point and tDCS type. For full detail regarding the language battery, see Gervits et al. (2016).

Outcome Measures

The tests employed in our language battery assess many domains of language performance, some of which are more or less severely affected in patients with nfvPPA and lvPPA. We created three composite measures that reflected common clinical features of these PPA variants. Speech repetition was assessed via performance on the Sentence Repetition test. Grammatical comprehension was assessed via performance on the Penn-TROG (Charles et al., 2014). Semantic processing was assessed via composite performance across the BNT, PPT and Category Fluency tests. Finally, scores across all tests within the language battery[3] were combined into one composite measure to facilitate assessment of overall language performance across domains (Global Performance). **Table 2** shows the distribution of performance across participants at T0.

Data Analysis

Scores on each test within the language battery were separately converted to z-scores based on the mean and standard deviation across all participants and time-points (T0–T6). These transformations facilitated comparisons of performance following tDCS across tests with different scoring metrics and different numbers of items (e.g., the BNT has 15 items, while the Penn-TROG has 36 items). Where scores from multiple tests were combined into composites, data were rescaled such that z-score differences would be considered under one distribution. Difference scores were computed for each time-point relative to the most recent baseline (T1-T0; T2-T0; T3-T0; T4-T3; T5-T3; T6-T3) in order to assess the magnitude of change from baseline as measured in units of standard deviation. Thus, for the first arm of tDCS, we used T0 as the baseline measure for computing difference scores for T1 through T3; for the second arm of tDCS, we used T3 as the baseline for computing difference scores for T4 through T6. This was done to account for any possible order effects regarding the administration of tDCS.

All data analyses were performed using R (R Core Team, 2016), and the R packages *lme4* v1.1-9 (Bates et al., 2015), *languageR* v1.4.1 (Baayen, 2013) and *LMERConvenienceFunctions* v2.10 (Tremblay and Ransijn, 2015) using multilevel modeling with maximum-likelihood estimation (Faraway, 2006; Baayen et al., 2008). For each outcome measure, we performed linear mixed-effects modeling analyses to examine: (1) the effect of tDCS Type (real vs. sham) as a sole predictor of performance; and (2) the possible interactive effects of tDCS Type × Baseline Performance (median split) on performance. In the present set of analyses, we did not have specific *a priori* predictions about the time-course of possible tDCS-related benefits nor sufficient power to detect any potential three-way interaction between tDCS, time-point and baseline performance. **Figure 4** shows the data across all time-points for descriptive purposes. For the most part, the general pattern of outcomes shows the largest change immediately following stimulation and decaying over time. An additional analysis of each of our outcome variables restricted to the post-stimulation time-point only revealed no substantial differences in statistical findings (with the exception of Speech Repetition[4]; see "Results"

[2]It was not possible to ensure that a single tester administered all assessments. To account for the potential confounding factor of test administrator, we included this variable as a covariate in a linear mixed-effects modeling analysis of global performance on the battery and found no significant effect of test administrator on performance.

[3]See Gervits et al. (2016) for full details. We elected to leave the Speech Production metric out of the current analyses. This composite score is computed from several aspects measured in spontaneous speech production during the Cookie Theft Picture Narrative task. Analysis of this rich data set is beyond the scope of this analysis, and will be addressed a separate future manuscript.

[4]Speech Repetition was the only domain for which a difference in statistical outcomes was observed when comparing results at the post-stimulation time-point to results across all time-points (see **Figures 5**, **6**). Specifically, the reduction in Speech Repetition scores following sham tDCS for participants who scored high at baseline was not significant at the post-stimulation time-point, indicating that the decline in scores seen in the overall analysis is likely driven by change at the 6- and/or 12-week time-points. It is difficult to draw conclusions regarding this outcome without appealing to interpretation of null findings in the real tDCS condition, but we suggest that this decline over later time-points may reflect progression of symptoms in high performers, and address this further in the "Discussion" Section.

TABLE 2 | Spread of low and high performers across tasks at baseline.

		Grammatical comprehension	Semantic processing			Speech repetition
Subject	**First arm**	**Penn-TROG (out of 36)**	**BNT (out of 15)**	**Category fluency (no ceiling)**	**PPT (words and pictures: out of 52)**	**Sentence repetition (out of 5)**
DM017	Real	High	High	High	High	Low
GM016	Real	High	Low	High	High	High
KC012	Real	Low	Low	Low	Low	Low
UG015	Real	High	High	High	High	High
EH021	Sham	High	High	High	High	High
KC014	Sham	Low	Low	Low	Low	Low
TN009	Sham	Low	High	Low	Low	High
	Low performer mean	21.33	5.33	10.67	38.00	0.67
	Low performer SD	2.31	4.04	4.04	2.65	1.15
	High performer mean	28.25	14.00	21.50	48.75	4.00
	High performer SD	3.20	1.41	11.90	3.40	0.82

Section and **Figures 5**, **6**), thus we have opted to present data collapsed across time-points both due to enhanced power as well as a potentially more stable, conservative estimate of the effects of tDCS without specific time-course predictions.

RESULTS

Safety and Tolerability

Generally, participants reported experiencing mild itching during the initial period of stimulation that declined after the first few minutes. One participant experienced slight skin irritation during both real and sham stimulation under the F7 electrode that dissipated after stimulation ended. As mentioned above, one participant withdrew from the study on the third day of sham stimulation due to dislike of the sensation associated with stimulation. There were no other adverse effects reported during either real or sham stimulation.

Baseline Performance

Participants were categorized as low performers or high performers based on their language outcomes at T0. Because we are using a linear mixed-effects approach, we chose to classify performance on each language task individually, to better account for individual variability in performance. For example, a patient with nfvPPA may be relatively more impaired on tasks that require speech production as compared to tasks that can be completed without speech. Rather than assigning a composite "average" level of performance to each participant (e.g., for our Global Performance metric), which may obscure possible across-task variance within a subject, we used a median split procedure for each task and retained this level of resolution in our linear mixed-effects analyses. **Table 2** shows the division of participants into low- and high-performing categories for the tasks comprising the composite measures we present here, as well as the tDCS condition in which each individual began the study.

Assessment of Model Viability

Due to our small sample size, we examined the residuals of each of the four interaction models presented below to ensure that our data did not violate the assumption of normally distributed model residuals. **Table 3** provides estimates of the mean, median and skewness for the residuals of all models, each discussed in more detail below.

Global Performance

Effect of tDCS Type

Linear mixed-effects modeling revealed no main effect of tDCS Type on global performance change from baseline, $F_{(1,453)} < 1$.

tDCS Type × Baseline Performance

This analysis demonstrated no significant main effect of tDCS Type, $F_{(1,451)} < 1$. There was a marginally significant main effect of Baseline Performance, $F_{(1,451)} = 3.37$, $p = 0.067$. The two-way tDCS Type × Baseline Performance interaction was significant, $F_{(1,451)} = 6.76$, $p = 0.0096$ (see **Figure 5A**). Examination of the fixed effects structure in the model revealed that individuals who scored lower at baseline improved significantly following real tDCS ($M = 0.255$) relative to their own sham tDCS ($M = -0.062$), $t_{(452.2)} = -2.491$, $p = 0.013$. There was no such difference in performance following real vs. sham tDCS for participants who scored high at baseline, $t_{(452.2)} = 1.19$, $p = 0.233$. Additionally, performance change following real tDCS was significantly greater for low baseline scorers ($M = 0.255$) relative to high baseline scorers ($M = -0.176$), $t_{(367.3)} = 3.08$, $p = 0.0022$. There was no difference in performance change between low and high baseline scorers following sham tDCS ($Ms = -0.062$ and -0.022, respectively), $t_{(367.3)} = -0.281$, $p = 0.779$.

Grammatical Comprehension

Effect of tDCS Type

Linear mixed-effects modeling revealed no main effect of tDCS Type on grammatical comprehension change from baseline, $F_{(1,33)} < 1$.

tDCS Type × Baseline Performance

This analysis demonstrated no significant main effect of tDCS Type, $F_{(1,31)} < 1$. There was also no main effect of Baseline Performance, $F_{(1,31)} = 2.22$, $p = 0.146$. The two-way tDCS

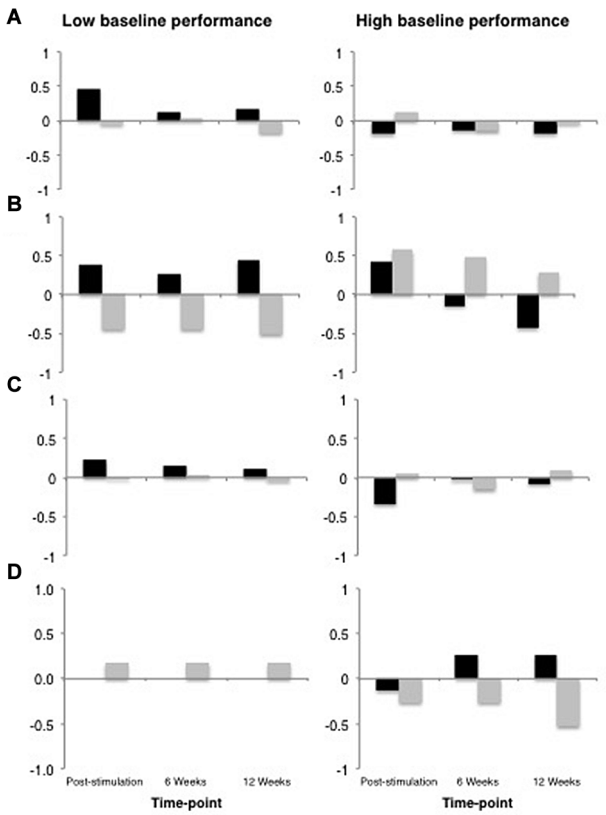

FIGURE 4 | Data from across all time-points plotted for descriptive purposes. In all panels, real tDCS outcomes are depicted in black and sham outcomes are depicted in gray, and the *y*-axis represents z-score change from the most recent baseline. **(A)** Global Performance. **(B)** Grammatical Comprehension. **(C)** Semantic Processing. **(D)** Speech Repetition.

Type × Baseline Performance interaction was significant, $F_{(1,31)} = 4.56$, $p = 0.0005$ (see **Figure 5B**). Examination of the fixed effects structure in the model revealed that individuals who scored lower at baseline improved significantly following real tDCS ($M = 0.364$) relative to sham tDCS ($M = -0.471$), $t_{(38)} = -3.24$, $p = 0.003$. Conversely, for participants who scored high at baseline, performance improved significantly following sham ($M = 0.449$) compared to real tDCS ($M = -0.048$), $t_{(38)} = 2.23$, $p = 0.032$. Following sham tDCS, low baseline scorers ($M = -0.471$) improved significantly less than high baseline scorers ($M = 0.449$), $t_{(38)} = -3.82$, $p = 0.0004$. There was no difference in performance change between low and high baseline scorers following real tDCS ($Ms = 0.364$ and -0.048, respectively), $t_{(38)} = 1.71$, $p = 0.096$. However, given the bimodal distribution of model residuals (see **Table 3**), these results must be interpreted with caution. Bimodal model residuals suggest some systematicity to prediction error in the model that may reflect a non-linear relationship between grammatical comprehension performance and PPA severity. However, it is also possible that this finding is related only to the size of the dataset, and that model residuals would approach normality with an increased sample size. More data are needed to clarify this finding.

Semantic Processing

Effect of tDCS Type

Linear mixed-effects modeling revealed no main effect of tDCS Type on semantic processing change from baseline, $F_{(1,159)} < 1$.

tDCS Type × Baseline Performance

This analysis demonstrated no significant main effect of tDCS Type, $F_{(1,157)} < 1$, or of Baseline Performance, $F_{(1,157)} < 1$. The two-way tDCS Type × Baseline Performance interaction was marginally significant, $F_{(1,157)} = 3.38$, $p = 0.068$ (see **Figure 5C**). Examination of the fixed effects structure in the model showed that performance change for individuals who scored low at baseline ($M = 0.164$) improved significantly following real tDCS relative to those who scored high at baseline ($M = -0.152$), $t_{(130.4)} = 2.12$, $p = 0.036$. No other comparisons were significant (all ps > 0.15).

Speech Repetition

Effect of tDCS Type

Linear mixed-effects modeling revealed no main effect of tDCS Type on speech repetition change from baseline, $F_{(1,33)} = 1.91$, $p = 0.176$.

tDCS Type × Baseline Performance

This analysis demonstrated no significant main effect of tDCS Type, $F_{(1,31)} = 2.17$, $p = 0.150$, and no main effect of Baseline Performance, $F_{(1,31)} < 1$. The two-way tDCS Type × Baseline Performance interaction was significant, $F_{(1,31)} = 5.73$, $p = 0.023$ (see **Figure 5D**). Evaluation of model residuals revealed only a slight deviation from normality according to our skewness cutoff at the $p = 0.05$ level (-1.062 vs. 0.963, respectively; see Doane and Seward, 2011). However, we note that we have employed a conservative skewness cutoff (based on sample size of $n = 10$ rather than $n = 7$) in making this determination. Examination of the fixed effects structure in the model revealed that individuals who scored higher at baseline improved significantly following real tDCS ($M = 0.132$) relative to sham tDCS ($M = -0.353$), $t_{(33)} = -2.68$, $p = 0.011$. There was no such difference in performance following real vs. sham tDCS for participants who scored low at baseline, $t_{(33)} = 0.85$, $p = 0.404$. No other comparisons were significant.

DISCUSSION

The present study employed a randomized, sham-controlled design to assess the potential of tDCS as a therapy to modulate language difficulties in patients with PPA. Whereas a previous open-label study demonstrated large effects across all domains assessed (see Gervits et al., 2016), the same comparisons made with our sham-controlled design revealed no significant findings in any domain. However, when we took into account each individual's language performance at the baseline

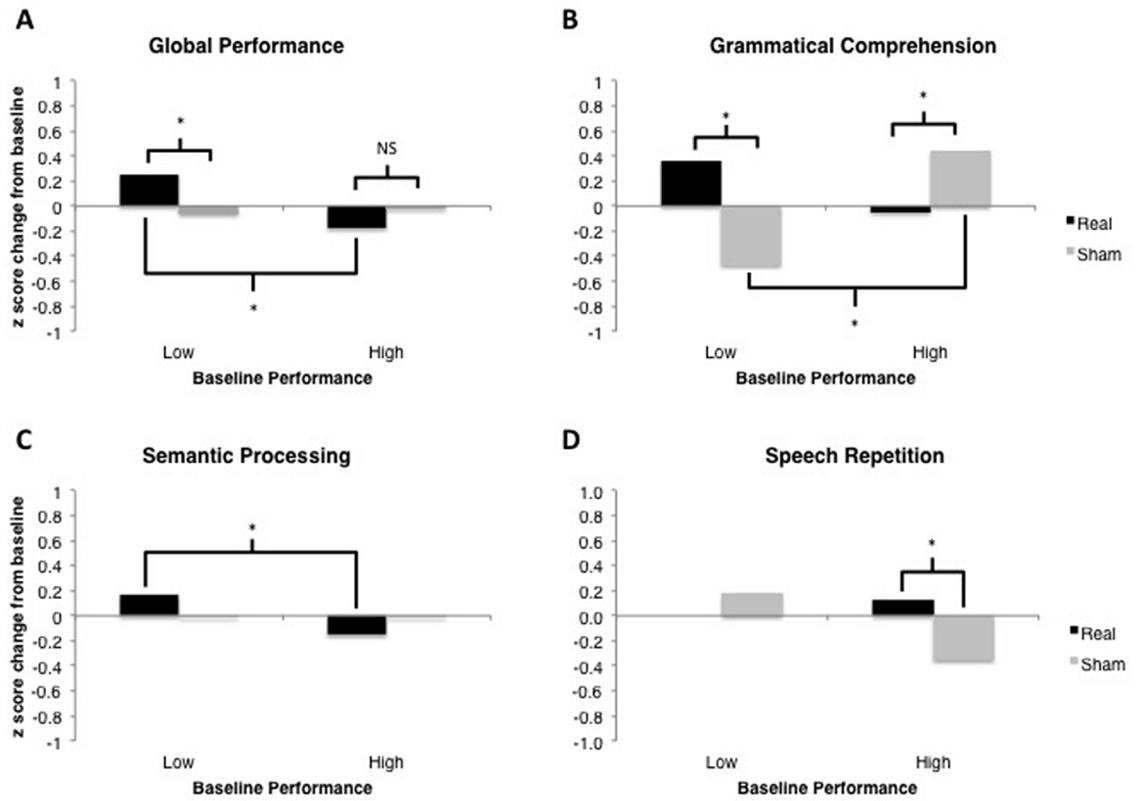

FIGURE 5 | Results of linear mixed-effects tDCS × Baseline Performance analyses for each language domain of interest. Model-estimated means are plotted in units of z-scores measured as change relative to the most recent baseline (i.e., standardized different scores). Asterisks represent significant comparisons at the $p < 0.05$ level. **(A)** Global Performance of low and high performers at baseline. **(B)** Grammatical Comprehension of low and high performers at baseline. **(C)** Semantic Processing of low and high performers at baseline. **(D)** Speech Repetition of low and high performers at baseline.

assessment (T0), we were able to demonstrate the importance of baseline performance in predicting which patients will respond positively to tDCS, as indexed by an improvement in language performance. Generally speaking, individuals whose performance was lower at baseline demonstrated greater propensity to improve after receiving real tDCS relative to sham tDCS. This was the case for our metric of Global Performance. We also observed this pattern of results for Grammatical Comprehension performance, though there was observable bimodality in the residuals of this model that must be taken into account when interpreting the outcome of the present analysis. Individuals whose performance was lower at baseline also demonstrated significant improvement in Semantic Processing following real tDCS compared to individuals who performed better at baseline, although this improvement was not significant relative to the sham condition.

The only measure in which higher performance at baseline was associated with tDCS-specific outcomes was in our Speech Repetition test (**Figure 4D**). However, the significant difference in performance between real and sham conditions appeared to reflect a *decline* in performance following sham tDCS rather than a tDCS-related improvement. Relative to baseline performance, there was no significant improvement following real tDCS. It is difficult to interpret this finding given the lack of statistically significant improvement following real tDCS relative to baseline. It is possible that this pattern of results is due to a "protective" effect of real tDCS, such that the application of tDCS may prolong the maintenance of speech repetition in the course of the disorder. That is, individuals who started out with better performance may have experienced greater decline in speech production abilities over the course of the 6 months of the study, possibly related to selective disease progression, whereas individuals whose speech was already affected may have shown more stable error rates. Anecdotally, individuals who made many errors in speech repetition tended to make the same errors consistently, which may be reflected in stable change scores. However, another caveat to this interpretation is the nature of the Speech Repetition task itself, which comprises a total of five items. Given the small range across which to assess performance, it may be that low performers demonstrate a floor effect, such that any potential decline in ability cannot adequately be detected with this task. Further investigation is required to clarify the nature of this finding.

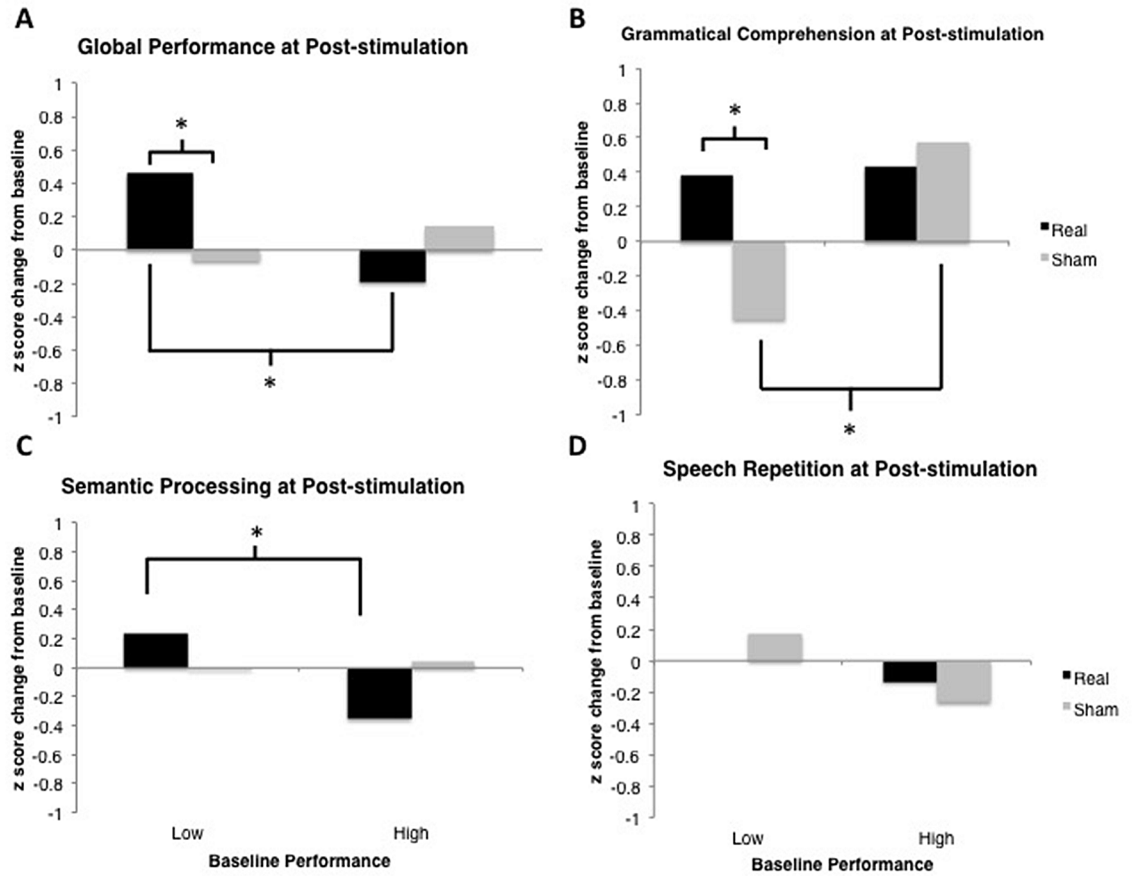

FIGURE 6 | Results from the post-stimulation time-point only. Model-estimated means are plotted in units of z-scores measured as change relative to the most recent baseline (i.e., standardized different scores). Asterisks represent significant comparisons at the $p < 0.05$ level. **(A)** Global Performance at post-stimulation time-point. **(B)** Grammatical Comprehension at post-stimulation time-point. **(C)** Semantic Processing at post-stimulation time-point. **(D)** Speech Repetition at post-stimulation time-point.

TABLE 3 | Model residuals for each domain of analysis.

Domain	Mean	Median	Skewness[a]	Shape
Global performance	−2.16E-12	0.0012	0.756	Unimodal
Grammatical comprehension	7.14E-11	0.0856	−0.278	Bimodal*
Semantic processing	−3.57E-11	−0.0239	0.401	Unimodal
Speech repetition	−9.52E-11	0	−1.062*	Unimodal

Asterisks indicate a violation of the expected normal distribution. [a]Data simulations support a skewness cutoff of ±0.963 for a study with n = 10 sample size (see Doane and Seward, 2011 for detail). Generally speaking, skewness cutoffs scale in inverse proportion to sample size, thus we conservatively use this n = 10 cutoff for our evaluations.

Given variability in the outcomes across tDCS studies, it is particularly important to examine potential modulating factors of individual response to tDCS. Participants who scored lower at baseline demonstrated greater tDCS-related benefits overall, suggesting (perhaps counter-intuitively) that tDCS may be more beneficial for patients who are treated at a later stage in the course of their disease. These findings are consistent with previous brain stimulation studies in which baseline performance was measured as a potentially influential factor on results. Benwell et al. (2015) found that bi-parietal left anodal/right cathodal tDCS effects were relative to a participant's baseline performance on a perceptual line bisection task. In a cohort of cognitively healthy individuals, Turkeltaub et al. (2012) observed that tDCS-induced enhancement of reading efficiency was most consistently among subjects who had weaker reading efficacy at baseline. Moreover, Sarkar et al. (2014) found that otherwise healthy subjects who had high math anxiety (a predictor of poorer mathematical performance) temporarily benefitted from a mathematical (arithmetic) training task paired with tDCS, while participants who had low baseline math anxiety (and presumably higher math ability) got transiently worse as a result of receiving tDCS. A similar

study also found that greater cognitive gains were achieved by individuals with lower baseline performance on a mathematical video game when paired with anodal tDCS (Looi et al., 2016).

Assessing baseline performance in patients with neurodegenerative disorders who are slated to receive tDCS may be especially important due to the theoretical mechanism of tDCS in influencing neuronal function. Because tDCS is thought to alter resting excitability of populations of neurons (Stagg and Nitsche, 2011), the degree of atrophy (likely related to the severity of symptoms at baseline) in affected regions may be a critical factor in deciding to whom tDCS should be prescribed and when. The current results suggest that application of tDCS in PPA patients whose symptoms are too mild may not be beneficial. On the other hand, if progression is too far along, it is also possible that tDCS intervention would be unhelpful due to advanced tissue loss in brain regions necessary for language function. Future work should further investigate the possible inverted-U "critical period" for tDCS intervention in PPA. Though we did not assess baseline cortical thickness in the present study, future exploration of the influence of baseline symptom severity should take into account the progression of cortical atrophy as a possible predictor of response to tDCS.

Participants who score higher on tests of language performance at the baseline assessment may not benefit as much from tDCS due to the mildness of deficits. Since our analyses focused on *change* in performance rather than overall performance, higher performing participants may have delivered more stable performances across time points, leaving less room for the tDCS intervention to have an effect. On the other hand, participants who scored lower at baseline may have had more room for improvement, and thus exhibited greater performance gains following tDCS. Previous studies (e.g., Cotelli et al., 2014) have purposely enrolled patients with mild language deficits, but have paired tDCS with intensive, targeted language therapies. Combining therapies in this way may help improve symptoms in individuals with milder deficits, whereas tDCS alone may provide some benefit in individuals whose symptoms have progressed further. The degree to which combination speech therapy-tDCS interventions may help with more severe PPA symptoms is currently unknown. A caveat of this explanation is that our metrics may not have been sensitive enough to detect performance change in participants who were high-performing at baseline. Since all individuals enrolled were experiencing language-related difficulties at the time of study, it is possible that evaluating language performance in other ways (e.g., via metrics that combine performance accuracy and speed to assess language *efficiency* rather than absolute test scores) may be more sensitive to the possible tDCS-related enhancement of performance in individuals whose symptoms are less severe. Elucidating the capacity of tDCS to remediate symptoms with and without concurrent speech therapy at different stages of PPA progression will be critical to determining the application of tDCS as a therapy for people with PPA.

We did not expect to find such a dramatic difference in the outcome of the present study as compared to Gervits et al. (2016). Whereas the previous open-label sample demonstrated significant language gains across all domains tested, similar analyses on the current dataset revealed no significant tDCS-related improvements until baseline performance was taken into account. A few key factors may explain these differences. First, there was an unequal representation of lvPPA and nfvPPA subjects in each study. The prior study included four individuals with lvPPA and two with nfvPPA, while the current study included only one lvPPA patient and six nfvPPA patients. Though both of these PPA variants involve difficulties biased toward language production (as compared to comprehension), the symptomatology of these two neurodegenerative diseases is expressed differently and may explain varied outcomes on language measures following tDCS. Since a key characteristic of nfvPPA is difficulty with grammatical comprehension and repetition (Gorno-Tempini et al., 2011), this may have had an effect on performance of these language measures. Similarly, we encourage future studies to develop more granular *a priori* hypotheses regarding which language abilities could be affected by the inclusion of a more specific task paired with stimulation. This additional specification would allow for stronger inferences to be made regarding the effects of stimulation within the language network. Finally, the findings across our two studies emphasize the importance of cautious interpretation in the setting of a potential placebo effect, and the critical role of a sham control condition. Future studies should delineate further distinctions between the variants of PPA and the associated improvements or lack thereof across different language measures.

Limitations of the Current Study

One limitation of our study is the small sample size and skewed distribution of PPA variants. We do not have a large enough sample to assess whether nfvPPA or lvPPA patients are relatively more likely to benefit from tDCS, or whether this may be true to different extents across different domains of language.

Additionally, the natural time-course of language decline in PPA is not well understood. This is of particular relevance in determining whether tDCS is a useful therapy for PPA patients, since the degree to which *improvement* and *lack of decline* may both be reflective of a positive tDCS outcome. In the latter instance, it may be the case that early tDCS intervention delays decline in individuals who are higher-performing at baseline, but we cannot currently distinguish such an outcome from a null effect.

The current study did not aim to develop specific hypotheses regarding the interaction between performing a task and tDCS. We can infer that the act of narrating wordless picture stories requires engagement of the language network, specifically object recognition, semantic processing, verbal working memory, grammatical processing and phonological processing among other language functions. This unstructured task was employed to broadly enhance language production during stimulation, however no further predictions were made regarding this interaction.

Finally, in the current study we did not have enough power to examine the time-course tDCS-related language

benefits to determine how long improvement lasts, which may also be affected by baseline performance and will be important in assessing the therapeutic value of tDCS intervention.

CONCLUSION

The current results suggest that language abilities at baseline are a strong predictor of tDCS-mediated symptom management in individuals with PPA. Further research is needed to clarify the role of tDCS at different stages of this progressive disorder, specifically to assess whether tDCS may be more effective in treating symptoms in specific PPA variants, and when to begin therapy.

AUTHOR CONTRIBUTIONS

RHH, HBC, MG and SA designed the experiments; FG, NCW and EMM performed the experiments and designed analysis methods; NCW analyzed the data; and EMM, NCW and RHH wrote the manuscript.

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frontiers in Human Neuroscience

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Transcranial Direct Current Stimulation in Post-stroke Chronic Aphasia: The Impact of Baseline Severity and Task Specificity in a Pilot Sample

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Emerging evidence suggests that transcranial direct current stimulation (tDCS) can improve aspects of language production in persons with chronic non-fluent aphasia due to left hemisphere stroke. However, to date, studies exploring factors that predict response to tDCS in this or any patient population remain sparse, as are studies that investigate the specific aspects of language performance that are most responsive to stimulation. The current study explored factors that could predict recovery of language fluency and which aspects of language fluency could be expected to improve with the identified factor(s). We report nine patients who demonstrated deficits in fluency as assessed using the Cookie Theft picture description task of the Boston Diagnostic Aphasia Examination. In the treatment condition, subjects received a 2.0 mA current through 5 cm × 5 cm electrodes for 20 min at a site previously shown to elicit a patient-dependent optimal response to tDCS. They were then tested 2-weeks and 2-months after treatment. In the sham condition, a subset of these subjects were tested on the same protocol with sham instead of real tDCS. The current study assessed language fluency improvements in measures of production at the word-level and sentence level, grammatical accuracy, and lexical selection as a function of baseline aphasia severity. A more severe baseline language profile was associated with larger improvements in fluency at the word-level after real tDCS but not sham stimulation. These improvements were maintained at the 2-week follow-up. The results suggest that for at least some outcome measures, baseline severity may be an important factor in predicting the response to tDCS in patients with chronic non-fluent aphasia. Moving forward, the ability to identify patient factors that can predict response could help refine strategies for the administration of therapeutic tDCS, focusing attention on those patients most likely to benefit from stimulation.

Keywords: aphasia, baseline severity, stroke, tDCS, neurorehabilitation

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INTRODUCTION

With 80,000 new cases in the US each year and a total of 6.4 million affected individuals, aphasia—acquired loss of language ability—is one of the most common and debilitating post-stroke cognitive disorders (Wade et al., 1986; National Stroke Association, 2008; Kyrozis et al., 2009). Post-stroke aphasia typically arises from injury to the left (dominant) hemisphere, in a network of language-related regions that surround the Sylvian fissure. The degree to which individuals recover from aphasia is variable, and chronically persistent deficits are common (Mimura et al., 1998; Rosen et al., 2000; Heiss and Thiel, 2006; Saur et al., 2006). Unfortunately, the efficacy of behaviorally-based rehabilitation approaches has proven limited (Winhuisen et al., 2005). However, a growing body of encouraging evidence now suggests that non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS) may have the capacity to improve aspects of language production in persons with chronic aphasia (Monti et al., 2008; Baker et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011).

TDCS modulates brain activity by delivering a weak polarizing electrical current, which is believed to induce incremental shifts in the resting membrane potentials of neurons (Nitsche and Paulus, 2001). These shifts, while insufficient to depolarize neurons acutely, can result in changes in neuronal firing rates, which in turn are associated with measurable changes in cognition and behavior (Schlaug et al., 2009). Repeated sessions of tDCS paired with a behavioral task have been associated with enduring changes in both neural activity and performance (Boggio et al., 2007; Reis et al., 2009; Brunoni et al., 2012) which has given rise to considerable interest in the use of tDCS as an adjunctive treatment in patients with post-stroke deficits, including hemiparesis (Peters et al., 2016), neglect (Yi et al., 2016), and aphasia (Monti et al., 2008; Baker et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011; Medina et al., 2012).

To date, at least 19 papers have been published employing tDCS as a potential treatment for post-stroke aphasia (Cappon et al., 2016). Most of these studies have focused on patients with non-fluent aphasia, that is deficits primarily in language production. While non-fluent aphasia manifests itself in a variety of symptoms, including but not limited to slow effortful speech and agrammatism, the majority of tDCS studies in the field have focused on picture naming (Monti et al., 2008; Baker et al., 2010; Fiori et al., 2011; Flöel et al., 2011; Fridriksson et al., 2011; Richardson et al., 2015; Wu et al., 2015). There are both theoretical and practical reasons for this; difficulty with naming is a ubiquitous property of all conventional post-stroke aphasia syndromes, and it is one of the most straightforward language abilities to evaluate experimentally. However, while studies of the effect of tDCS on naming ability undoubtedly provide some insight into the utility of tDCS as a language intervention, these studies fall short in determining whether tDCS is likely to be helpful in restoring the ability to generate fluid, spontaneous, self-directed speech to patients who have lost this capacity.

In a previous work, we reported improvement of language abilities in a cohort of patients with chronic non-fluent aphasia 2 weeks and 2 months after a course of tDCS (2 mA × 20 min for 10 days; Shah-Basak et al., 2015). Depending on the results of an individual montage-testing phase, treatment was delivered on a subject-by-subject basis to either the left frontal lobe (targeting perilesional areas of the language dominant hemisphere) or the right frontal lobe (targeting presumed homologs of damaged left hemisphere language areas) using either anodal or cathodal tDCS. Compared to sham stimulation, patients showed significant and sustained improvement on the Western Aphasia Battery Aphasia Quotient (WAB-AQ), a global measure of aphasia severity. In the current study, we further explored the data obtained from these patients, in an attempt to determine whether and in what ways tDCS affected speech fluency. Our approach to examining fluency changes was informed by a prior investigation in which we employed quantitative production analysis (QPA; Saffran et al., 1989) to explore changes in spontaneous speech in chronic non-fluent patients who had received repetitive transcranial magnetic stimulation (rTMS), a different form of non-invasive neuromodulation (Medina et al., 2012). In that investigation, we explored changes in spontaneous speech at the level of word production, sentence generation, grammar, or lexical selection (speech efficiency), and found that subjects who had received TMS experienced an improvement in fluency that was largely due to increased production at the word level. Based on these prior findings, in this study we hypothesized that any improvement in speech fluency that was identified following tDCS would likely be most notable at the word level, rather than the level of sentences or overall narrative.

In addition to characterizing the specific language abilities that are likely to be affected by tDCS in patents with aphasia, it is important for investigators of begin to determine the clinical properties of patients that predict response to stimulation. One clinical characteristic that we argue should be considered is baseline symptom severity. Although clinical studies with tDCS have not yet fully explored the impact of baseline performance on tDCS-induced recovery, a few recent studies in healthy subjects have suggested that individuals who demonstrate weaker performance at baseline may be more likely to benefit from stimulation. For instance, Sarkar et al. (2014) enrolled healthy subjects to undergo a mathematical training task paired with tDCS. The investigators also measured subjects' mathematics anxiety, which is generally negatively correlated with mathematical proficiency. They found that subjects who were worse at mathematics and had high mathematics anxiety at baseline experienced a significant increase in math performance after tDCS to the dorsolateral prefrontal cortex, while those with strong baseline mathematical ability worsened after tDCS. In the language domain, Turkeltaub et al. (2012) found that, in healthy adults who underwent a single session of tDCS over the left posterior temporal cortex, reading efficiency improved more robustly in subjects whose baseline performance was below the mean level of performance of the study cohort. Both studies suggest that poor initial performance on cognitive tasks may predict greater tDCS-induced improvement. Moreover, an association

between poor baseline functioning and a greater post-stimulation improvement has also been shown in non-cognitive tasks like motor coordination (Uehara et al., 2015). The same effect has been observed in studies of fine motor control that compared non-musicians to professional musicians (Furuya et al., 2014). Taken together, one interpretation of these studies is that brain networks associated with relatively weak performance on tasks may be more amenable to beneficial modulation via tDCS, while those associated with strong performance may already be closer to their optimal state and may thus benefit less—or may even be adversely affected—by further modulation.

However, while a small but growing body of evidence in healthy subjects suggests an association between weaker baseline performance and greater improvement after tDCS, it not yet been determined whether this relationship also pertains to the application of tDCS in persons with neurologic deficits, such as patients with post-stroke aphasia. At least two very different scenarios seem plausible. One possibility is that, as previous studies in healthy subjects have suggested, persons who perform poorly at baseline have language networks that can be improved further by tDCS, whereas patients who perform well at baseline may have language networks that are closer to an optimal state, and thus less likely to be enhanced by additional neuromodulation. However, it is also possible that patients who perform poorly at baseline have language networks that are so severely degraded by stroke that they cannot be enhanced substantively by tDCS, while better baseline language function may signal more robust residual language networks, which can be modulated beneficially by stimulation. This would be consistent with studies of the natural history of aphasia recovery, which suggest that patients who exhibit poorer language recovery early in their post-stroke course are less likely to have substantive improvement in aphasia severity compared to patients with less severe initial symptoms (e.g., Laska et al., 2001).

In the current study we sought to address two questions. First, using QPA (Gordon, 2006) we sought to determine whether there are the distinct elements of production within spontaneous speech that are preferentially affected by tDCS in patients with chronic non-fluent aphasia after stroke. We used the Cookie Theft narrative picture description from the Boston Diagnostic Aphasia Examination (BDAE) to assess language fluency. Based on our prior findings in a related population receiving TMS, we hypothesized that the most robust effects of tDCS on spontaneous speech would be in word level production. Secondly, we examined relationships between baseline severity on measures of speech fluency and response to tDCS in our cohort of patients with chronic aphasia. In light of the evidence in healthy subjects discussed above, we hypothesized that weaker baseline performance on measures of speech production would be associated with greater improvement tDCS. Finally, integrating the above two hypotheses, we predicted that the relationship between baseline severity and response to tDCS would be most robust in measures of word level production, the aspect of spontaneous speech that we expected to be most responsive to therapeutic neuromodulation.

METHODS

Overview

This was a two-phase study. In the first phase the optimal stimulation montage was identified. The second phase introduced tDCS as a treatment, utilizing a sham-controlled partial crossover design with 2 weeks (10 days) of stimulation followed by a 2-week and a 2-month follow-up. The methods summarized here are described in more detail in our previous work (Shah-Basak et al., 2015).

Subjects

Subjects had a history of a first time single left-hemispheric chronic stroke ($\geq$6 months post-stroke-onset), had mild-to-severe non-fluent aphasia, were premorbidly right-handed (Edinburgh Handedness Inventory) (Oldfield, 1971), and had no concurrent history of neurological, psychiatric or unstable medical conditions, or any contraindication to either MRI or tDCS (**Table 1**). Aphasia symptoms and severity were screened using the Western Aphasia Battery (WAB) (Kertesz, 1982), to avoid ceiling effects, individuals with a WAB-Aphasia Quotient (WAB-AQ) above 90 were excluded. Out of 26 screened subjects, 3 were medically ineligible, 5 did not meet the eligibility criterion, and 1 was lost to follow-up, resulting in 11 enrolled subjects, and 9 of which progressed to phase 2 (2 females; age: 62.0 $\pm$ 10.8, range = 53–84 years; **Figure 1**). None of the enrolled subjects initiated new language therapies or engaged in other treatment studies during the course of the study. A single neurologist (RHH) used clinical scans (MRI/CT) obtained during or after each patient's medical treatment for stroke to delineate lesion locations. The study was approved by the Institutional Review Board of the University of Pennsylvania, and each subject, or his or her legally authorized representative, provided informed consent.

Transcranial Direct Current Stimulation

As described in our earlier paper (cf. Shah-Basak et al., 2015; **Figure 1**), the stimulation paradigm is as follows. In both phases of the study we used a Magstim Eldith 1 Channel DC Stimulator Plus (Magstim, Whitland, UK). A recent review by Bikson and colleagues explored the safety of tDCS. They defined conventional tDCS protocols as $\leq$40 min, $\leq$4 miliamperes, and $\leq$7.2 Coulombs. This review covered 33,200 sessions and 1,000 subjects and found no reports of serious adverse effect or irreversible injury after repeated sessions (Bikson et al., 2016). In line with widely used and safe parameters (Brunoni et al., 2011; Kessler et al., 2012; Russo et al., 2013; Bikson et al., 2016), stimulation was delivered for 20 min at 2.0 mA using 5 $\times$ 5 cm^2 sponge electrodes (current density: 0.80 $\mu A/mm^2$) with a 30-s ramp-up and ramp-down period. For sham, stimulation was ramped up to 2.0 mA and then down to 0 mA in the first minute of stimulation, and subjects were randomized to either receive tDCS with either the anode or cathode over either the left

TABLE 1 | Subject demographics.

Subject	Sex	Age, y	Time since stroke, mo	Type of stroke	Lesion distribution	Lesion volume (cm^3)	WAB-AQ	Optimal montage	Number of nouns (baseline)	Number of nouns (2 weeks)	Number of nouns (2 months)
REAL tDCS											
R1	M	65	27	Ischemic	Left MCA	~	29.1	Anode F3	0		0
S1/R2	M	53	67	Ischemic	Fronto-parietal cortical and subcortical, including internal capsule, basal ganglia, anterior IFG	165.49	87.8	Anode F3	14	20	14
R3	M	54	8	Ischemic	Large fronto-temporo-parietal lesion involving STG, parietal cortex, IFG, and subcortical white matter Caudate and thalamus spared	271.02	38.9	Cathode F3	4	8	1
R4	M	76	100	Ischemic	Fronto-temporo-parietal subcortical, including corona radiata Internal capsule, deep gray structures, and IFG spared	145.94	69.6	Cathode F3	27	27	17
S2/R5	M	61	28	Hemorrhagic	Fronto-parietal lesion involving sensorimotor and superior parietal cortices, and subcortical white matter IFG, inferior parietal gyrus, temporal cortex, deep gray structures, and thalamus spared	134.04	83.0	Cathode F4	30	20	23
S4/R6	M	67	10	Ischemic	Fronto-parietal lesion involving supramarginal gyrus, temporo-parietal-occipital junction, insula, IFG, and underlying subcortical white matter Basal ganglia and thalamus spared	89.8	69.5	Cathode F3	22	19	19
S5/R7	F	84	26	Ischemic	Left MCA	~	78.1	Anode F3	8	8	9
S6/R8	F	50	116	Ischemic	Left MCA	~	78.7	Anode F4	14	15	15
Mean (StdDev)		62.0 (±1 0.8)	50.5 (± 41.2)						15 (± 10.7)	17 (± 6.9)	12 (± 8.3)
SHAM tDCS											
S1/R2	M	53	67	Ischemic					14	12	15
S2/R5	M	61	28	Hemorrhagic					30	22	23
S3	M	61	12	Ischemic	Large fronto-temporo-parietal lesion involving STG, parietal cortex, left IFG and subcortical white matter Deep gray structures and thalamus spared	266.29	23.2		1	0	0
S4/R6	M	67	10	Ischemic					22	19	15
S5/R7	F	84	26	Ischemic					8	5	10
S6/R8	F	50	116	Ischemic					14	12	17
Mean (StdDev)		57.3 (± 4.6)	35.7 (±2 8.3)						15 (± 10.1)	12 (± 8.3)	13 (± 7.8)

MCA, Middle cerebral artery; IFG, Inferior frontal gyrus; STG, Superior temporal gyrus; SD, Standard deviation. Of note, structural images were reviewed during subject screening and enrolment but were not available during data analysis or results reporting (~). Additionally, areas in gray under the sham tDCS section represent previously stated demographics for the same subjects in the real tDCS.

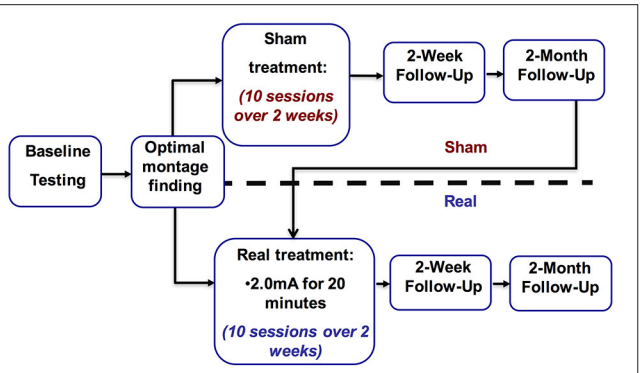

FIGURE 1 | Study overview.

frontal lobe or right frontal lobe, or sham stimulation, leading to a total five conditions (i.e., anode left, cathode left, anode right, cathode right, and sham). In all conditions, the countervailing electrode was positioned over the contralateral mastoid. The order of five conditions was counterbalanced across subjects, who were blinded to whether they were receiving real or sham-tDCS (Gandinga et al., 2006). The person administering tDCS was not blinded to tDCS conditions.

Phase 1: Optimal Montage Identification

Over five non-consecutive days, subjects underwent tDCS with the four active conditions and one sham condition, one condition per session. These sessions were separated on average by at least 5 days. Frontal lobe stimulation sites were identified using the 10–20 EEG measurement system (F3 = left; F4 = right). Thus, the active conditions were F3-anode, F3-cathode, F4-anode, and F4-cathode. These frontal sites overlie brain areas that are superior to the inferior frontal gyrus, which is often lesioned in patients with non-fluent aphasia. We theorized that F3 stimulation would likely be associated with perilesional stimulation in the left hemisphere.

Previously described in our earlier paper (cf. Shah-Basak et al., 2015), picture-naming ability was assessed before and immediately after each stimulation session with an 80-item task using images from the International Picture Naming Project database (IPNP) (Szekely et al., 2004). The 80-item picture sets were matched for word-frequency, word-length, and semantic category. Different item lists were assigned to each days and to the pre- and post- tDCS assessment. The difference between the number of items that were named correctly before and following each stimulation session was calculated (post- vs. pre-stimulation). To examine variability in responsiveness to tDCS, we first compared the change in subjects' performance across all active montages with respect to the sham montage. Second, in line with previously reported methods (Naeser et al., 2005; Medina et al., 2012), an electrode montage was defined as optimal for each subject if the subject (1) showed the greatest change in accuracy after stimulation using a particular montage and (2) if the accuracy post-stimulation with that montage was $\geq$ the upper limit of the 90% confidence interval (CI) of pre-stimulation performance across all montages.

Phase 2: Stimulation of Individually-Selected Montages

At the conclusion of Phase 1, 11/26 subjects exhibited significant transient improvement in naming after stimulation with at least one active electrode arrangement. Ten subjects entered the sham controlled partial crossover portion of the study; one subject declined further study participation. Another subject completed only the sham arm, but declined to participate in the real-tDCS phase. The data included in this analysis is from the 9 subjects that participated in phase 2. Each of the 9 subjects was randomized to receive either real-tDCS treatment only ($N = 3$), or sham stimulation followed by real-tDCS ($N = 6$). There were no significant differences in the demographics of the 9 subjects apart from their initial severity at baseline (2 females; age: 62.0 $\pm$ 10.8, range = 53–84 years; baseline WAB: 62.0, range 23.2–87.8).

To establish a stable pre-tDCS baseline of aphasia severity, the Cookie Theft narrative picture description was administered 3 times in separate behavioral sessions prior to initiating real or sham treatment. During treatment, subjects received tDCS for a total of 10 days (Monday–Friday for two consecutive weeks). Stimulation parameters were identical to those described during optimal montage identification. Subjects engaged in the training task described above during both the real- and sham-tDCS sessions (Maher et al., 2006). Subjects repeated the assessment with the Cookie Theft narrative picture description at 2 weeks and 2 months after treatment. Following 2-month follow-up, subjects in the sham arm crossed over into the real arm and received real-tDCS, followed by 2-week and 2-month follow-up assessments (**Figure 2**). Subjects who initially received real-tDCS were blinded to their treatment condition. Subjects receiving sham stimulation were blinded to their condition until they crossed over into the real arm of the study, at which point they were by necessity informed of their condition (as required by our IRB).

Language Training Task

As described in our earlier paper (cf. Shah-Basak et al., 2015), during the 20 min of active- or sham-tDCS, subjects completed a picture-naming task that was based on (but was not identical to) constraint-induced language therapy (CILT), in that it minimized non-verbal communication between subjects and the experimenter (Pulvermuller et al., 2001; Maher et al., 2006). Subjects were shown 20 black-and-white images taken from the IPNP database, one at a time. A physical barrier between subjects and the experimenter was erected to constrain subjects to produce verbal responses and also to prevent unanticipated visual cues from the experimenter (Maher et al., 2006).

Measures of Fluency

The Cookie Theft narrative picture description is a subtest of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass et al., 2001) that measures spontaneous speech—a combination of information content and fluency. At baseline and at each of the follow-up time points, subjects described the Cookie Theft picture stimulus. They were not given a time limit. Their responses were digitally recorded, then stripped of all identifiers, and transcribed.

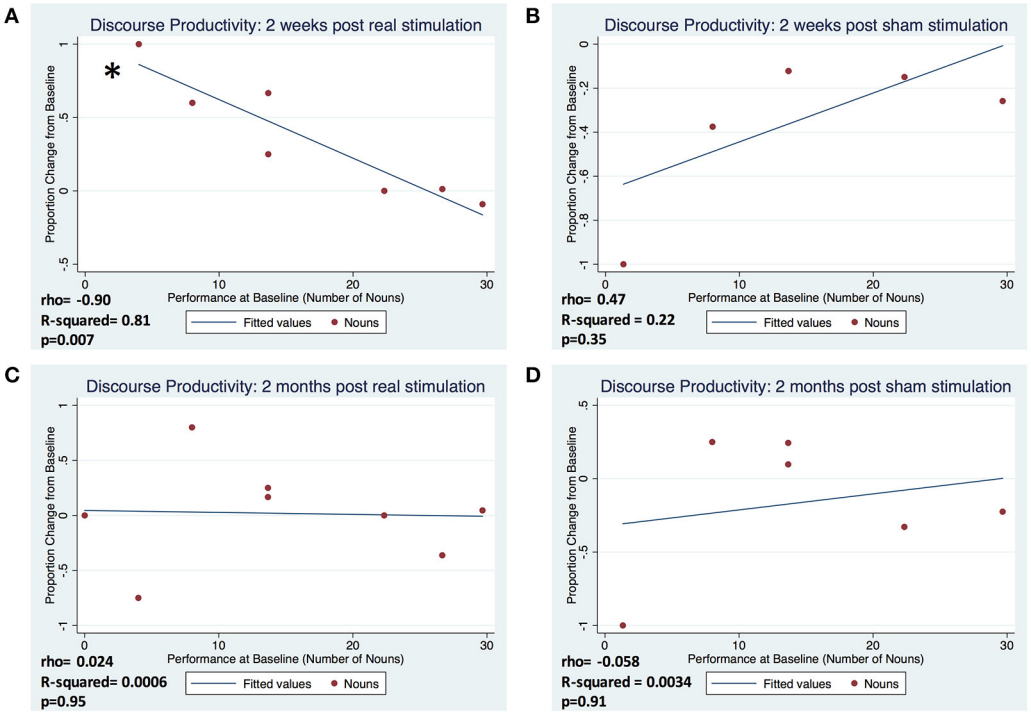

FIGURE 2 | Proportion change in baseline of discourse productivity according to average baseline performance, represented by nouns, at 2 weeks following real **(A)** and sham **(B)** stimulation and 2 months following real **(C)** and sham **(D)** stimulation. Proportion change from baseline was calculated as: (follow-up performance–baseline performance)/baseline performance. (*Represents $p < 0.05$).

The spontaneous speech or fluency component of the Cookie Theft can be analyzed with respect to 3 distinct conceptual areas: (1) production, elaboration, and complexity, (2) conciseness, and (3) information imparted. These areas were assessed using Quantitative Production Analysis (QPA; Saffran et al., 1989). We categorized these variables based on four aspects of speech fluency: discourse (i.e., word level) productivity, sentence productivity, grammatical accuracy, and lexical selection (Gordon, 2006). In this study, these four aspects of speech were represented in our analysis by four specific measures: the number of nouns generated, sentence length, the proportion of well-formed sentences, and the proportion of pronouns, respectively.

Analysis

STATA was used for all statistical analyses. In order to determine if subjects that received real stimulation improved significantly from baseline compared to those that received sham, we conducted a group analysis using Wilcoxon ranked sign test. In this analysis we measured changes in performance between baseline and 2-week and 2-month follow-up, contrasting subjects who received real and sham tDCS. We used a non-parametric test because our sample size was small, and as a result we were unable to determine whether the data could be distributed normally. In this analysis all those that received real stimulation composed one group and all those that received sham composed a separate group. The threshold of significance for this initial analysis was a $p \leq 0.05$.

We subsequently used Spearman correlations to explore associations between the degree of language improvement on each of our measures and baseline aphasia severity. The degree of language improvement was measured by change from baseline at the 2-week and the 2-month follow-up sessions for the 9 subjects - those that received real stimulation, less the one subject that that withdrew after only completing sham ($N = 8$) and those that received sham ($N = 6$) stimulation.

Finally, because this was a partial crossover study, one potential concern was that subjects who had received only real stimulation might have systematically performed differently than those who had received sham followed by real stimulation. In order to evaluate this possibility, we conducted Mann-Whitney U tests to compare performance in these two subgroups. Once again, the threshold of significance was a $p \leq 0.05$.

RESULTS

tDCS and Measures of Fluency

Using a Wilcoxon ranked sign test to be assessed the within group effect of tDCS on measures of fluency. We found no significant change from baseline performance at the 2-week follow up compared to no change [discourse productivity ($p = 0.35$), sentence length ($p = 0.08$), proportion of well-formed sentences ($p = 0.40$), and proportion of pronouns ($p = 0.74$)]

or at the 2 month follow up [discourse productivity ($p = 0.40$), sentence length ($p = 0.09$), proportion of well-formed sentences ($p = 0.12$), and proportion of pronouns ($p = 0.67$)].

Influence of Baseline Severity on tDCS Effects

In subjects that completed one or both arms of the study (real and sham), factors of interest were separated by QPA categories—discourse productivity, sentence productivity, grammatical accuracy, and lexical selection. We demonstrated a very strong correlation between number of nouns produced at baseline and the change from baseline at 2 weeks post-real stimulation ($\rho = -0.90$, R-squared= 0.81, $p = 0.007$) compared to the 2 weeks post-sham stimulation ($\rho = 0.47$, R-squared = 0.22, $p = 0.35$). However, this pattern of association was not maintained at 2 months post-real stimulation ($\rho = 0.024$, R-squared = 0.0006, $p = 0.95$) and sham ($\rho = -0.058$, R-squared = 0.0034, $p = 0.91$) (**Figure 2**). There were no significant correlations between severity of baseline performance and degree of improvement at 2 weeks or 2 months in any of the other measures of fluency (sentence lengths, proportion of well-formed sentences, and proportion pronouns; all p's > 0.5). Similarly, no significant correlations were observed for sham stimulation for any of the outcome measures at 2 weeks or 2 months post-stimulation (all p's > 0.5) (**Table 2**). Additionally, we did not appreciate a significant correlation between years of education and degree of improvement from baseline at the 2 week or 2 month follow-ups ($\rho = -0.691$, $p = 0.13$) [2 weeks] ($\rho = -0.572$, $p = 0.18$) [2 months]. Pearson correlations were used to explore associations between the degree of language fluency improvement and education.

Observing a robust correlation between baseline severity and change on discourse productivity resulting from tDCS, we further quantified the influence of low and high baseline language ability by comparing to mean change in noun production in the 4 patients with the most severe baseline aphasia to that of the 4 least severe patients in both real and sham conditions. Because the exploratory analysis was in small samples and was driven by the observation of a strong directional relationship, employed a one-tailed Mann-Whitney U test. Patients with more severe baseline aphasia responded positively ($p = 0.038$) to tDCS in measures of word-level production at 2 weeks when compared to the less severe group at 2 weeks ($p = 0.14$). This difference was not found in the sham condition for either more or less severe patients.

We used a Mann-Whitney U analysis to demonstrate that there were no significant differences in performance between subjects who received sham stimulation followed by real tDCS ($n = 6$) and those that only received real stimulation ($n = 3$) on any of the study measures at either the 2-week or 2-month follow up time points (all p's > 0.5). Finally, of the 8 subjects who received real stimulation, we note that there was a fairly even distribution between those that received sham stimulation followed by real and those that only received real tDCS with respect to baseline severity. In the most severe group 2 of the 4 received sham prior to real and in the least severe group 3 of the 4 subjects received sham prior to real stimulation.

TABLE 2 | Proportion change in baseline of sentence productivity, grammatical accuracy, and lexical selection according to average baseline performance, represented by mean sentence length, proportion of well-formed sentences, and proportion proportion of pronouns at 2 weeks and 2 months following real and sham stimulation.

	Simulation type	Time point	Spearman correlation		
			ρ	*R* squared	*p*-value
Discourse Productivity: Number of nouns	Real	2 weeks	−0.9009	0.8116	0.0056
		2 months	0.0241	0.0006	0.9548
	Sham	2 weeks	0.4706	0.2215	0.3462
		2 months	−0.058	0.0034	0.9131
Sentence Productivity: Mean sentence length	Real	2 weeks	−0.0748	0.0056	0.8734
		2 months	0.4419	0.1953	0.273
	Sham	2 weeks	−0.1715	0.0294	0.7453
		2 months	−0.1715	0.0294	0.7453
Grammatical Accuracy: Proportion well-formed sentences	Real	2 weeks	0.5714	0.3265	0.1802
		2 months	0.4791	0.2295	0.2297
	Sham	2 weeks	−0.4058	0.1647	0.4247
		2 months	−0.6	0.3600	0.208
Lexical Selection: Proportion of pronouns	Real	2 weeks	0.2143	0.0459	0.6103
		2 months	0.2143	0.0459	0.6103
	Sham	2 weeks	−0.2571	0.0661	0.6228
		2 months	−0.2571	0.0661	0.6228

*Proportion change from baseline was calculated as: (follow-up performance – baseline performance)/baseline performance. *Represents $p < 0.05$.*

The initial lesion volume assessment was completed with lesion tracings of pre-stimulation MRI images from the post-stroke population. Lesion volumes were calculated in cm^3 for the 7 of the 9 subjects. 2 subjects' initial MRI had excessive motion artifact, which made an accurate calculation of the volume impossible. For those that received real tDCS ($n = 7$), there was a mean lesion volume of 161.26 cm^3 ($\pm$67.36 cm^3). And for those that received sham tDCS ($n = 5$), there was a mean lesion volume of 163.91 cm^3 ($\pm$74.99 cm^3). Pearson correlations were used to explore associations between the degree of language fluency improvement and lesion volume. The degree of language improvement was measured by change from baseline at the 2-week follow-up. We demonstrated a very strong correlation between lesion volume and change in number of nouns produced at 2 weeks post-real stimulation ($\rho = 0.81$, $p = 0.05$) compared to the 2 weeks post-sham stimulation ($\rho = 0.69$, $p = 0.31$).

Regarding the time since stroke, for those that received real tDCS ($n = 8$), there was a mean time post stroke of 48 months ($\pm$41.9 months). And for those that received sham tDCS ($n = 6$), there was a mean lesion volume of 43 months ($\pm$41.0 months). Pearson correlations were used to explore associations between the degree of language fluency improvement and time post stroke. The degree of language improvement was measured by

change from baseline at the 2-week follow-up. There was no correlation between time post stroke and change in number of nouns produced at 2 weeks or 2 months post-real stimulation ($\rho = -0.266, p = 0.56$) [2 weeks] ($\rho = 0.096, p = 0.82$) [2 months] compared to the 2 weeks or 2 months post-sham stimulation ($\rho = 0.50, p = 0.32$) [2 weeks] ($\rho = 0.62, p = 0.19$) [2 months].

DISCUSSION

The current study focused on identifying factors that can predict recovery of language fluency and which aspects of language fluency can be expected to improve with the identified factor(s). Influenced by previous studies in different patient populations that sought to establish factors that influence response to tDCS (Turkeltaub et al., 2012; Furuya et al., 2014; Uehara et al., 2015), we predicted that baseline severity would influence the improvement in chronic non-fluent aphasic patients. Our study demonstrated that there was an association between language severity at baseline and degree of improvement post-stimulation. We also predicted that there would be improvement at the word level, because of our previous rTMS study demonstrated that after therapeutic neuromodulation, language improvement was seen only in measures of discourse (word level) productivity (Medina et al., 2012). The pattern of language improvement we observed, in which only those who were more severely affected at baseline improved, was seen only in the category of discourse productivity. In other words, participants improved only on measures of word level production, and only if their initial presentation at baseline was severe. This association was striking, accounting for 81% of the variability of performance of the cohort. Additionally, because the groups were fairly evenly distributed between subjects who only received real and those that received sham followed by real and our analysis did not reflect a significant difference between them, it is unlikely that the correlation we identified can be attributed to an order effect. Of note, group analyses, which compared all those that who received real stimulation to those who received sham stimulation, were negative. The fact that the pattern of improvement was only observed when the groups were separated by severity, underscores the importance of elucidating the factors that influence response to tDCS.

We found that, while there was a wide range in severity as measured by the WAB aphasia quotient (WAB-AQ), there was no correlation between initial WAB performance and fluency outcomes, nor was there a clear correlation between age and fluency outcomes. It is possible then that the correlation that was seen between baseline severity in discourse productivity and degree of improvement in that measure was task specific. In other words, one's severity in a discourse productivity task may predict one's degree of improvement in that specific aspect of language. The WAB-AQ, however, contains measures of discourse productivity in addition to other categories of language assessment. It is therefore possible that the severity of one's WAB-AQ may not be predictive of degree of improvement in discourse productivity as an isolated measure.

While a few prior investigations have evaluated predictors of language recovery after stroke, these have largely focused on the acute stage of the disease (Lazar et al., 2008, 2010), since it is generally acknowledged that the majority of language improvement occurs approximately in the first 3 months after stroke (Robey, 1998; Berthier, 2005). Contrary to what we found in our study, several studies have suggested that baseline aphasia severity is a negative predictor of language recovery (Laska et al., 2001; Pedersen et al., 2004; Lazar et al., 2010). Many of these studies, however, focused on patients in the acute setting (Fillingham et al., 2006; Lazar et al., 2010), did not involve any additional intervention, and were not specific to aphasia type (Pedersen et al., 2004). Our finding however, has potential implications for interventions in chronic and more severely affected individuals.

To our knowledge no prior studies have evaluated the impact of baseline severity on response to neuromodulation therapy in the chronic non-fluent aphasic population. Previously the relationship between baseline severity and response to tDCS has been reported primarily in healthy subjects, but not in patient populations (Turkeltaub et al., 2012; Furuya et al., 2014; Sarkar et al., 2014; Uehara et al., 2015). For this chronic patient population, the possibility that more severe initial language deficits are associated with greater improvement introduces the possibility that more severe patients may have a recovery window that extends beyond a traditional 3-month recovery period. Importantly, our results demonstrate that specific symptoms, like word level production deficits, that respond to treatment can be identified. Furthermore, we found that patient subgroups respond differently to tDCS, wherein the worse affected patients improve more in word-level production compared to milder patients. Overall this could be important for appropriate stratification in clinical studies and may someday influence clinical care.

Although ultimately in line with our predictions, it is intriguing that the association between baseline severity and post-tDCS change was very high for word-level production and non-existent for other fluency measures. One possible way to account for this stark disparity is to consider the role that the cognitive task performed during stimulation might have had on post-stimulation behavioral changes. We have previously observed in healthy subjects that the degree to which a cognitive training task engages particular mental abilities during tDCS directly influences the extent to which performance on tasks that require similar abilities are affected by stimulation (Gill et al., 2015). In the current study, patients received stimulation while they were performing a picture-naming task using a protocol that constrained them to communicate by producing verbal responses (Maher et al., 2006). The pictures being named were all objects (i.e., nouns). One possibility is that the nature of the training performed during tDCS specifically reinforced language production at the word level, and perhaps even more specifically the generation of nouns. While this notion of near transfer between related tasks may be an attractive account, strong confirmation of this hypothesis would require further experiments involving manipulation of the training task in order determine whether other aspects of fluency could be selectively influenced.

Considering the results of our prior work in this cohort of subjects demonstrated an improvement in overall aphasia severity that was maintained at 2 months (Shah-Basak et al., 2015), we did not expect our improvement to be limited to 2 weeks after stimulation. The primary difference between these two studies is how language improvement was measured. In the previous study the WAB aphasia quotient was used. This is a composite measure of several language domains including fluency as well as comprehension, repetition, and naming. In the current study, however, we evaluated only aspects of language fluency as measured by changes in spontaneous elicited speech. It is possible then that the improvement that was maintained at 2 months in our previous study was mediated by multiple domains of language production and not fluency alone.

There are clear limitations in this study. Most notably, the study employed a small sample size. Several factors contributed to this. First, given the relatively high rate of exclusion from the study, enrolling a large number of subjects with chronic aphasia proved challenging. Elements of the study design also limited the number of subjects who participated. For instance, the only subjects who participated in phase 2 of the study were those that had an optimal montage identified in phase 1, further limiting the sample size. Participation in the study also required a considerable time commitment; it took over 2 months to complete the real arm and at least an additional 2 months to complete the sham followed by the real arm. This resulted in one subject withdrawal. Additionally, this study was designed as a partial crossover. This designed allowed all subjects to receive real-tDCS eventually, however, it also resulted in unequal subject groups. This complicated the direct comparison between the real and sham conditions. It was helpful to demonstrate that the real only and sham-then-real data were similar to one another and thus collapsible, however, future studies should to follow a full crossover design then compare the two groups. Importantly, future studies should also employ sample sizes that are sufficient to provide greater statistical power. However, we would also note that we have, in previously published work, been able to demonstrate a significant effect of non-invasive brain stimulation on language ability in cohorts of persons with aphasia with similarly small sample sizes - 6 and 10 (Medina et al., 2012; Shah-Basak et al., 2016). In these studies, we were able to demonstrate an effect on overall aphasia severity following tDCS (Shah-Basak et al., 2016) and an effect on fluency following TMS (Medina et al., 2012).

In recent literature there has been some discussion regarding the potential lasting effects of single session tDCS. Single session tDCS has been shown to have an immediate transient effect in various cognition related tasks (Kekic et al., 2017). The effects of tDCS have been observed up to an hour following a single stimulation session and with repeated stimulation may persist for days or even months after multiple days of stimulation (Reis et al., 2009). A recent study suggests that there may be a delayed cognitive effect on multitasking tasks after receiving a single course of tDCS (Nelson et al., 2016). In our study, however, when establishing optimal stimulation parameters all subjects returned to within 2 standard deviations of their pre-stimulation baseline scores prior to proceeding with the next montage suggesting that the improved that they experienced after a single course of stimulation was only transient.

There have been several recent reviews that have explored the distant effects of non-invasive brain stimulation (Siebner et al., 2009; Siebner and Ziemann, 2010). More recently a study by Polania and colleagues used a graph theoretical approach to evaluate the effects of tDCS on fMRI connectivity. This analysis demonstrated that anodal tDCS over M1 reduced the functional connectivity between the stimulated M1 and the premotor and superior parietal regions (Polanía et al., 2011). The same group later showed that anodal tDCS of the M1 also increased connectivity between the stimulated region and the ipsilateral subcortical regions (Polania et al., 2012). These findings have been supported by MRI profusion studies (Stagg et al., 2013). Literature supports an effect of montage regarding the distant effects of tDCS on cortical connectivity. Sehm et al. demonstrated during bilateral, and non-unilateral, tDCS resting state changes can be seen in both local and distant areas (Sehm et al., 2013). Our study employed unilateral tDCS in presumed reorganized language regions. While the effects of tDCS in this context may be mediated by remote connections, this issue as it related to this patient population and stimulation approach has yet to be fully explored.

Currently there is controversy regarding the reliability of the effect of tDCS. Some have argued that the effects of tDCS on cognition and neurophysiology are modest, highly variable, or possibly even non-existent (e.g., Horvath et al., 2015, 2016, but also Price et al., 2015). One of the primary challenges in making inferences about the efficacy of tDCS is that investigators have yet to define which specific aspects of behavioral performance are most likely to be influenced by tDCS. Additionally, it is not yet clear which subject characteristics may predispose them to respond differentially to tDCS. Elucidating these fundamental properties will prove especially important as tDCS is employed increasingly in clinical studies and perhaps someday in clinical care. Future studies, especially clinical investigations, will need to replicate and extend analyses like these in order to better address who will benefit from stimulation and which specific deficits can be influenced.

ETHICS STATEMENT

University of Pennsylvania Institutional Review Board. Informed consent was obtained by the PI or other designated members of the research team. Because this protocol involved the enrollment of subjects who are known to have language deficits, some subjects had difficulty understanding what has been explained to them about the protocol, either verbally or in writing. In other cases, subjects with relatively mild deficits or deficits restricted to the domain of language production were able to understand what has been explained to them quite readily. In cases where individuals suffer from deficits of verbal or reading comprehension (as assessed by the PI, a behavioral neurologist) we required that informed consent be obtained from both the patient and a legally authorized representative.

The Informed Consent (IC) form was provided to the subject (and to their legally authorized representative, when needed) and was reviewed in detail by the PI or another designated member of the research team. After reading and verbally reviewing the document, the subject (and their representative, as needed) were asked if there are any questions or concerns. If the subject (and their representative, as needed) indicated agreement with the participation by signing the ICF, indicated that there were no additional questions, and met inclusion/exclusion criteria, the subject was included in the study. In cases where subjects have intact language comprehension and do not require a legally authorized representative, we documented on the consent form that a cosignatory by such an individual is not needed by writing or N/A on the signature line of the legally authorized representative. All subjects were told in clear and explicit terms that they are not required to participate in the study. They were also explicitly told that not participating in the study or withdrawing from the study at any time would have no adverse consequences in any respect to their future care or standing with the University of Pennsylvania System or Medical School. Subjects were told that if they wish to withdraw from the study at any time, including during the tDCS application, they are free to do so; the study would be terminated immediately. They were also told that they would be paid for their time should they withdraw. All of this information was also made clear to the subjects' legally authorized representative.

AUTHOR CONTRIBUTIONS

CN contributed substantially to the conception of the work, was responsible for data collection, drafting the manuscript, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DS contributed substantially to the conception of the work, was responsible for data collection, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RH contributed substantially to the conception of the work, was responsible for revising the manuscript critically for important intellectual content, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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frontiers in Human Neuroscience

MINI REVIEW
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Transcranial Direct Current Stimulation over the Dorsolateral Prefrontal Cortex in Schizophrenia: A Quantitative Review of Cognitive Outcomes

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Cognitive deficits are a core and disabling feature of psychotic disorders, specifically schizophrenia. Current treatments for impaired cognition in schizophrenia remain insufficient. Recent research suggests transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex can potentiate cognitive improvements in healthy individuals and those with psychiatric conditions, such as schizophrenia. However, this burgeoning literature has not been quantitatively evaluated. Through a literature search and quantitative review, we identified 194 papers on tDCS, psychosis, and cognition. Selection criteria included pre/post design and sham control to achieve specific sham-adjusted effect sizes. The 6 retained studies all address schizophrenia populations and include single and repeated stimulation, as well as within and between subject designs. Small positive effects were found for anodal stimulation on behavioral measures of attention and working memory, with tentative findings for cognitive ability and memory. Cathodal stimulation yielded a small positive effect on behaviorally measured cognitive ability. Neurophysiological measures of attention showed a small to medium down-modulation effect for anodal stimulation. Implications of these findings and guidelines for future research are discussed. As revealed by this report, due to the paucity of data available, much remains unknown regarding the clinical efficacy of tDCS in schizophrenia.

Keywords: cognition, dorsolateral prefrontal cortex, quantitative review, Schizophrenia, transcranial direct current stimulation

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INTRODUCTION

Impaired cognition is a significant and disabling feature of psychotic disorders such as schizophrenia. Deficits in executive functions (working memory, attention, response inhibition) are the most commonly reported, and the most predictive of functional outcome (Green, 1996). Despite the central role of these impairments, current treatments, including pharmacological interventions, have proven ineffective at ameliorating cognitive dysfunction (Fusar-Poli et al., 2015). New or adjunctive treatment options are needed.

A large body of evidence implicates impaired frontal cortical activity as a causal factor in cognitive dysfunction in schizophrenia (Minzenberg et al., 2009). Specifically, hypoactivation of the dorsolateral prefrontal cortex (DLPFC) has been suggested as the core deficit (Potkin et al., 2009; Lesh et al., 2011). Given the pivotal role of the DLPFC in mediating a wide range of executive functions (Niendam et al., 2012), interventions that target this region are of great clinical interest. Non-invasive methods of neuromodulation provide a safe, cost-effective and robust means to enhance DLPFC function.

Transcranial current stimulation (tCS) is a non-invasive neuromodulation technique that uses small, specifically directed electrical currents to alter cortical brain activity (Nitsche and Paulus, 2001). Though there are several forms of tCS, transcranial direct current stimulation (tDCS) has by far been the most commonly employed. TDCS involves the use of two electrodes, a positively charged anode and a negatively charged cathode. Studies in both animals and humans demonstrate that anodal stimulation produces a shift in excitability that depolarizes neurons, while cathodal stimulation has opposite effects (Nitsche and Paulus, 2000; Cambiaghi et al., 2010). Though the mechanisms underlying tDCS are still under investigation, it is postulated that these shifts in excitability are induced by altering membrane polarization at the cellular level (Fritsch et al., 2010; Kronberg et al., 2017). Due to its safety (Bikson et al., 2016), tolerability, and low cost, the use of tDCS has grown substantially. Recent research demonstrates that tDCS targeted to the DLPFC has the ability to potentiate changes in cognition in both healthy individuals (Fregni et al., 2005) and those with various psychiatric conditions, such as schizophrenia (Dedoncker et al., 2016).

As a clinical intervention, the use of tDCS to enhance cognition in schizophrenia is especially promising. Anodal tDCS, directed at the DLPFC, has now been evaluated in several trials as a possible rehabilitation technique or adjunct to existing treatments (Minzenberg and Carter, 2012; Palm et al., 2016). However, research has indicated contradictory effects of stimulation in some patient populations (Berryhill et al., 2014) and differential effects on various cognitive domains are not well understood.

To address these ambiguities, we undertook a quantitative review of studies on tDCS in schizophrenia using the PubMed database and identified 194 articles. This number was reduced to 6 articles after excluding studies on populations without psychosis, without cognitive outcomes, and including only those with a sham stimulation condition to create a sham-adjusted effect size. Study outcomes and heterogeneity of designs were aggregated and variance-weighted.

METHODS

Literature Search

A literature search was conducted in the PubMed Database searching titles and abstracts for the following key words and Boolean terms: ("psychosis" OR "schizophrenia" OR "schizoaffective disorder" OR "bipolar disorder") AND ("tDCS" OR "direct current"). Published articles were collected up until May 2016 returning 194 results.

Eligibility Criteria

Criteria for inclusion were: (a) psychosis; (b) randomized and sham-controlled designs; (c) pre-post within-subject or between-subject designs. Duplicates, reviews, case studies, and studies with <3 participants were excluded. Studies were also excluded due to the inability to calculate independent groups pre-post effect sizes (Becker, 1988; Lipsey and Wilson, 1993) See **Figure 1**. Specific study characteristics extracted for discussion are presented in **Table 1**. No formal quality assessment was performed.

Quantitative Review

Effect Sizes

Effect sizes were calculated by combining elements of repeated measures and independent groups designs as described by previous meta-analytic work (Becker, 1988; Morris and DeShon, 2002, Equation 6):

$$d = \frac{Stimulation\ Mean_{post} - Stimulation\ Mean_{baseline}}{Stimulation\ SD_{baseline}} - \frac{Sham\ Mean_{post} - Sham\ Mean_{baseline}}{Sham\ SD_{baseline}}$$

Baseline standard deviations are assumed to be more comparable across studies before different treatments are applied. Sham-adjustment is important because research has observed non-zero changes in control groups (sham) over time (Lipsey and Wilson, 1993; Carlson and Schmidt, 1999).

Sampling Variance

Sampling variance calculations were selected to match the combined effect size (Becker, 1988), drawn from Morris and DeShon (2002), computing each group's variance separately (Equation A1) and adding them together, where $df = n-1$, d is the effect size, and c is the bias function $1 - \frac{3}{4df-1}$ (Equation 23):

$$sampling\ variance = \left(\frac{1}{n}\right)\left(\frac{df}{df-2}\right)\left(1 + n * d^2\right) - \frac{d^2}{c(df)^2}$$

Meta-analytic procedures detailed in Lipsey and Wilson (2001) and Morris and DeShon (2002) were used to calculate weights as the inverse of the squared standard error for each effect size. Variance-weighted mean effect sizes (d_W) and mean effect sizes without weights (d_{UW}) should be interpreted carefully as not all studies examined each cognitive domain discussed. There are an inadequate number of measures in each domain to detect a significant effect for a specific hypothesis (e.g., Z-test), even if sample-dependent measures are treated as sample-independent.

EFFECT SIZES FOR COGNITION

Sham-adjusted effect sizes for anodal stimulation are reported in **Table 1**. As a complement to effect sizes, ranks for variance-weighted effect sizes are also included in the table, with

larger, positive descriptive effects ranked highest and the rest in descending order. Confidence intervals are included below as a measure of variability. For comparison to the greater literature (without any specific hypothesis testing) effect sizes are discussed according to Cohen's conventions of 0.2, 0.5, and 0.8 as putative measures for small, medium, and large descriptive, non-inferential effects (Cohen, 1992). These distinctions were originally a proposed route for accurate foresight in power analysis and are not strictly indicative of clinical efficacy (Abelson, 1985; Prentice and Miller, 1992). Results from other areas provide a benchmark: small classes rather than large had an effect of 0.20 on educational achievement (Hedges and Stock, 1983), therapy for test anxiety in college students showed an effect of 0.58 on anxiety and test performance (Harris, 1988). Other effects beneath Cohen's conventions that may be worth implementing include individualized education program's effects on achievement at 0.10 (Bangert-Drowns et al., 1983) and 0.17 (Hood, 1991). Therefore, these conventions should not underrepresent the importance of the effects of stimulation.

Overview

The 194 studies were screened according to inclusion and exclusion criteria at title, abstract, and full text levels and subsequently reduced to 6 studies for quantitative review. A flow diagram indicating successive exclusion is provided in **Figure 1**. Although, search terms were determined in order to garner citations involving psychosis, it is important to note that our search rendered only populations diagnosed with schizophrenia and schizoaffective disorder. All studies evaluated individuals with schizophrenia; three included schizoaffective disorder. All articles meeting eligibility criteria stimulated the DLPFC. Cathodal stimulation is reported where applicable or omitted from results when not. Domains of cognition included in the retained articles are discussed herein.

Attention

Smith et al. (2015) reported the only behavioral measures of attention, with a variant of the continuous performance task. The mean effect size for anodal stimulation was small to medium ($d_w = 0.40$, 95% CI: −0.15, 0.96; $d_{uw} = 0.40$). No behavioral

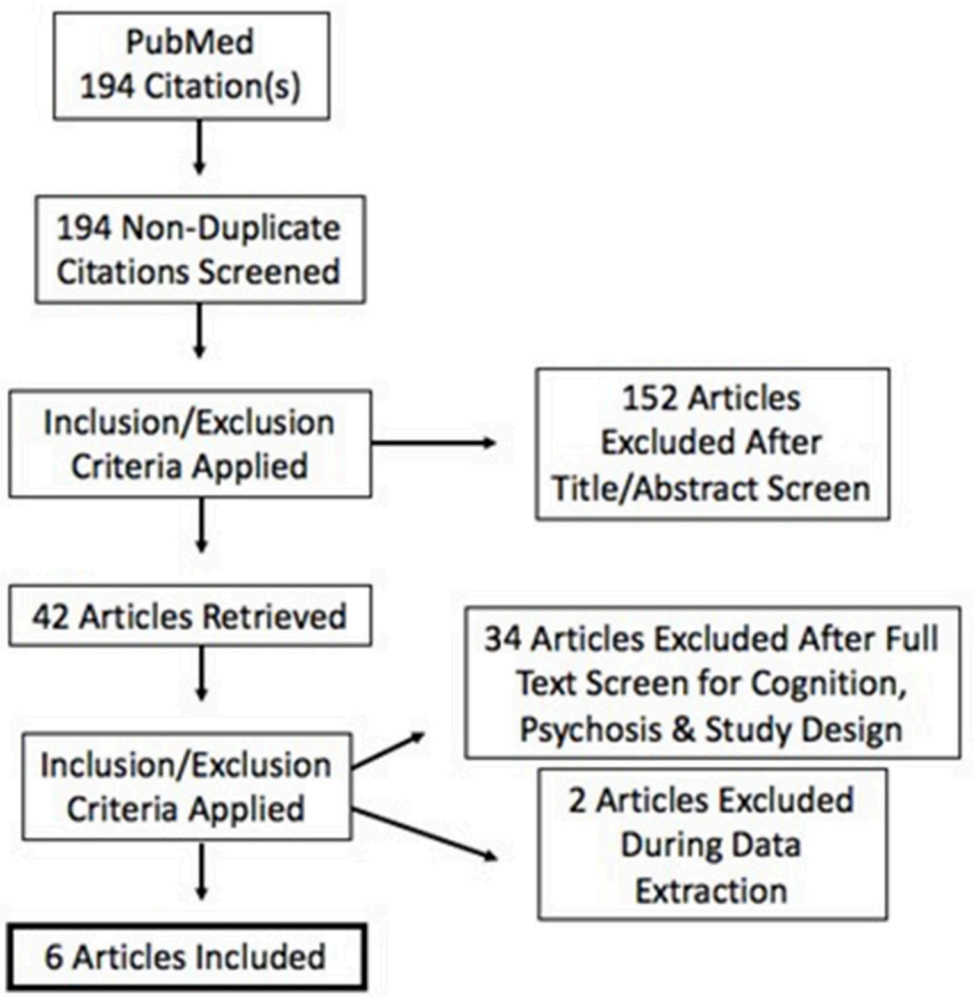

FIGURE 1 | Literature Search and Study Eligibility Determination.

TABLE 1 | Anodal tDCS studies: cognitive domains, measures, and design parameters.

Study	Measures	Active electrode	Reference electrode	Stimulation target	On/Offline	Amplitude (mA)	Sessions	Unweighted effect size (d_{uw})	Weighted effect size (d_w)	d_w Ranking (high/low)
ATTENTION										
Dunn et al., 2016	P300 (μV)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	2	0.16	0.78	8
Dunn et al., 2016	Mismatch Negativity (μV)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	2	−1.54	−4.05	22
Mean Effect	(Neurophysiological)							−0.69	−0.44	
Smith et al., 2015	MCCB Attention-Vigilance (accuracy)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.49	3.01	2
Smith et al., 2015	MCCB Reasoning/Problem Solving (seconds)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.32	1.99	4
Mean Effect	(Behavioral)							0.40	0.40	
MEMORY										
Smith et al., 2015	MCCB Verbal Learning (recall and recognition scores)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.21	1.33	7
Smith et al., 2015	MCCB Visual Learning (recall and recognition scores)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.10	0.55	10
Mean Effect								0.21	0.16	
PROCESSING SPEED										
Smith et al., 2015	MCCB Speed of Processing (accuracy)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	−0.18	−1.12	20
Palm et al., 2016	Trail-Making Test A (seconds)	F3	Supraorbital (R)	Left DLPFC	Offline	2	10	−0.14	−0.49	17
Palm et al., 2016	Trail-Making Test B (seconds)	F3	Supraorbital (R)	Left DLPFC	Offline	2	10	0.11	0.41	11
Mean Effect								−0.16	−0.16	
SOCIAL COGNITION										
Rassovsky et al., 2015	TASIT (total score)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	1	−0.12	−0.59	18
Rassovsky et al., 2015	PONS (total score)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	1	−0.13	−0.65	19
Rassovsky et al., 2015	FEIT (accuracy)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	1	0.44	2.02	3
Rassovsky et al., 2015	MSCEIT (total score)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	1	0.02	0.08	16
Smith et al., 2015	MCCB Social Cognition (total score)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.26	1.54	6
Mean Effect								0.14	0.15	
WORKING MEMORY										
Hoy et al., 2016*	2-back (Letters) (accuracy)	F3	Supraorbital (R)	Left DLPFC	Offline***	2	1–2	−0.46	−1.18	21
Nienow et al., 2016**	2-back (Words) (accuracy)	F3	Supraorbital (R)	Left DLPFC	Online	1	28	0.53	0.24	14
Nienow et al., 2016**	2-back (Pictures) (accuracy)	F3	Supraorbital (R)	Left DLPFC	Online	1	28	0.58	0.31	13
Palm et al., 2016	Self-Ordered Pointing Task (accuracy)	F3	Supraorbital (R)	Left DLPFC	Offline	2	10	0.19	0.73	9
Smith et al., 2015	MCCB Working Memory (recall score)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.51	3.12	1
Mean Effect								0.21	0.23	
COGNITIVE ABILITY										
Nienow et al., 2016**	MCCB Composite (total score)	F3	Supraorbital (R)	Left DLPFC	Online	1	28	0.14	0.12	15
Rassovsky et al., 2015	MCCB Composite (total score)	Fp1/Fp2	Upper Arm (R)	Bilateral DLPFC	Offline	1	1	0.07	0.34	12
Smith et al., 2015	MCCB Composite (total score)	F3	Supraorbital (R)	Left DLPFC	Offline	2	5	0.30	1.89	5
Mean Effect								0.17	0.20	

All studies stimulated for 20 min at a time, electrode area was 35 cm^2 for all but Smith et al. (2015) which was 5.08 cm^2.

**Randomized between sessions for transcranial alternating, direct, and sham current stimulation. Only tDCS and sham conditions included in review.*

***Includes cognitive remediation training (48 h) for both tDCS and sham groups.*

****Study includes stimulation concurrent to task, although effect sizes were calculated from pre-post assessments.*

measures were used with cathodal stimulation in the studies reviewed. Only Dunn et al. (2016) included neurophysiological measures of attention and error, using an auditory oddball task to elicit event related potentials, specifically P300 and mismatch negativity. Different effects were observed between the anodal stimulation group ($d_w = -0.44$, 95% CI: −1.17, 0.28; $d_{uw} = -0.69$) and the cathodal stimulation group ($d_w = 0.10$, 95% CI: −.53, 0.73; $d_{uw} = 0.10$). These neurophysiological outcomes are included for the purposes of the review, yet are not a part of other calculated mean effects.

Memory

Only Smith et al. (2015) included measures for memory with a letter-number span task. The mean anodal effect was marginal to small ($d_w = 0.16$, 95% CI: −.41, 0.73; $d_{uw} = 0.21$).

Processing Speed

Two studies employed symbol-coding tasks to measure processing speed. The mean anodal effect for processing speed was marginal ($d_w = -0.16$, 95% CI: −.78, 0.46; $d_{uw} = -0.16$).

Social Cognition

The mean anodal effect for social cognition was marginal ($d_w = 0.15$, 95% CI: −0.44, 0.75; $d_{uw} = 0.14$) as calculated from two studies that included the same broad measure (Mayer-Salovey-Caruso Emotional Intelligence Test). For cathodal conditions, the effect ($d_w = 0.06$, 95% CI: −0.39, 0.51; $d_{uw} = 0.06$) was calculated as the mean effect for all measures included in the one study that examined social cognition (Rassovsky et al., 2015; see **Table 1**).

Working Memory

The mean anodal effect for working memory was small ($d_w = 0.23$, 95% CI: −0.31, 0.77; $d_{uw} = 0.21$). The effect was calculated from four studies using n-back tasks to measure working memory (variants of the N-Back task). Two of these studies carried out anodal tDCS concurrent with administration of the working memory task (Hoy et al., 2016; Nienow et al., 2016). Nienow et al. (2016) used picture and word n-backs to avoid direct practice effects from treatment sessions. The combined interpretation suggests a small effect at this time. The variance-weighted mean effect without Nienow et al. and Hoy et al. is almost double, but still a small effect ($d_w = 0.39$, 95% CI: −0.23, 1.01; $d_{uw} = 0.35$). These three studies were particularly low in variability, which also explains the difference between weighted and unweighted effect sizes when Nienow et al. is excluded.

Cognitive Ability

Across three studies, the mean anodal effect for general cognitive ability was small to marginal ($d_w = 0.20$, 95% CI: −0.37, 0.76; $d_{uw} = 0.17$). Although, one of the studies included here also employed cognitive remediation in tandem with tDCS (Nienow et al., 2016), this summary category also has the advantage of using the same measure (Matrics Consensus Cognitive Battery; Nuechterlein and Green, 2006). Only Rassovsky et al. (2015) included a cathodal stimulation condition, for which the effect size was small ($d_w = 0.29$, 95% CI: −0.61, 1.18; $d_{uw} = 0.29$). For the studies without a direct measure for general cognitive ability (Hoy et al., 2016; Palm et al., 2016), effect sizes within the studies were averaged as a general measure. Including the additional studies, general cognitive ability showed a marginal mean weighted effect for anodal stimulation ($d_w = 0.06$, 95% CI: −0.41, 0.52; $d_{uw} = 0.06$).

EFFECT SIZES FOR STUDIES BY METHODS USED

Unless otherwise noted, methodological issues are discussed across all domains and are not specific. Examining bilateral stimulation through the two studies that used such a montage (Rassovsky et al., 2015; Dunn et al., 2016) resulted in different effects for behavioral and neurophysiological outcomes. For the purposes of this review, bilateral stimulation refers to montages containing two stimulating electrodes of the same polarity with a separate, third electrode serving as the reference electrode. Therefore, they were not averaged so as to not understate their differences, nor were confidence intervals reported. These effects were positive and small to marginal for mean behavioral outcomes in Rassovsky et al. (2015; $d_w = 0.24$, $d_{uw} = 0.05$) with anodal stimulation and with cathodal stimulation medium to marginal ($d_w = 0.51$, $d_{uw} = 0.11$). For neurophysiological outcomes (event related potential measures of P300 and mismatch negativity), the mean effects of anodal stimulation were negative and medium to large ($d_w = -1.64$; $d_{uw} = -0.69$), whereas cathodal stimulation resulted in a marginal to near-medium effect ($d_w = 0.48$, $d_{uw} = 0.10$; Dunn et al., 2016). These divergent effects likely result from different results within the study, particularly given a large negative effect for one measure as seen in **Table 1**. Unilateral anodal stimulation ($d_w = 0.06$, 95% CI: −0.48, 61; $d_{uw} = 0.23$) was used by four studies (Smith et al., 2015; Hoy et al., 2016; Nienow et al., 2016; Palm et al., 2016) with behavioral outcomes and yielded marginal to small effect sizes calculated using the average of all effects in each behavioral study. Only one study (Hoy et al., 2016) showed a negative finding in this area, but that study only included a single measure (working memory).

Current intensity was also examined for differences in effects between 1 and 2 mA stimulation on behavioral outcomes and was only conducted for anodal stimulation. Based on two studies (Rassovsky et al., 2015; Nienow et al., 2016), marginal to small effects were found for 1 mA stimulation ($d_w = 0.09$, 95% CI: −0.76, 0.93; $d_{uw} = 0.24$). Based on three studies (Smith et al., 2015; Hoy et al., 2016; Palm et al., 2016), marginal effects were observed for 2 mA stimulation ($d_w = 0.04$, 95% CI: −0.51, 0.60; $d_{uw} = -0.05$). Only one study, which was excluded for only using a post-test, did have multiple amplitudes (Hoy et al., 2014) and only found improvements for the 2 mA anodal stimulation.

The number of active stimulation sessions constitutes another methodological difference common in the literature. Two studies (Rassovsky et al., 2015; Hoy et al., 2016) using a single session of anodal tDCS found marginal to small negative effects ($d_w = -0.13$, 95% CI: −0.85, 0.59; $d_{uw} = -0.20$) that appear driven by one study, highlighting the challenge of summarizing the literature at this time. Three studies (Smith et al., 2015; Nienow

et al., 2016; Palm et al., 2016) using more than one session of anodal tDCS, ranging from 5 to 28 sessions showed a positive marginal to small effect ($d_w = 0.19$, 95% CI: −0.42, 0.80; $d_{uw} = 0.24$). Currently, a direct trend has not been identified between the amount of stimulation sessions and cognitive enhancement. Such empirical evidence would prompt establishing an accepted dose of stimulation.

The most studied areas of cognition with tDCS in psychosis are working memory, attention, and cognitive ability (Smith et al., 2015; Hoy et al., 2016; Nienow et al., 2016; Palm et al., 2016). This may be due to their overall importance in the literature for the treatment of cognitive deficits in psychosis. Variety exists in measurement time points used in study designs, for example, post-test only (Hoy et al., 2014, 2015), or stimulation concurrent to task and assessment (Vercammen et al., 2011; Schretlen et al., 2014; Reinhart et al., 2015a,b). This is an especially pertinent source of variability as recent research has demonstrated that tDCS effects are highly state dependent (Elmasry et al., 2015; Gill et al., 2015; Dedoncker et al., 2016), suggesting that the combination of a task with stimulation might yield greater modulation of cognitive domains. As an example, one of our reviewed studies (Nienow et al., 2016) used stimulation concurrent with cognitive remediation and found positive effects. Another important source of variability may stem from differences in the overall electrode montage. It has been shown that even minor changes in placement of the reference electrode affect the distribution and intensity of electrical current (Bai et al., 2014).

SUMMARY

This report captures the current state of the literature as it pertains to the cognitive outcomes from tDCS targeted at the DLPFC in schizophrenia. Although, none of the effects observed in this small sample rule-out the possibility of null effects, we were able to quantitatively summarize current knowledge and provide the central tendency of the effects on cognitive outcomes following tDCS over the DLPFC. Small effects of anodal stimulation were observed on behavioral measures of attention and working memory. More tentative small effects were observed for cognitive ability and memory, with marginal effects observed on processing speed. Cathodal stimulation paired with behavioral outcomes suggested a small effect on cognitive ability and a marginal one for social cognition, though this area of the literature is currently underdeveloped.

Neurophysiological measures were restricted to attention and were associated with a small to medium negative effect for anodal stimulation that is driven by a strong modulation of mismatch negativity (Dunn et al., 2016). A marginal effect for cathodal stimulation was also found. A closer reading of that study suggests minor differences in negative symptoms at baseline in the anodal stimulation group. However, another study not indexed in the PubMed database showed a null finding for several neurophysiological measures (Knechtel et al., 2014) included in Dunn et al. (2016).

Bilateral stimulation with behavioral measures seems to produce tentative small effects with anodal stimulation and medium effects with cathodal. Behavioral measures with a unilateral montage were only assessed with anodal stimulation, which appears to produce either marginal or small effects. More research in unilateral stimulation is important, even though it is more commonly used than bilateral stimulation. Future reviews might seek to address the more specific placement of active or reference electrodes according to the international 10–20 system or more detailed schemas where available.

For behavioral outcomes, no particular current intensity seemed critical for modulation with anodal stimulation. Some studies incorporate an alternating current condition and find promising effects (Göder et al., 2013; Hoy et al., 2016). The number of anodal stimulation sessions differed such that a single session of stimulation showed a marginal to small negative effect, whereas multiple sessions showed a marginal to small positive effect.

One general limitation of this review is that the overall and domain-specific weighted averages for cognition must be interpreted carefully, as the sample size and statistical dependence of measures makes inference premature, and few studies report power analyses. Researchers must report means and standard deviations for all groups and time points or other statistics to aid in producing effect sizes. Additionally, few authors studying cognition with multiple measurement time points use neurophysiological measures. One of the largest discrepancies in this review emerges from that fact. With anodal stimulation, behavioral measures of attention showed small, non-significant improvements, but neurophysiological measures showed a decline with a near-medium effect size. More studies using neurophysiologically grounded outcomes (i.e., EEG, fMRI) are critical to understanding the efficacy of tDCS as a potential modulator for cognition in schizophrenia.

This review of tDCS over the DLPFC in schizophrenia highlights methodological heterogeneity that reflects no current gold standard. Although, the review was conducted without specific hypothesis testing, a positive effect is observed for anodal stimulation on several domains of behaviorally measured cognition, with a negative effect on neurophysiologically measured attention. Some support exists for a positive effect of cathodal stimulation on cognition with measures that are behavioral. Future research with larger sample sizes and combined behavioral and neurophysiological outcomes in the same studies are needed to push the field forward.

AUTHOR CONTRIBUTIONS

JM co-designed the project, conducted the analysis, and wrote all drafts of the manuscript. RC co-designed the project, supervised data collection, assisted in the analysis, and co-wrote manuscript drafts. EB provided conceptual guidance on project design and co-wrote all drafts of the manuscript. AM designed the project, supervised data analysis, and co-wrote all drafts of the manuscript.

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