Effects of single-session transcranial direct current stimulation on reactive response inhibition

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ABSTRACT

Transcranial direct current stimulation (tDCS) is widely used to explore the role of various cortical regions for reactive response inhibition. In recent years, tDCS studies reported polarity-, time- and stimulation-site dependent effects on response inhibition. Given the large parameter space in which study designs, tDCS procedures and task procedures can differ, it is crucial to systematically explore the existing tDCS literature to increase the current understanding of potential modulatory effects and limitations of different approaches. We performed a systematic review on the modulatory effects of tDCS on response inhibition as measured by the Stop-Signal Task. The final dataset shows a large variation in methodology and heterogeneous effects of tDCS on performance. The most consistent result across studies is a performance enhancement due to anodal tDCS over the right prefrontal cortex. Partially sub-optimal choices in study design, methodology and lacking consistency in reporting procedures may impede valid conclusions and obscured the effects of tDCS on response inhibition in some previous studies. Finally, we outline future directions and areas to improve research.

1. Introduction

The ability to inhibit an already initiated response is crucial for survival and everyday behaviour. For example, when crossing a street, we need to immediately stop walking when noticing that the traffic light just turned red and a speeding car is approaching. A better understanding of the neural circuits engaged in response inhibition and their potential modulation by neurostimulation may increase treatment success in various disorders associated with impaired response inhibition and impulse control, such as attention-deficit-hyperactivity-disorder, schizophrenia or pathological gambling (Lawrence et al., 2009; Lipszyc and Schachar, 2010; Weigard et al., 2019). One way to investigate and causally link activation in a given brain area to a cognitive process of interest is the use of non-invasive brain stimulation (NIBS) (Bergmann and Hartwigsen, 2020). Over the last decades, an increasing number of studies has used NIBS to modulate brain activity and influence a wide range of motor and cognitive functions (for reviews see Coffman et al., 2014; Nitsche and Paulus, 2011; Simonsmeier et al., 2018). In particular, transcranial direct current stimulation (tDCS) is increasingly being used because it is cheap, easy to apply and not prone to severe side effects (Bikson et al., 2016; Woods et al., 2016). Accordingly, over recent

years, several cognitive domains have been the target of tDCS research. For example, numerous studies have explored the potential of tDCS to modulate working memory (e.g. Friehs and Frings, 2020, 2019a, 2019b; Martin et al., 2014; Ruf et al., 2017; Wolkenstein and Plewnia, 2013; for reviews see for Hill et al., 2016; Mancuso et al., 2016), interference control (e.g. Friehs et al., 2019; Frings et al., 2018; Loftus et al., 2015) or language functions (e.g. Fiori et al., 2018; Hartwigsen, 2015; Monti et al., 2013). More recently, tDCS studies have focused on response inhibition (see below for details). This review aims to advance the current understanding of response inhibition by identifying key result patterns of modulatory tDCS effects on response inhibition, their implications for the underlying cognitive processes and structure-function relationships and methodological pitfalls of previous studies.

1.1. (Response) Inhibition as a fundamental cognitive process

In the seminal model of executive functions by Miyake and Friedman (Miyake et al., 2000; Miyake and Friedman, 2012), three "core" processes are identified: inhibition, set-shifting and updating. *Inhibition* is crucial for successfully withholding and overwriting prepotent responses in tasks such as the Stroop task or the Stop-Signal Task. In

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contrast, *set-shifting* refers to the process of flexibly moving between mental sets or tasks, which is important in tasks requiring different responses to multiple stimuli. Further, *updating* describes the continuous monitoring and modification of working memory contents, as would be required in tasks such as the n-back task where targets need to be loaded into and deleted from working memory on each trial. Notably, a particular task can tap into multiple executive functions; for example, random-number generation involves both the updating of responses by constantly keeping the generated sequence in mind and inhibition by suppressing response alternatives. Additionally, more complex higher-order competences such as reasoning, problem solving, or planning can be built from these core executive functions (Collins and Koechlin, 2012; Lehto et al., 2003). In a more recent version of their model of executive functions (the so-called unity and diversity model), Miyake and Friedman (2012) emphasize that all three basic executive functions rely on the individual ability to maintain task goals. Additionally, a selective information biasing process is strongly linked to all three executive components. Crucially for the present review, the inhibition factor was strongly correlated with the common information-biasing process, which indicates that inhibition is a fundamental executive component (Friedman et al., 2011, 2008).

An established tool to investigate response inhibition in the laboratory is the *Stop-Signal Task* (SST), (e.g. Lappin and Eriksen, 1966; Logan et al., 1984). In this paradigm, participants are asked to perform a choice reaction time task, which typically involves responding to either a left or right pointing arrow with a left or right keypress. In a random subset of trials, an auditory or visual stop-signal is presented after the onset of the go-stimulus and participants are instructed to withhold their already initiated response whenever a stop-signal is presented (see Fig. 1A). Based on the individual participant's performance, the *stop-signal reaction time* (SSRT) can be estimated, which represents the average length of the response inhibition process (for details on SSRT calculation, see

Verbruggen et al., 2013). A low SSRT represents a fast response inhibition process and vice versa. Put differently, an individual with a short SSRT is able to stop their already initiated action more successfully at a later point in the ballistic phase (i.e., after the presentation of the go-signal) compared to an individual with a longer SSRT (Logan, 2015). A particular advantage of this task is that SSRT is an indirect measure of response inhibition and not directly controllable by the participant. Moreover, the attempt to consciously manipulate response patterns and invalid responses can be validly detected with this paradigm (Band et al., 2003; Congdon et al., 2012; White et al., 2014). In summary, the SST thus represents a valid measure to assess response inhibition, a key process for human everyday behaviour.

The most recent cognitive model of SST performance distinguishes several different response stages in the SST (Verbruggen and Logan, 2009). First, after presentation of the go-signal, a "*go-process*" starts, which (if not stopped), initiates a *ballistic phase* that ultimately results in a response. However, if a stop-signal is presented after the go-signal, a *stop-process* is initiated, which races against the go-process (see Fig. 1B for a visualisation). This race between go- and stop-processes represents the key assumption of the *independent race model* (Logan et al., 1984; Verbruggen and Logan, 2009). According to the model, changes in general processing capabilities should influence go-reactions as well as inhibitory control capabilities of an individual equally. Yet, external influences such as modulation of cognitive processes by non-invasive brain stimulation may selectively affect one of these processes. For example, inhibitory or facilitatory neurostimulation may selectively influence the inhibition process without speeding up or slowing down general reaction times. Likewise, neurostimulation may selectively modulate the ballistic response phase as indicated by an overall tDCS-dependent change in reaction times, without influencing the effectiveness of the inhibition process (e.g. Bashir et al., 2019; Bender et al., 2017).
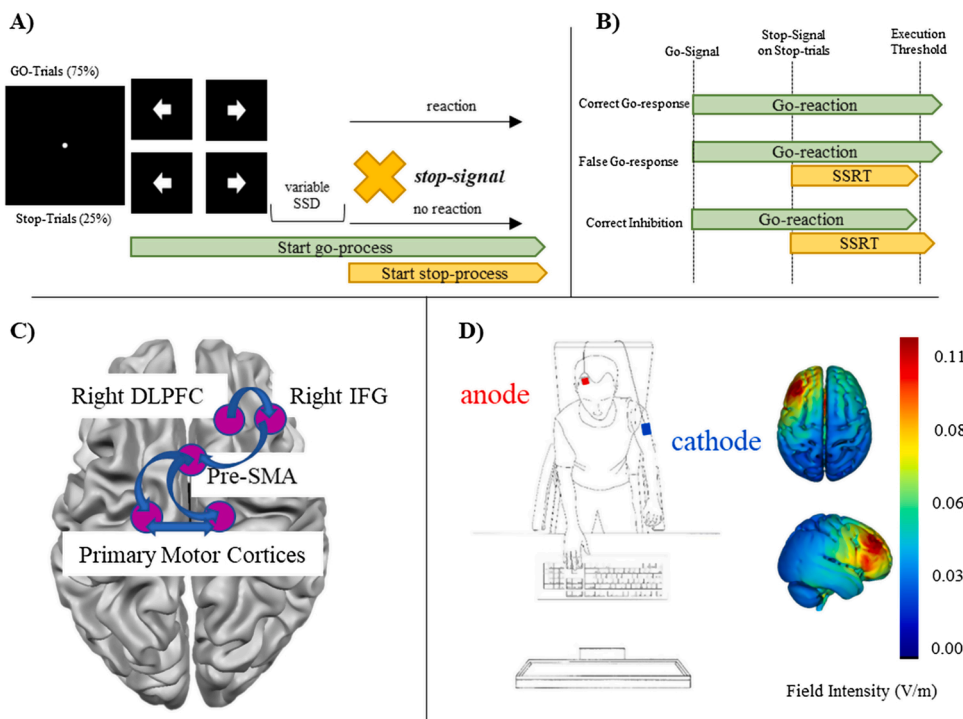
Fig. 1. A) Prototypical SST task. The top row represents a go-trial, in which no stop-signal appears and the participants can finish their response. The bottom row shows a stop-signal trial in which after a variable stop-signal delay (SSD), the stop-signal is displayed, requiring the participant to withhold the already initiated response. Beginning of stop- and go-process are marked below the trial sequence. B) Visualization of the horse-race model in the basic trial and response configurations. Top shows a correct go-reaction on a go-trial, when no stop-signal is presented. Middle shows a false go-response on a stop-signal trial; the stop-process as measured by SSRT is indicated in yellow below the go-process in green is slower. Bottom represents the horse-race underlying a correct inhibition of the response, whereas the stop-process is faster as compared to the go-process. C) Visualization of key cortical areas involved in SST performance. The arrows display a simplified flow of activation (without feedback loops) on a stop-trial, when a stop-signal is detected. D) Exemplary tDCS setup in the laboratory for a study investigating anodal tDCS effects over the right prefrontal cortex on SST performance. Left side: The cathode is placed over the contralateral upper arm to avoid concurrent inhibition of other brain areas. Right side: Simulation of the current flow shows that the strongest effect will be obtained in the right prefrontal cortex (simulation performed with SimNIBS; Saturnino et al., 2020), adapted from Friehs and Frings, 2018, 2019a, 2019b. Note that while this illustration represents an example setup of a tDCS experiment in a right-handed participant, response inhibition tasks can be performed with either hand or bimanually.

Important to note, there is a distinction between reactive and pro-active response inhibition. In short, *reactive inhibition* is triggered in a bottom-up fashion by a stimulus; e.g., a stop-signal occurring after a go-reaction has already been initiated. *Proactive inhibition* is a top-down directed form of inhibition that is applied to stimuli; e.g., preparing to withhold a reaction without the stimulus having appeared yet. Typically, the stop-signal task is viewed as measuring reactive inhibition, but it was recently argued that it contains a proactive component as well. Or, put differently, one could argue that the stop-signal task requires subjects to inhibit their response after a stop-signal (i.e. reactive inhibition), but also that participants may tentatively withhold their action even before the stop-signal is presented in anticipation of it (i.e., proactive inhibition; Kenemans, 2015; Verbruggen et al., 2014). Thus, neuro-stimulation may affect proactive as well as reactive inhibition.

1.2. Designing a valid Stop-Signal task study

After extensive research on the optimal SST design, a consensus has recently been reached (for more details see Verbruggen et al., 2019). In short, several important factors have to be considered when employing an SST design to ensure valid high-quality data. First, the stop-signal should only be presented on a minority of trials. It is recommended to include 25 % of stop trials, and any significant divergence should be explained as it bears the potential of influencing task performance. For instance, a larger number of stop-signal trials might lead to an increase in strategic slowing on all trials. While stop-signal trials should represent the minority of all trials, at least 50 stop-signal trials are necessary to accurately estimate stop-signal reaction-time (SSRT) as a proxy of the individual response inhibition capabilities. Second, to achieve maximum measurement validity, the *stop-signal delay* (SSD; i.e. the delay between the go-signal and the stop-signal on trials that require stopping) should be adjusted on a trial by trial basis using a staircase procedure. This implies that after successful stopping, the SSD is increased and after unsuccessful stops – in case of incorrect responses in a stop-signal trial – it is decreased. Third, SSRT should only be estimated if all requirements are fulfilled. This includes appropriate filtering of the data and checking if the race model is violated. The race model states that unsuccessful stops should have faster reactions compared to the mean go-reaction time. Additionally, SSRT should only be estimated if the probability of responding in stop-signal trials is not significantly different from 50 %. Simulation studies show that the probability of responding in a stop-trial should be a least between 25–75 %, and ideally between 40–60 % (Band et al., 2003; Verbruggen et al., 2019). This is achieved by continuously adjusting the delay between the go and the stop-signal on stop trials. Thus, ideally, for p(response|signal) = 50 %, half of all stop-trials – which encompasses 12.5 % of all trials – will lead to no response. Finally, if possible, the estimation of SSRT should be performed using the integration method, with replacement of omission errors with the maximum response time allowed, as this appears to be the most reliable procedure. In short, to calculate SSRT based on the integration method with replacement of go-omissions, all go-reactions are rank-ordered and go-omissions (i.e., go-trials in which the response was missed) are assigned the maximum response time to compensate for the lacking response. Afterwards, the most recent SSD is subtracted from the response time corresponding to the p(response|stop-signal)-percentile. The resulting value is termed SSRT.

In addition, several other issues should be considered to increase the measurement validity of the SST, such as instructing participants appropriately, providing feedback between blocks and choosing an appropriate go-task (see Verbruggen et al., 2019).

1.3. Neural correlates of response inhibition

Previous neuroimaging studies have explored the neural underpinnings of response inhibition and identified two key regions in the right prefrontal cortex: the dorsolateral prefrontal cortex (DLPFC) and

the inferior frontal gyrus (IFG) (Aron et al., 2014, 2004; Depue et al., 2016; Swann et al., 2013, 2012). In general, it is assumed that the DLPFC monitors the environment for the need to stop a response, and once that need arises, the DLPFC transfers this information to the right IFG, which in turn will act as a behavioral "brake" to stop the action (Aron et al., 2014, 2004). In turn, the IFG will modulate activity in the pre-supplementary motor cortex (pre-SMA) and signal the motor cortex via the subthalamic nucleus to execute the stop command (Depue et al., 2016; Rae et al., 2015). Converging evidence for a key role of right prefrontal regions in response control comes from research on epilepsy patients with intracranial recordings. These results show that the DLPFC is active during and shortly after a task cue (e.g. stopping cue for the present trial) is presented, whereas the IFG is active temporally closer to the actual (stopped) response (Swann et al., 2013, 2012).

Furthermore, a recent fMRI study revealed a common neural coding in the right PFC in inhibition tasks across domains (i.e. memory, emotional and action inhibition) (Depue et al., 2016). More specifically, these authors showed that the DLPFC is active in all tasks; unlike the IFG, which was only active in tasks requiring response inhibition. In particular, this study showed that the IFG receives input from the DLPFC whenever stopping is required and the IFG signals the subthalamic nucleus to stop the motor response. Thus, one might argue that the IFG is specialized for action inhibition whereas the DLPFC has a broader, domain-general function. These results fit prevailing theories of pre-frontal cortex function and inhibitory control (Schall et al., 2017). In general, it is argued that the PFC sits on top of the perception-action cycle and is responsible for directing behavior towards a goal. With regards to the right DLPFC, it has been proposed that this region is crucial for response selection and top-down biasing of processes, while the right IFG is important for the execution of the (stopping) response (Jamadar et al., 2010; Nee et al., 2007).

With regards to the neural underpinnings of proactive and reactive inhibition, imaging evidence suggests that both response inhibition networks partially share a neural substrate in dorsolateral, fronto-parietal areas with the reactive response inhibition network being more right-lateralized (Aron et al., 2014; van Belle et al., 2014; Zhang and Iwaki, 2019).

In summary, the role of the right DLPFC in the SST may be described as integrating all sensory inputs as well as representing and applying task rules to guide behavior, while the right IFG implements inhibitory control via its connections to the pre-SMA and the motor cortex (Aron et al., 2014; Jana et al., 2020; Schall et al., 2017; Suda et al., 2020). The proposed interaction between these areas is visualized in Fig. 1C. Consequently, modulation of activity within any area involved in the response inhibition process is assumed to impact different stages and parts of the process, thus potentially modifying behavior.

1.4. Modulating cognitive processes with transcranial direct current stimulation

tDCS is a type of non-invasive brain stimulation which can be used to modify the activity of the brain area under the stimulation electrodes (Nitsche et al., 2008) In short, the mechanism of action is time- and polarity-dependent, but effects may vary due to interindividual differences and external influences (Krause and Cohen Kadosh, 2014; Woods et al., 2016). With respect to the timing aspect, studies are typically classified into "online" or "offline" stimulation. Online tDCS refers to the application of the stimulation during a particular task, while offline tDCS is applied before the task. Broadly speaking, the mechanism of online tDCS is likely to revolve around a slight modulation of the membrane potentials and the spontaneous firing rate of the stimulated neurons while offline tDCS relies on the induction of plastic after-effects via alteration of neurotransmitter activity (Stagg et al., 2018). However, the duration of the after-effects depends on the stimulation duration (Vignaud et al., 2018; Vosskuhl et al., 2018), although this relationship varies across different studies and designs. Studies in the motor cortex

have further shown that the stimulation intensity does not linearly correlate with the after-effects (Jamil et al., 2017). Yet, it remains unclear how these results transfer to other areas such as the PFC. The polarity of a stimulation protocol usually refers to the electrode positioned over the target area. Consequently, an anode positioned over an area of interest typically is referred to as anodal stimulation; and vice versa for cathodal tDCS (Bikson et al., 2019). However, especially cathodal tDCS effects are variable. For example, at higher intensities, over 1 mA for a 35 cm^2 electrode over the motor cortex, cathodal tDCS resulted in reduced after-effects relative to anodal tDCS (Jamil et al., 2017) and paradoxical switches from inhibitory to excitatory excitability have been observed (Fricke et al., 2011) as well as paradoxical performance enhancements (Schroeder and Plewnia, 2016). There are several explanations for such, at first glance, paradoxical performance enhancements due to cathodal tDCS (e.g., Schroeder and Plewnia, 2016; Weiss and Lavidor, 2012; Weller et al., 2020). Some of the most common explanations are (a) the improvement of the signal-to-noise ratio in paradigms with large amounts of distracting information, (b) the return to homeostasis in overactive areas and (c) the induction of homeostatic plasticity due to a cathodal-tDCS induced perturbation and subsequent compensatory enhancement of processing within the targeted area.

In standard montages, the respective reference electrode is usually placed over the contralateral forehead, although other electrode positions (e.g., using extracephalic reference electrodes or using HD-tDCS setups) have been introduced (Bikson et al., 2010; DaSilva et al., 2011). However, since the current flow is directed from the anode to the cathode, this will lead to stimulation of at least two areas if both electrodes are positioned on the head. This may confound the observed effect since the concurrent stimulation under the reference electrode may influence the outcome. This issue may be to some degree circumvented by choosing a large reference electrode, because the stimulation intensity will be reduced under the larger electrode (Faria et al., 2011). Alternatively, researchers can use an extracephalic reference electrode to at least partially avoid the potential problem of additional stimulation of another brain area. It should be noted that some researchers make the distinction between active and return electrode, even when both electrodes are of equal size and positioned on the scalp. This is misleading since both electrodes are inherently active and stimulate the underlying brain area. The term reference is only valid if the respective electrode is placed extracephalically or of such a size that the current density is negligible. An exemplary tDCS setup is illustrated in Fig. 1D.

More recently, high-definition (HD-tDCS) montages have been introduced to increase the focality and efficiency of tDCS (Villamar et al., 2013). HD-tDCS typically utilizes multiple, small, gel-based electrodes that can be arranged in various configurations. One popular HD-tDCS setup employs 5 small electrodes (approx. 1−2 cm diameter) in a center-surround setup (i.e., one electrode in the middle and four equally spaced surrounding it). Given that tDCS studies ordinarily employ large electrodes over 20 cm^2 in size and focality is relatively low, a HD-tDCS setup can significantly enhance focality (Alam et al., 2016). Other technical aspects that should be considered when designing a tDCS study include the general electrode size, their specific position in relation to each other as well as the applied current intensity. Since all these parameters affect the current flow transcranially through the scalp, simulation of the current flow with realistic head models before the study helps to validate the stimulation procedure and assures that the target area is effectively stimulated (Faria et al., 2011; Miranda et al., 2009, 2006).

The present review aims to synthesize the existing tDCS studies on response inhibition with the SST (for a meta-analysis on the tDCS-specific modulation of response inhibition tasks in general, see Schroeder et al., 2020). Consequently, it is necessary to disentangle the influence of different tDCS protocols, varying SST procedures as well as study design decisions. To this end, tDCS studies that were designed to modulate SST performance in healthy adults were systematically analysed. Given the large parameter space in which both the SST as well the
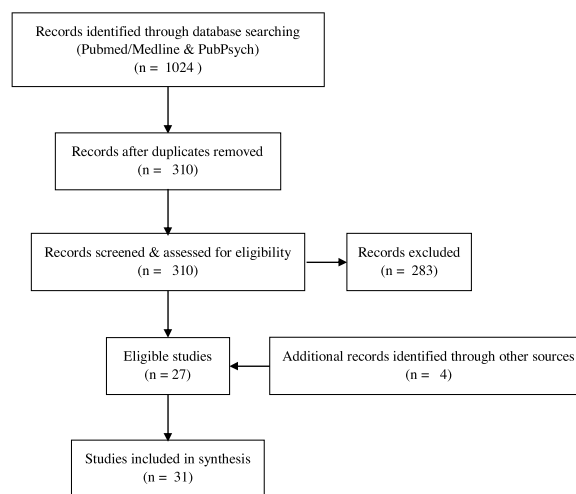
tDCS procedure can be manipulated, the resulting heterogeneity of studies and results is not surprising. In light of the strong impact of stimulation timing, intensity and polarity on the observed outcome (Batsikadze et al., 2013; Stagg et al., 2018), it is reasonable to assume that all these factors influence response inhibition and may interact with the specific SST design, which likely contributes to the large variation of results reported in the literature. We aim to raise awareness for these parameters and provide some guidelines how to design an optimal tDCS study on response inhibition. Thereby, we hope to advance the current understanding of the neural underpinnings of response inhibition and outline future pathways. This could lead to insights into the neural basis of impaired response inhibition processes and inspire new and improved interventions for disorders, such as substance abuse, binge-eating, problem gambling, ADHD and obsessive compulsive disorder; all of which correlate with reduced response inhibition (Goudriaan et al., 2006; Lijffijt et al., 2005; Lipszyc and Schachar, 2010; Woolley et al., 2008). In fact, preliminary evidence already suggests that tDCS may be effective in reducing response inhibition deficits in patients with ADHD (Breitling et al., 2016; Nejati et al., 2020; Salehinejad et al., 2019).

Aside from tDCS, other non-invasive brain stimulation protocols have also been used to modulate response inhibition as measured by the SST. For example, transcranial magnetic stimulation (TMS) research shows stimulation over the right IFG or DLPFC can lead to a performance deficit in the SST (Chambers et al., 2007, 2006; Obeso et al., 2013), although some studies also report null-results (Lee et al., 2016; Chambers et al., 2006; Dambacher et al., 2014; Upton et al., 2010).

2. Methods

2.1. Literature search

The search methods follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines (Moher et al., 2014). For a detailed description of all search steps, see Fig. 2. Table 1 provides an overview of all included studies. In short, PsychInfo as well as PUBMED/MEDLINE were searched through August 2020, using the following keywords to identify and compile all peer-reviewed studies that were designed to modulate a variant of the SST using tDCS in healthy volunteers: "tDCS" or "transcranial direct current stimulation" and "response inhibition" or "inhibitory control" or "stop-signal task" or "stop signal task".

Records identified through database searching
(Pubmed/Medline & PubPsych)
(n = 1024)

Records after duplicates removed
(n = 310)

Records screened & assessed for eligibility
(n = 310)

Records excluded
(n = 283)

Eligible studies
(n = 27)

Additional records identified through other sources
(n = 4)

Studies included in synthesis
(n = 31)

Fig. 2. PRISMA flowchart. The process of literature screening is displayed. Databases were searched using the search string "tDCS" or "transcranial direct current stimulation" in combination with "response inhibition", "inhibitory control", "stop-signal task" or "stop signal task". After exclusion of irrelevant articles and identification of further studies, the final sample consists of 31 studies. The cut-off date for the publication of studies was August 2020.

Table 1

Summary of all included studies in the review (in alphabetical order). Note that the amount of go-trials included in each SST measure is 3-4 times larger compared to the amount of stop-trials. For a more detailed overview of effects depending on the stimulated region see Fig. 2 and Table 2. For studies comparing standard and high-definition tDCS, both electrode locations are listed. Studies employing dual-prefrontal tDCS are listed as using both anodal and cathodal tDCS in line with their respective hypotheses. The majority of studies do not use an extra-cephalic reference electrode or a reference electrode of larger size.

Study [first author, year, journal]	N	Stop-Signal Task				tDCS							
		Stop-Signal Trials per measurement	Repeated within session	Data validation	Stop-Signal modality	Design	Polarity	Timing	Target area(s)	Target electrode size [cm^2]	Current [mA]	Extracephalic reference	Duration [min]
Bashir et al., 2019, Psychological Reports	36	not reported	no	not reported	auditory	between	anodal	online	left DLPFC	3.14	2	no	20
Bell et al., 2020, Social Cognitive and Affective Neuroscience	124	not reported	no	not reported	auditory	between	anodal	offline	right IFG	25	1.5	no	20
Bender et al., 2017, NeuroImage	18	144	yes	not reported	auditory	between	Anodal cathodal	offline	pre-SMA	25	0.7	yes	9
Cai et al., 2016, Journal of Cognitive Neuroscience	22	64	yes	yes	visual	within	anodal	offline	primary visual cortex right IFG right inferior parietal lobe	25	1.5	yes	15
Castro-Meneses et al., 2016, Experimental Brain Research	14	96	yes	not reported	visual	within	anodal	online offline	right PFC	25	1.5	yes	15
Chen et al., 2019, Neuroscience letters	57	24 or 40	yes	partially	visual	between	anodal	offline	right IFG	25	1.5	yes	20
Cunillera et al., 2014, PlosOne	22	108	no	not reported	visual	within	anodal	online	right IFG	9	1.5	no	18
Cunillera et al., 2016, NeuroImage	13	113	no	yes	visual	within	anodal	online	right IFG	9	1.5	no	20
Ditye et al., 2012, Experimental Brain Research	22	not reported	no	not reported	auditory	between	anodal	offline	right IFG	35	1.5	no	15
Fehring et al., 2019, Neuro-psychologia	73	150	yes	partially	visual	within	anodal	offline	left DLPFC	10	1.5	no	10
Friehs and Frings, 2018, Journal of Experimental Psychology: Human Perception and Performance	56	75	yes	yes	visual	between	anodal	offline	right DLPFC	9	0.5	yes	20
Friehs and Frings, 2019c, Cognitive, Affective and Behavioral Neuroscience	42	75	yes	yes	visual	between	cathodal	offline	right DLPFC	9	0.5	yes	20
Friehs et al., 2021, Experimental Brain Research	45	75	yes	yes	visual	between	Anodal cathodal	offline	right DLPFC right IFG	9	0.5	no	20
Friehs et al., 2020b, International Journal of Human Computer Studies	45	75	yes	yes	auditory	between	anodal	offline	right DLPFC	9	0.5	yes	20
Hogeveen et al., 2016, Brain Stimulation	46	32 or 48	yes	not reported	auditory	between	anodal	online offline	Right IFG Primary visual cortex	35 or 1.5	1	no	20
Hsu et al., 2011, NeuroImage	28	60	no	not reported	visual	within	Anodal Cathodal	offline	pre-SMA	16	1.5	yes	10
Jacobson et al., 2011, Journal of cognitive neuroscience	11	32	no	not reported	auditory	within	Anodal Cathodal	offline	right IFG left IFG bilateral IFG	25	1	no	10
Kwon and Kwon, 2013a, Neural regeneration research	40	33	yes	not reported	visual	between	Anodal	online offline	pre-SMA	35	1	no	10
Kwon and Kwon, 2013b, Journal of physical therapy science	40	33	yes	not reported	visual	within	Anodal	offline	pre-SMA primary motor cortex	35	1	no	10
Kwon et al., 2013, Neuro Rehabilitation	40	33	yes	not reported	visual	within	Anodal	online offline	primary motor cortex	35	1	no	10–15
León et al., 2020, Behavioral Brain Research	61	not reported	yes	partially	auditory	between	Anodal	offline	right orbitofrontal cortex	9	1.5	yes	20
Li et al., 2019a, Brain	24	37	no		visual	within		online	right IFG	8	2	yes	4

(*continued on next page*)

Table 1 (*continued*)

Study [first author, year, journal]	N	Stop-Signal Task — Stop-Signal Trials per measurement	Repeated within session	Data validation	Stop-Signal modality	tDCS — Design	Polarity	Timing	Target area(s)	Target electrode size [cm²]	Current [mA]	Extracephalic reference	Duration [min]
Li et al., 2019b, NeuroImage	22	37	no	not reported	visual	within	Anodal Cathodal	online	right IFG	8	2	yes	4
Liang et al., 2014, NeuroImage	18	90	no	not reported	visual	within	Anodal Cathodal	offline	pre-SMA	16	1.5	yes	10
Mansouri et al., 2017, Scientific Reports	73	75	yes	not reported	visual	within	Anodal	offline	left DLFPC	10	1.5	no	10
Ouellet et al., 2015, Journal of Psychiatric Research	45	48	yes	partially	auditory	between	Anodal cathodal	offline	bilateral orbitofrontal cortex	35	1.5	no	30
Sandrini et al., 2020, Brain stimulation	30	not reported	no	not reported	visual	between	anodal	offline	right IFG	25	1.5	no	20
Stramaccia et al., 2015, Experimental Brain Research	115	32	no	not reported	auditory	between	Anodal cathodal	offline	right DLPFC right IFG	16	1.5	no	20
Stramaccia et al., 2017, Neurobiology of learning and memory	72	32	no	not reported	auditory	between	Anodal cathodal	online	right IFG	16	1.5	no	20
Thunberg et al., 2020, Scientific Reports	18	108	yes	yes	visual	within	anodal	online offline	bilateral IFG primary visual cortex	25	2	no	20
Yu et al., 2015, Human Brain Mapping	23	180	no	not reported	visual	within	anodal	offline	pre-SMA	16	2	yes	20

2.2. Study screening and selection

Once all papers were extracted from the databases, each paper underwent several screening steps. First, all duplicate papers were removed. Second, all remaining papers were reviewed by independent evaluators with regards to their eligibility. Only studies published in English in a peer-reviewed journal, using healthy adults as their sample were eligible. Moreover, studies had to measure SST performance and use tDCS. Additional studies were then added to the list via other sources (e.g., by employing the snowball method and searching Google Scholar). The final set of studies was examined in detail.

2.3. Data extraction

From the remaining studies, all information with respect to the sample, study design, stimulation procedures and performance measures as well as their change in response to tDCS was extracted.

3. Results

The following sections provide an overview of four main study principles (study design and sample, tDCS design, task and tDCS effects) using descriptive statistics. For a graphical overview of results, see Fig. 3. First, the overall study design and the sample selection is discussed. Second, the tDCS procedure is analyzed. This includes the whole process from localization of the target area to the employed stimulation parameters. Third, details of the administered SST or SST-variants are discussed. This includes – among other factors – the structure of trials, adjustments of the stop-signal delay as well as the method used for SSRT estimation. Fourth, we briefly detail the effects of tDCS on SST performance in a qualitative manner. Table 2 and Fig. 4 show the effects of tDCS on the response inhibition process as indicated by a potential change in SSRT.

3.1. Study design and sample

The analyzed studies employed samples ranging from 11 to 124 healthy adults (mean = 41.77; SD = 27.50). 16 studies employed a between group design, with each group receiving a different type of stimulation. The mean number of participants per group or condition was 24.1 (SD = 13.91). Overall, samples consist of approximately twice as many females as males. Most studies (25 out of 31) were designed to allow for a comparison of tDCS-modulated performance against some baseline, either within or across sessions. 18 studies employed repeated performance measures within each session.

3.2. tDCS procedures

A total of 20 studies used offline stimulation whereas only 7 used online stimulation and 5 studies considered both offline and online stimulation effects on SST performance. Electrode sizes ranged from small ~3cm² ring-electrodes in one study employing HD-tDCS to large, rectangular 35cm² electrodes. However, almost half (13 out of 31) of all studies utilized electrodes of 25 or 35cm² to stimulate the target area. To localize the target area, 29 studies used the EEG 10–20 system, and 2 studies used fMRI-guided localization. The most common target area was the right prefrontal cortex (PFC; 25 out of 31 studies). Within the larger PFC area, 18 studies reported stimulation of the right IFG, and 5 studies stimulated the right DLPFC. Other target areas included for example the left PFC (5), dual-prefrontal stimulation (2), primary visual or motor areas (5) or the pre-SMA (6). Note that some studies included several stimulation conditions targeting different areas. To increase the efficiency of the stimulation, it is generally recommended that authors simulate the current flow of the electrode position before the study (see Bergmann and Hartwigsen, 2020). However, only 9 out of 31 studies reported current flow simulation. 13 out of 31 studies utilized an
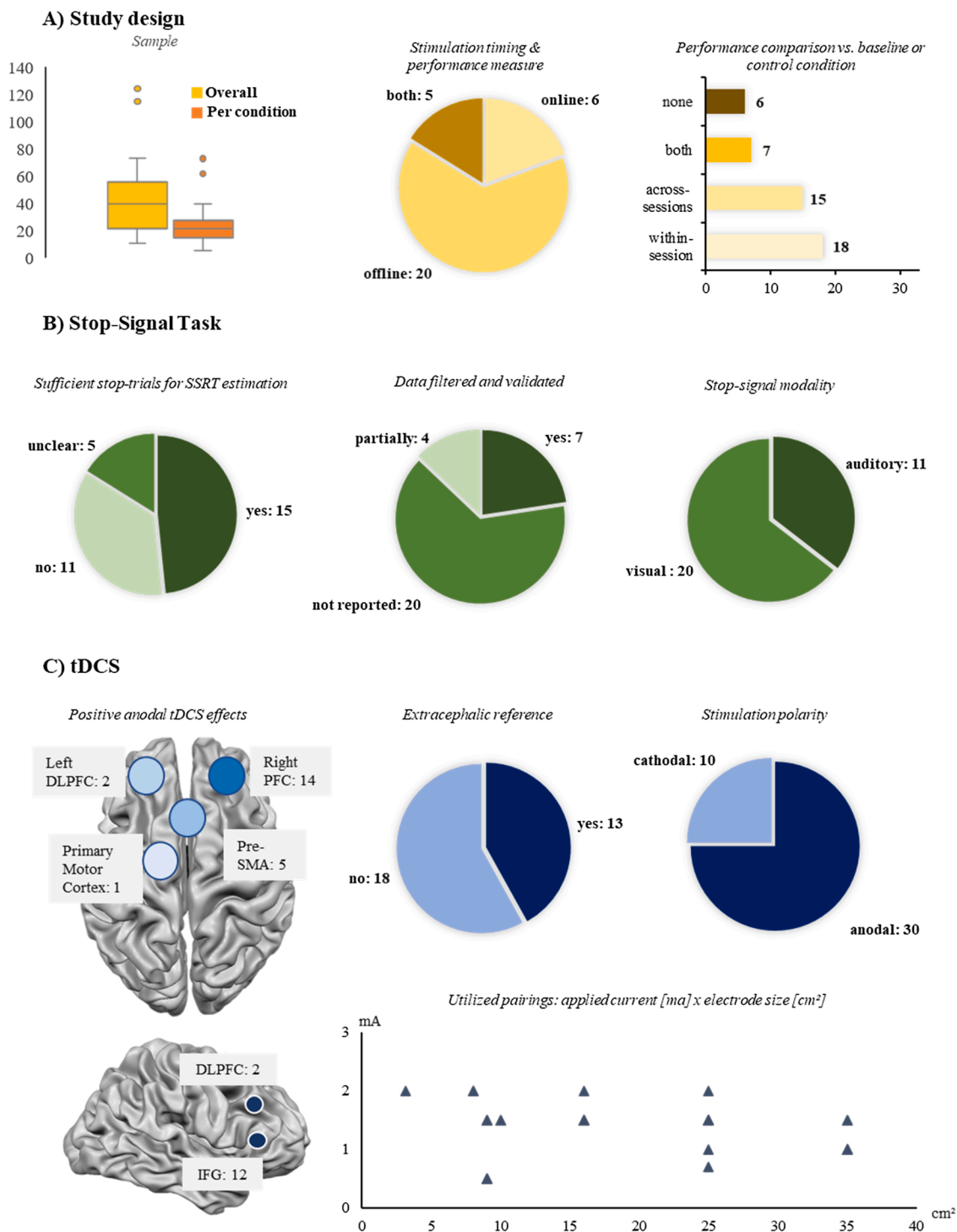
Fig. 3. Variability of tDCS studies on SST with respect to (A) general study design, (B) the Stop-Signal Task and (C) the tDCS procedure. **A)** Left: Total sample sizes, regardless of the study design differ widely with most studies utilizing approximately 40 participants. Middle: Most of the 33 included studies measured performance after the stimulation, only approximately 1/3 of all studies analyzed online effects of tDCS. Right: Differences in outcome measures across studies. 16 of 31 experiments used across-session comparisons of performance (i.e. comparing performance in an active stimulation condition vs. performance in a separate sham session). 18 of 31 studies report within-session comparisons for performance (i.e. measuring performance before stimulation and during or after active stimulation). 7 studies report both within and across session comparisons against a baseline. Additionally, 6 studies do not provide a sufficient control measurement **B)** Left: Only 15 of 31 studies utilize sufficient stop-signal trial numbers according to the recommendations by Verbruggen et al. (2019). Middle: Most studies (25) do not provide sufficient information on data filtering and validation. Right: The majority of studies focused on visual SST versions. **C)** Left: This panel denotes all positive anodal tDCS effects that were reported in the included studies. Most studies targeted the right prefrontal cortex (PFC), which mainly refers to the dorsolateral prefrontal cortex (DLPFC) and the inferior frontal gyrus (IFG). Other stimulation targets include the left PFC, primary sensory areas as well as the pre-supplementary motor area (pre-SMA). Note that technical variables such as timing and reference electrode positioning were omitted from the graphic (for a detailed overview see Table 2 and Fig. 4). Middle: More than half of all studies placed both electrodes on the scalp. Right: The majority of studies used anodal tDCS, while only about 1/3 of all studies included cathodal tDCS. Bottom: Pairing of electrode size and applied current strength.

Table 2

List of all reported tDCS effects from the studies included in the systematic review. The table is sorted alphabetically; studies reporting multiple tDCS effects are listed several times. Please note that the column "target area" refers to the brain area that was targeted in that condition according to the authors of the respective paper. Due to different electrode sizes, localization procedures and mountings, studies targeting the same area might result in different current flow patterns. "Polarity" denotes the polarity of the electrode over the target area; thus if anodal stimulation was used the electrode over the target area was the anode while the reference was the cathode. The column "Effects on SSRT" refers to the statistically significant, tDCS specific effect on SSRT, given a specific stimulation procedure; + = performance improvement, - = performance impairment and 0 = no significant effect on performance. Note that not all studies report all effects.

Study [First author, year, journal]	Target area	Reference	Polarity	tDCS timing	Effect on SSRT
Bashir et al., 2019, Psychological Report	left DLPFC	right supraorbital area	anodal	online	0
Bell et al., 2020, Social Cognitive and Affective Neuroscience	right IFG	left supraorbital area	anodal	offline	not reported
Bender et al., 2017, NeuroImage	pre-SMA	right mastoid	anodal	offline	0
	pre-SMA	right mastoid	cathodal	offline	0
	right IFG	left cheek	anodal	offline	+
Cai et al., 2016, Journal of Cognitive Neuroscience	right IPL	left cheek	anodal	offline	0
	primary visual cortex	left cheek	anodal	offline	0
Castro-Meneses et al., 2016, Experimental Brain Research	right PFC	left cheek	anodal	online	+
	right PFC	left cheek	anodal	offline	+
Chen et al., 2019, Neuroscience letters	right IFG	left check	anodal	offline	+
Cunillera et al., 2014, PlosOne	right IFG	left IFG	anodal	online	+
Cunillera, 2016, NeuroImage	right IFG	left IFG	anodal	online	0
Ditye et al., 2012, Experimental Brain Research	right IFG	left orbitofrontal area	anodal	offline	0
Fehring et al., 2019, Neuropsychologia	left DLPFC	right supraorbital area	anodal	offline	+
Friehs and Frings, 2018, Journal of Experimental Psychology: Human Perception and Performance	right DLPFC	left deltoid muscle	anodal	offline	+
Friehs and Frings, 2019c, Cognitive, Affective and Behavioral Neuroscience	right DLPFC	left deltoid muscle	cathodal	offline	–
	right DLPFC	right IFG	anodal	offline	0
Friehs et al., 2021, Experimental Brain Research	right DLPFC	right IFG	cathodal	offline	0
	right IFG	right DLPFC	anodal	offline	0
	right IFG	right DLPFC	cathodal	offline	0
Friehs et al., 2020b, International Journal of Human Computer Studies	right DLPFC	left deltoid muscle	anodal	offline	+
	right IFG	vertex	anodal	online	not reported
	right IFG	vertex	anodal	offline	+
	right IFG	right hemisphere (HD-tDCS setup)	anodal	online	not reported
Hogeveen et al., 2016, Brain Stimulation	right IFG	right hemisphere (HD-tDCS setup)	anodal	offline	+
	primary visual cortex	vertex	anodal	online	not reported
	primary visual cortex	vertex	anodal	offline	0
Hsu et al., 2011, NeuroImage	pre-SMA	left cheek	anodal	offline	0
	pre-SMA	left cheek	cathodal	offline	0
	right IFG	left orbitofrontal area	anodal	offline	+
Jacobson et al., 2011, Journal of Cognitive Ceuroscience	right IFG	left orbitofrontal area	cathodal	offline	0
	right IFG	left IFG	anodal	offline	0
	right IFG	left IFG	cathodal	offline	0
Kwon and Kwon, 2013a, Neural Regeneration Research	pre-SMA	left cheek	anodal	online	+
	pre-SMA	left cheek	anodal	offline	+
	pre-SMA	left supraorbital area	anodal	offline	+
Kwon and Kwon, 2013a, Journal of Physical Therapy Science	primary motor cortex	left supraorbital area	anodal	offline	0
	primary motor cortex	left supraorbital area	anodal	online	+
Kwon et al., 2013, NeuroRehabilitation	primary motor cortex	left supraorbital area	anodal	offline	0
León et al., 2020, Behavioural Brain Research	right OFC	left trapezium	anodal	offline	0
Li et al., 2019a, Brain	right IFG	right shoulder	anodal	online	+
	right IFG	right shoulder	cathodal	online	0
Li et al., 2019b, NeuroImage	right IFG	right shoulder	anodal	online	+
	right IFG	right shoulder	cathodal	online	0
Liang et al., 2014, NeuroImage	pre-SMA	left cheek	anodal	offline	+
Mansouri et al., 2017, Scientific Reports	left DLPFC	right supraorbital area	anodal	offline	+
Ouellet et al., 2015, Journal of Psychiatric Research	right OFC	left OFC	anodal	offline	0
	right OFG	left OFC	cathodal	offline	0
Sandrini et al., 2020, Brain stimulation	right IFG	left supraorbital area	anodal	offline	+
	right IFG	left supraorbital area	anodal	offline	+
	right IFG	left supraorbital area	cathodal	offline	0
Stramaccia et al., 2015, Experimental Brain Research	right DLPFC	left supraorbital area	anodal	offline	0
	right DLPFC	left supraorbital area	cathodal	offline	0
Stramaccia et al., 2017, Neurobiology of Learning and Memory	right IFG	left supraorbital area	anodal	online	0
	right IFG	left supraorbital area	cathodal	online	0
	bilateral IFG	bilateral parietal cortex	anodal	online	0
Thunberg et al., 2020, Scientific Reports	primary visual cortex	bilateral parietal cortex	anodal	online	0

(continued on next page)

Table 2 (*continued*)

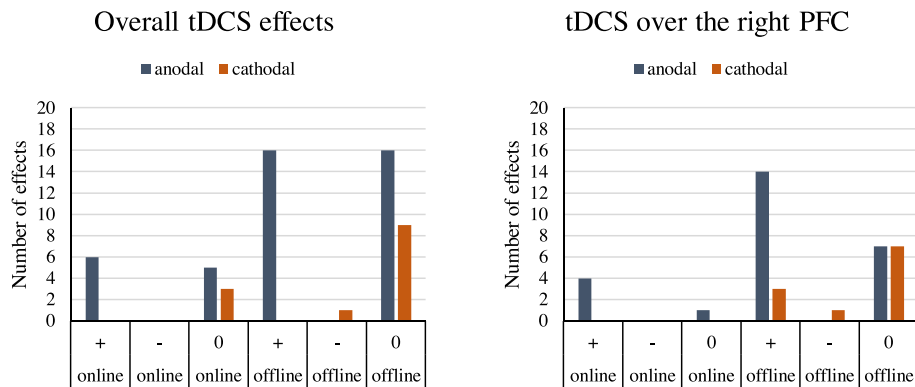| Study [First author, year, journal]	Target area	Reference	Polarity	tDCS timing	Effect on SSRT
	bilateral IFG	bilateral parietal cortex	anodal	offline	0
	primary visual cortex	bilateral parietal cortex	anodal	offline	0
Yu et al., 2015, Hum Brain Mapp	pre-SMA	left cheek	anodal	offline	+

Fig. 4. Visualization of qualitative effects on SSRT across all reviewed studies. The left panel shows all effects depending on timing (online vs. offline) and polarity (anodal vs. cathodal) across all electrode montages as well as all stimulated areas. The right panel focusses on the right PFC, which includes stimulation of the DLPFC and IFG. + = performance improvement, - = performance impairment, 0 = no effect on performance.

extracephalic reference electrode. Note that three studies used dual prefrontal stimulation which precludes the use of an extracephalic electrode. Current densities under the target electrodes ranged from 0.028 to 0.637 mA/cm^2 (mean =0.106 mA/cm^2) and the duration of stimulation ranged from 4−30 min (mean =15.88 min). With respect to the polarity of the stimulation, almost all studies (30 out of 31) employed anodal tDCS, while only about one-third (10 out of 31) used cathodal tDCS. Although the best control condition when using tDCS is debatable (Horvath et al., 2014; Kessler et al., 2012), the use of a control condition is especially important if no pre-stimulation performance baseline is assessed. Overall, 27 studies utilized some variation of the "classical" sham condition which entails either one or multiple ramp-up/down sequences throughout the supposed stimulation period. 2 studies did not stimulate at all during their control session and 2 more studies stimulated a different area that was likely irrelevant to task performance (active control site). Overall, only 8 studies employed anodal, cathodal as well as a sham stimulation condition. Another important aspect is the timing of the stimulation. About 2/3 of all studies investigated offline effects (i.e., after-effects of the stimulation), while only 6 studies looked into the effect of online tDCS (i.e., applied tDCS during the task) on SST performance. 5 studies employed a design which made it possible to measure both online and offline effects. For offline protocols, it is particularly important to control what participants are doing during the stimulation procedure (e.g., rest with their eyes open, fixate a cross or watch a movie). 10 out of 20 offline tDCS studies did not report what subjects were doing during the stimulation, 5 studies provided easy reading materials to the participants, 2 study used a filler task and 3 studies had participants resting with their eyes open. With respect to the inclusion of neurophysiological measures to monitor brain activity during tDCS application, 7 out of 31 offline tDCS studies relied on such measures (i.e., EEG (3) and fMRI (4)). Out of all fMRI studies, two used fMRI during SST performance with concurrent tDCS application (Li et al., 2019a, b), one study used fMRI to investigate task and tDCS induced connectivity changes (Sandrini et al., 2020), and another study recorded fMRI only after tDCS application (Yu et al., 2015). EEG was recorded simultaneously with tDCS and task performance (Cunillera et al., 2016), after tDCS (Liang et al., 2014) or both during and after

tDCS application (Thunberg et al., 2020).

3.3. Stop-signal task

20 out of 31 studies used a visual stop-signal, while 11 studies used an auditory one. All articles were screened and evaluated with respect to their adhesion to state-of-the-art recommendations (see Verbruggen et al., 2019). According to these guidelines, at least 50 stop-trials are needed for an accurate estimation of the SSRT (i.e. the average length of time needed to successfully inhibit an already initiated action). Yet, only 15 out of 31 studies included sufficient stop-signal trials in their experiments. Since the amount of stop-signal trials is directly linked to the overall amount of go-trials, about half of all examined studies did include a low number of go-trials as well. This may impact the overall power of the study. Furthermore, some studies used inconsistent numbers of trials across a session; for example, Chen et al. (2019) report using 24 stop-trials pre-tDCS and 40 stop-trials post-tDCS in their SST. Before analyzing SST data, it is advised to check for the validity of the data and assure that the data quality is sufficient for statistical analysis. About 2/3 of all studies did not report any data validation procedure and 4 out of 31 studies only reported some of the required steps. To accurately calculate SSRT, the stop-signal delay (SSD) has to be adjusted in an adaptive staircase procedure (i.e., shortening the SSD after unsuccessful inhibition and vice versa). Only 24 out of 31 used this procedure, while the remaining 8 did not use it or did not report on it. A second procedure that can be used to enhance SSRT estimation is the use of a specific method of SSRT calculation: the integration method with replacement of omission errors. However, for 26 out of 31 studies, it is either unclear which method was employed, or an inferior method was used. Besides SSRT, many other performance indicators can be measures in a stop-signal paradigm. These performance measures include *omission and commission errors* for go-trails, the *probability of responding given a stop-signal*, as well as *signal and no-signal reaction times*. 18 out of 31 studies do not report error rates at all, while 13 studies report or analyzed them at least partially. That being said, only 2 studies do not report reaction time data at all, while an additional 13 studies did not report signal reaction times.

3.4. tDCS effects on SSRT

Despite the aforementioned differences and heterogeneity of studies, the analysis was performed with a liberal inclusion criterion. All effects regardless of the specific tDCS procedure, the sample, or the SST characteristics were included. Although 30 studies employed anodal stimulation, one did not report any SSRT analysis. 2/3 of all studies using and reporting upon some forms of anodal stimulation do report a performance increase with respect to the inhibition process (as indicated by a decrease of SSRT), while 9 out of 10 studies employing cathodal tDCS report no significant effect of the stimulation. However, considering the results on a study-wide level would be misleading since one study might report multiple results and potentially employ multiple stimulation conditions. Overall, anodal tDCS produced 22 significant positive effects and 21 null results. Cathodal tDCS in sum led to 12 non-significant effects and 1 negative effect. In detail, studies successfully used anodal tDCS over multiple areas to produce significant performance improvement: (i) primary motor cortex = 1, (ii) left PFC = 2, (iii) preSMA = 5 and (iv) right PFC = 14. Put differently, online tDCS produced overall 6 positive effects (all anodal tDCS) and 8 null results (5 anodal and 3 cathodal). This is further exemplified when only right PFC stimulation studies are considered: 4 out of 5 anodal online tDCS studies show a performance enhancing effect. Similarly, 16 out of 42 positive offline effects (10 of which are cathodal tDCS effects) were reported. Finally, 14 out of 21 anodal, offline tDCS effects indicate a performance enhancement. To further explore the effect of anodal tDCS on SSRT, we calculated a chi^2 test for the significant number of significant positive anodal effects across brain areas regardless of the timing of stimulation. The results show that the amount of positive anodal effects does not occur with equal probability across brain areas – left PFC (2), right PFC (14), preSMA (5) and primary motor cortex (1) – $X^2(3) = 19.09$, $p < .001$[1]. Again, it should be noted that the number of studies employing anodal online and offline tDCS over the right PFC and other areas is substantially different (see Fig. 4).

3.5. Open science

All studies were screened for the following criteria: (1) pre-registration of the whole study design and procedure or hypothesis and (2) data availability statement. Analysis revealed that no study included a pre-registration statement and only 9 out of 31 studies included a data availability statement, with varying degrees of accessibility (5 studies provide a direct link to the data, 2 studies provide incomplete supplementary data and 2 studies state that they will provide data upon reasonable request).

4. Discussion

This systematic review reveals an extremely large heterogeneity of studies in the field of tDCS induced modulation of response inhibition. This may be especially problematic in light of the general replicability crisis in studies of psychology and cognitive neuroscience (Barch and Yarkoni, 2013; Pashler and Wagenmakers, 2012; Tackett et al., 2017). Further, considering that the oldest study included in the present review was published in 2011, it is noteworthy that only 9 studies provide data availability statements and no study was pre-registered. Note that with changing legislations (e.g., with regards to data protection laws) and lacking direct participant approval for data sharing in the original studies, it may be difficult and ethically questionable to provide the raw data for some studies. In the following, we discuss the results as well as the practical and theoretical implications of this review. Specifically, we will consider the results with respect to study design and sampling, tDCS

procedures, tDCS effects on SSRT and the stop-signal task.

4.1. Study design and sample

Many of the analysed studies included relatively small sample sizes and did not report an a priori power analysis. The power issue has long been a problem for tDCS studies and results reveal a large divergence in total sample sizes as well as in the number of participants per measurement (Horvath et al., 2014; Minarik et al., 2016). Consequently, it is recommended to perform an a priori power analysis and assume small to intermediate tDCS effects, unless the literature suggests otherwise. Additionally, variations in study designs and tDCS conditions between and within participants leads to potential problems. From an experimental standpoint, within-subject designs are preferable to reduce the influence of inter-individual differences. Yet, they bear the risk of ineffective blinding, since tDCS is associated with distinct physical sensations. Participants' beliefs about specific stimulation conditions and potential side effects should at least be assessed with standard questionnaires after the experiment (e.g. Fertonani et al., 2010; Poreisz et al., 2007). Of note, the challenge to design appropriate and realistic sham conditions affects non-invasive brain stimulation in general and might be even more severe for methods that produce direct muscle twitches such as transcranial magnetic stimulation (TMS) (Kessler et al., 2012; Loo et al., 2000). In tDCS studies, sham stimulation is usually realized by ramping up the current to target intensity for 10–30 s and immediately ramping it down again. This produces some cutaneous sensations such as tingling, itching or burning in the beginning, when they are also strongest for effective tDCS, with the aim to make effective and sham tDCS indistinguishable (Gandiga et al., 2006). However, recent evidence shows that, even if low stimulation intensities are used, participant blinding is compromised (Greinacher et al., 2019; Turi et al., 2019). A recently introduced sham protocol combines a multielectrode montage with controlled shunting of currents via a model-based quantification of transcutaneous and transcranial effects, ensuring constant scalp sensations across the whole stimulation procedure and similar sensations relative to effective stimulation (Neri et al., 2020). This protocol was suggested to be superior in participant blinding relative to conventional bifocal ramp-up, ramp-down sham protocols and may provide a realistic sham condition. Nevertheless, carefully matched active control montages are the "gold standard" for all non-invasive brain stimulation studies, and an additional sham session with the same montage should serve only as low-level baseline (see Bergmann and Hartwigsen, 2020). Polarity specificity should additionally be tested by applying both anodal and cathodal tDCS over the target area of interest. We note that the majority of studies included in the present review did not include anodal and cathodal tDCS over the same area. Finally, while between-subject tDCS conditions do reduce the risk of unsuccessful blinding, they increase the subject-specific variance and necessitate larger sample sizes.

With regards to the experimental design, we recommend the use of repeated measures of task performance whenever possible; thus each tDCS session should contain a pre-tDCS performance measurement. In the analyzed studies, only just over half report such a measurement. There are two advantages in the use of repeated measurements within each session; if the task and theoretical hypothesis allows it. First, inter-individual variability and individual baseline performance has less influence on the results, since the change from pre- to peri/post-stimulation can be analyzed. Further, it is possible to look at effects dependent on baseline performance, which is in line with some studies reporting increased tDCS effects for poor baseline performers (e.g. Learmonth et al., 2015). Second, using this design, fewer overall participants are needed to achieve sufficient statistical power.

The measurement validity of performance in the SST varies considerably across studies. However, there are numerous studies that do not report specific aspects of the SST procedure. It thus remains unclear whether or not best-practice guidelines were adhered to, which may

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[1] It should be noted that the baseline number of studies per targeted brain area also differs.

have affected the validity of the reported results.

4.2. tDCS procedures

Furthermore, similar to the results of the SST, the employed tDCS procedures show strong variations with respect to electrode size, electrode position, current strength (and current density under the electrodes) and stimulation duration. Different stimulation setups lead to varying stimulation effects in the brain, even if two studies target the same region. For instance, in a hypothetical example, two studies target the right DLPFC with anodal tDCS by placing the anode over the F4 position, and applying 15 min of tDCS at 1 mA. As a critical difference,

the first study uses a 9 cm^2 electrode positioned over the F4 position and an extracephalic reference, while the second study uses 35 cm^2 electrodes and mounts the cathode over the left supraorbital area. Although both studies aim to stimulate the right DLPFC, it is obvious that the resulting current flow will substantially differ (see Fig. 5). Consequently, it is important to not only report the technical tDCS parameters such as electrode position as well as size, localization method, applied current and duration, but also simulate the current flow based on these parameters to ensure stimulation of the target area and guide specific interpretation of the modulatory effects. However, about 2/3 of the analyzed studies did not report any current flow simulation. Taken together, these results show that the stimulation parameters of tDCS
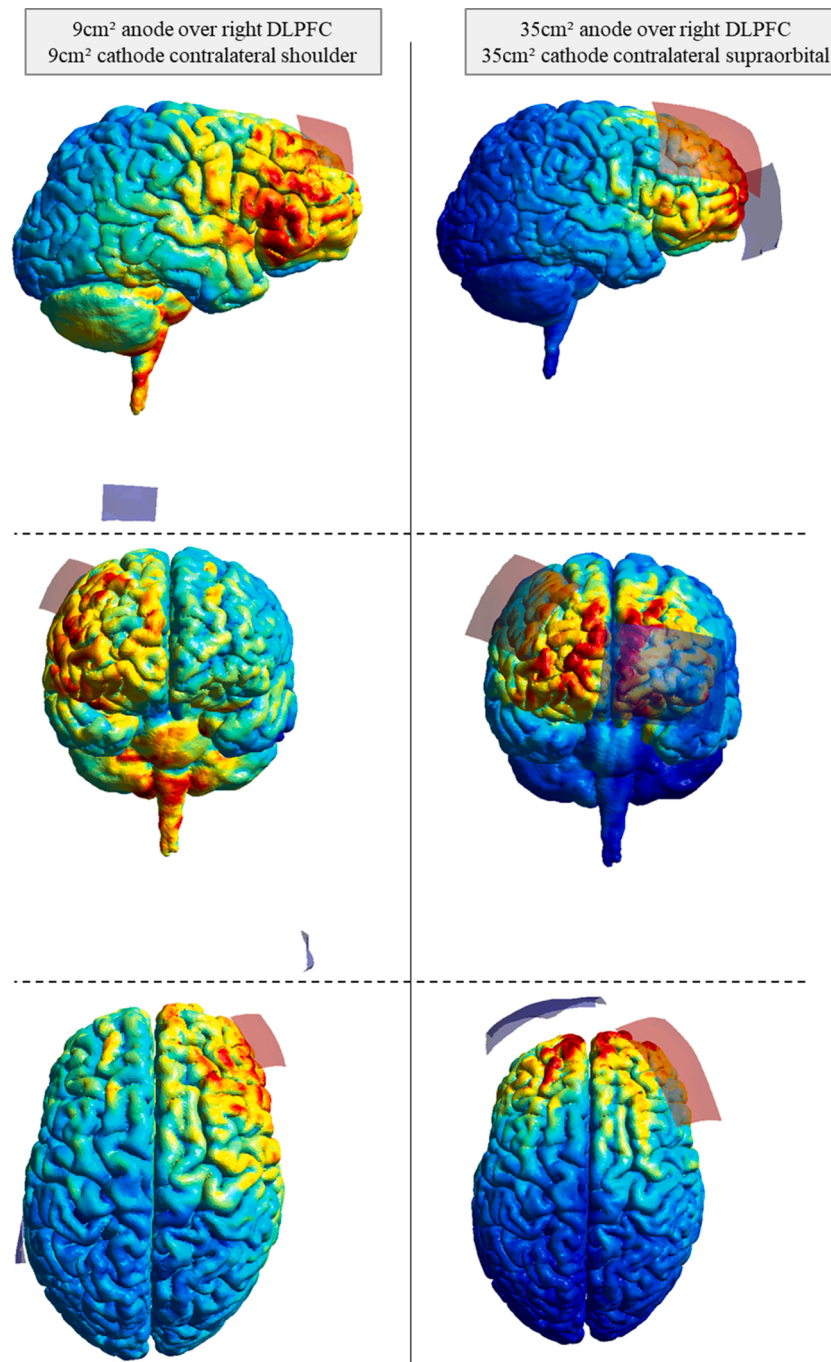
Fig. 5. Simulation of current flow for two different stimulation setups. Left: 9cm^2 electrodes over the right DLPFC (F4-position) and the left upper shoulder area. Right: 35cm^2 electrodes over the right DLPFC (F4-position) and the left supraorbital area. The anode is displayed in red, while the cathode is displayed in blue. Simulation performed with SimaNIBS (Thielscher et al., 2015).

studies on response inhibition are highly diverse. This affects the replicability of the results and the reliability and validity of the conclusions that can be drawn from these studies, especially with respect to effects that are currently underexplored, such as the potential impact of cathodal tDCS effects on response inhibition.

4.3. tDCS effects on SSRT

Despite these methodological inconsistencies, the results in this review demonstrate that anodal tDCS over the right PFC has the highest potential of inducing a significant positive effect on SSRT; that is, performance improvement. Based on the evidence extracted from the analyzed studies, two tentative conclusions may be drawn. First, anodal stimulation over the right PFC is most likely to result in performance enhancement, regardless of timing. Secondly, while both online and offline tDCS over the right PFC may enhance performance, the number of studies using offline tDCS is about four times higher than the number of online tDCS studies. In line with the second conclusion, a recent meta-analysis on tDCS effects on inhibition across multiple behavioural paradigms reported no significant modulatory effect of timing (Schroeder et al., 2020). However, given the large variability and heterogeneity in tDCS and task parameters, a direct comparison of online and offline tDCS studies is difficult and results should be interpreted with caution. This is especially crucial when considering the large discrepancy in the number of studies, which may be further evidence for a publication bias as already pointed out by Schroeder and colleagues (2020). Importantly, changes in SSRT were not accompanied by widespread changes in go-reaction times. This suggests that tDCS has a specific effect on the cognitive response inhibition process while leaving the general response speed unaffected. The high process-specificity of the stimulation effect may be surprising given that tDCS is relatively unfocal and offline non-invasive brain stimulation (NIBS) protocols induce plastic after-effects that are unlikely to be limited to the stimulated area but may rather affect processing at a larger network level (see Hartwigsen, 2018). Yet, the highly specific effect of anodal tDCS over the right PFC fits with a recent meta-analysis that reported a small but significant modulatory effect of tDCS on inhibitory control (Schroeder et al., 2020). Together, the present results and the previous meta-analysis support the previously assigned key role of the right PFC for response inhibition (e.g. Aron et al., 2014, 2004). However, these results do not allow to distinguish the precise contribution of different prefrontal regions to response inhibition and their specific role across the time-course of the inhibition process. Moreover, the majority of the included studies used anodal offline stimulation and the potentially disruptive effects of cathodal tDCS remain largely inconclusive. It should be noted that the effects of online and offline stimulation rely on different neurophysiological mechanisms. Given the overall weaker effects of cathodal tDCS in the present review, we may speculate that for disruptive stimulation, online TMS may be preferable over cathodal tDCS (but see discussion below). Nevertheless, the potential of cathodal online tDCS to impair response inhibition should be further explored. Future studies should also systematically address the effect of tDCS over other areas outside the right prefrontal cortex.

4.4. Stop-signal task

Further, it seems clear that SST task performance specifically and response inhibition in general requires the interplay of motor as well as cognitive inhibition processes (e.g. Jana et al., 2020). Thus, different tDCS montages should influence specific sub-processes due to the targeting of different regions. While there is sufficient evidence that tDCS over the right PFC can potentially impact performance, the number of studies investigating motor processes is comparatively small (8 out of 31; 6 targeting the pre-SMA and 2 targeting the primary motor cortex). Consequently, it is still somewhat unclear what effect tDCS has on motor processes in response inhibition tasks such as the SST. Additionally, it

may be possible that the stimulation of both cognitive- and motor-inhibition associated areas leads to similar behavioural changes. Consequently, to fully disentangle the effect of tDCS on those processes, additional methods need to be employed, such as electromyography to measure muscle activity or neuroimaging techniques to localize process-specific activity.

4.5. Theoretical implications

Based on the evidence from previous neuroimaging as well as NIBS studies, it appears safe to conclude that the right PFC is a key region for response inhibition and sensitive to modulatory neurostimulation effects. Yet, the process-specific interaction of the right IFG and DLPFC remains largely elusive. While tDCS can be used establish causal links between brain activity and performance, the spatial resolution is lower compared to other NIBS procedures such as TMS. Similar to tDCS, TMS may either facilitate or inhibit task processing, with the specific effect depending on the stimulation parameters and the cortical brain state (e. g. Sandrini et al., 2011; Silvanto and Cattaneo, 2017). In contrast to tDCS, TMS can target a more focal area with a higher stimulation intensity that is able to produce direct outputs such as action potentials (Bergmann and Hartwigsen, 2020). Previous studies have applied TMS to probe the functional relevance of different frontal areas for response inhibition and SST performance (e.g. Chen et al., 2009; Zandbelt et al., 2013), but the interaction of the specific subregions within the right PFC and their individual contribution to the response inhibition process remains unclear. Similar to the reviewed tDCS studies, the results of these studies are heterogeneous. For instance, some TMS studies reported that stimulation over the right IFG disrupts performance in the SST (Chambers et al., 2007, 2006; Obeso et al., 2013), while others did not find significant modulatory effects (Lee et al., 2016). Even fewer TMS studies investigated the role of the right DLPFC in response inhibition with the SST, and the results show no significant modulatory effects of TMS on the response inhibition process (Chambers et al., 2006; Dambacher et al., 2014; Upton et al., 2010). This contrasts with other results and existing models of response inhibition which predict that perturbation of this area should impact performance (Aron et al., 2014; Depue et al., 2016; Jana et al., 2020; Miller and Cohen, 2001; Suda et al., 2020). Consequently, future research should dissociate the contribution of specialized subregions in the right PFC and characterize their interaction during response inhibition. Such findings may be transferred and generalized to other tasks involving inhibition processes. Indeed, many response inhibition tasks, such as negative priming or stroop task, involve the selection of the appropriate response in the face of interference by a competing response. Thus, the underlying cognitive system has to bias information processing to achieve the task goal; with the information biasing process entailing the inhibition of the competing, false response (Carlisle, 2019; Miyake and Friedman, 2012; Munakata et al., 2011).

Additionally, to better understand the neural underpinnings of tDCS-induced changes on behaviour, correlative neurophysiological measures such as fMRI, functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) should be combined with tDCS. For example, previous studies combining fMRI and tDCS in a subsequent or simultaneous fashion provide evidence that the modulatory effects of tDCS are not restricted to the stimulated area but rather affect task-related activity and connectivity in distributed areas, including both neighbouring regions as well as remote network nodes (see for example, Fiori et al., 2018; Meinzer et al., 2013; Weber et al., 2014; Zheng et al., 2011). A better understanding of the induced effects of different NIBS techniques at the neural network level is particularly crucial for therapeutic applications in neurological and psychiatric diseases because many diseases can be considered as network disorders and stimulation of densely connected hub regions may be particularly effective (see also Hartwigsen, 2018).

As another future direction, it should be mentioned that studying

response inhibition in basic laboratory tasks is the first step towards understanding this process in ecologically valid real-life situations. To the authors best knowledge, only two studies have investigated performance in more complex stopping environments so far. Firstly, Verbruggen et al. (2014) varied the focality of the stop-signal and the presence of visual distractors. They showed that a stop-signal presented in the visual periphery and visual distractors both hampered task performance. Secondly, the Stop-Signal Game (SSG) has been developed to increase the ecological validity of the inhibition measurement by presenting the task in a visually-complex environment, while also keeping participants motivated to perform well (Friehs et al., 2020a,2020b). Additional research shows that the improvement due to anodal, offline tDCS are comparable in the SST and SSG (Friehs et al., 2020a; Friehs and Frings, 2018). Further, games or gamified tasks can be used to gain access and more reliable measurements from clinical populations. For example, a child with ADHS may not be willing to perform several hundred trials in the context of the SST, however this may be different if performance was measured in a more compelling game-like environment. Schroeder et al. (2021) utilized another version of a gamified SST to investigate inhibitory control in overweight participants. Results showed that inhibitory control deficits persisted in the gamified SST for overweight participants and that this deficit was in fact larger in the game-version. However, even these tasks are too simple compared to real-life situations. In daily life, one always needs to keep track of several different goals simultaneously to successfully navigate a multi-modal environment. Every-day stop situations such as sudden changes of traffic lights usually require correct and efficient responses. This is especially important in situations where unsuccessful or inefficient stopping can be dangerous. To understand how a stop signal is processed in the brain and how this is translated into the inhibition of a certain action is also key to increase the current understanding of disorders with impaired response inhibition and ultimately improve treatment options disorders such as attention-deficit-hyperactivity-disorder, pathological gambling and certain eating disorders (Jennings et al., 1997; Lawrence et al., 2009).

4.6. Practical implications

In summary, based on the included studies on tDCS-specific modulation of SST performance, it is safe to conclude that anodal tDCS over the right prefrontal cortex has the potential to improve response inhibition, at least if applied before the task. In general, non-invasive brain stimulation can help to uncover the neurophysiological underpinnings of critical cognitive processes such as response inhibition and future studies should aim to disentangle the process-specific contributions of specific brain areas as well as their interactions. Notably, the existing studies strongly vary in terms of the employed methodological approaches, both with respect to tDCS parameters and Stop-Signal Task design. To increase the reliability and validity of future studies and increase the current understanding of response inhibition, we conclude with the following recommendations:

4.6.1. Study design

If possible, use within-subject designs for the task as well as the stimulation conditions. Each session should thus contain at least a pre-tDCS measurement to establish a baseline and additionally at least one measurement under the influence of the stimulation. tDCS sessions should be separated by a wash-out period. The specific length of the wash-out period in intervention studies is usually tied to the impact of the intervention itself. The exact duration of tDCS after-effects outside the motor cortex is not known, and clear guidelines for inter-session intervals in studies of cognition are missing. Carryover effects that should be considered in NIBS studies could result from the stimulation and the specific task(s) participants are performing in each session, as well as their interactions. In line with previous meta-analysis and general recommendations for NIBS studies (e.g., Bergmann and Hartwigsen,

2020; Dedoncker et al., 2016), we suggest that different stimulation conditions of plasticity-inducing NIBS protocols should always be conducted in separate sessions several days apart to avoid carry-over or learning effects. For within-subject designs, the order of conditions should be counterbalanced across subjects. Sample sizes should be based on an a priori power analysis which assumes small to medium sized tDCS effects; unless the existing literature suggests otherwise.

4.6.2. tDCS procedure

The target area of the stimulation should be based on recent neuro-imaging results and grounded in an established theoretical model. The electrode placement should be informed by a current flow simulation beforehand. Researchers should employ an appropriate sham procedure and have participants report the side effects as well as their beliefs about the stimulation. tDCS setups should be made as focal as possible, unless the underlying research hypothesis specifies otherwise; this may include the use of smaller electrodes, HD-tDCS setups, electrodes of unequal size or extracephalic references. However, it should be noted that if electrode sizes are changed without an adjustment of the current strength, the risk of discomfort is increased. For example, a tDCS setup with 35 cm^2 electrodes and 2 mA could be changed to 9 cm^2 and 0.5 mA to achieve a similar current density (0.057 mA/cm^2 and 0.056 mA/cm^2, respectively). The specific upper limits of current density are fixed by tDCS-device manufacturers and the current safety guidelines (e.g., Antal et al., 2017; Bikson et al., 2016). Initial piloting of different current strengths for specific electrodes could help to balance stimulation intensities and effective blinding without increasing the risk of discomfort for the actual study. Further, we recommend careful consideration of the stimulation timing and the impact of the current brain state on the outcome. One issue with the application of tDCS that complicates generalizability is the large number of experimental degrees of freedom as to how it is applied, and there is currently no consensus which parameters are most effective (see for example, Friehs and Frings, 2019b; Klaus and Hartwigsen, 2020). For example, when applying offline protocols, being at rest or engaged in a task may impact the stimulation effect (Bikson and Rahman, 2013; Gill et al., 2015; Horvath et al., 2014; Hsu et al., 2011). For tasks where repeated or prolonged measurement is feasible, task performance may be measured before, during and after stimulation. However, this bears the risk of practice or tDCS-enhanced learning effects, which may confound the impact of offline tDCS. Moreover, task-induced pre-activation of the targeted region may trigger homeostatic metaplasticity (Bergmann and Hartwigsen, 2020 for a discussion). Homeostatic metaplasticity has been demonstrated in the motor system, with facilitatory effects of anodal tDCS during stimulation switching towards behavioral inhibition after the end of the stimulation period (Lang et al., 2003; Murakami et al., 2012). However, the impact of such effects on cognitive tasks is largely unknown. Alternatively, one may consider the inclusion of a different task during stimulation to prime neuronal activity in the targeted area(s) and potentially increase the expected after-effects of the stimulation (Klaus and Hartwigsen, 2020). This idea is based on the observation that neuronal networks which are engaged in a concurrent task are preferentially selected by tDCS (Bikson and Rahman, 2013). Consequently, involving participants in a task which is expected to engage the targeted region during the application of tDCS may augment the neuronal effect, likely via gating mechanisms (Ziemann and Siebner, 2008). Indeed, some studies suggest that simple task engagement might pre-activate the network for the modulatory tDCS effect and increase the efficiency of the stimulation protocol (Nozari et al., 2014; Pisoni et al., 2018).

4.6.3. Stop-Signal task setup

The SST or any task based on it such as the Stop-Signal Game should consider the specific design recommendations in the literature (for details see Verbruggen et al., 2019). This includes the use of sufficient stop-signal trials, a staircase procedure for SSD adjustment as well as the use of the integration method with replacement of omission errors for

SSRT estimation. Prior to the analysis of the tDCS effects on performance, all behavioral data should be validated and participants that violate certain criteria (e.g., violation of race-test assumption, strategic behavior by waiting for the stop-signal) should be excluded.

4.6.4. Study reporting

We recommend researchers to report all study details in a way that enables other researchers to replicate their study. This may require the inclusion of additional information to supplement the original research article (e.g., research data, experimental tasks, analysis scripts). Further, we recommend researchers to publish unexpected results or null-results. Although parts of these recommendations are specific for the SST and its variants such as the SSG, they can easily be adapted to fit other tasks and procedures. Adhering to these recommendations could help to increase the reliability and validity of future tDCS studies on response inhibition.

Declaration of Competing Interest

The authors have no conflicts of interests to declare.

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