Combining Transcranial Direct Current Stimulation and Electrophysiology to Understand the Memory Representations that Guide Attention

2 authors:

Shrey Grover
Boston University
11 PUBLICATIONS   **52** CITATIONS

Robert M. G. Reinhart
Boston University
45 PUBLICATIONS   **1,328** CITATIONS

Combining Transcranial Direct Current Stimulation and Electrophysiology to Understand the Memory Representations that Guide Attention

Shrey Grover and Robert M. G. Reinhart

Abstract

How attention is used during visual search is intricately associated with memory. A considerable body of work has demonstrated that representations in both working memory and long-term memory can guide attention in a variety of different circumstances. Neural evidence of such memory-mediated attentional guidance has been elegantly shown using noninvasive electrophysiological measurements of human brain activity. Recently, with the rising popularity of noninvasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), researchers have been able to gain insight into the causal mechanisms of memory-guided attention. Here, we review our current understanding of the role of memory representations in guiding attention and how tDCS can be used to characterize the mechanisms and establish causal relationships. We further discuss the translational implications of using tDCS to alleviate memory-based attentional deficits in psychiatric disorders, such as schizophrenia.

Keywords Memory-guided attention, Attention, Working memory, Long-term memory, tDCS, CDA, Anterior P1, Schizophrenia, N2pc

1 Introduction

The human brain is constantly interacting with a complex environment. At any given moment, our senses are bombarded with numerous streams of information. Yet, for the most part, we function seamlessly. We identify what is relevant, disregard what is not, and store information in the "backs of our minds" for later use. The ability to selectively attend to targets within a field of distracting information is essential for goal-directed behavior. Whether it is food in the grasslands, an explosive among luggage, or an abnormal lesion in a mammogram, our attention plays a vital role in determining what is perceived, remembered, and processed for later action. But, what guides our perceptual attention toward some inputs in the environment and away from others?

Searching for something is easier when we know what we are looking for. When we hold a representation of a search target in memory, we are able to find it better. For example, remembering that the keychain attached to our car key is blue and shiny will help us see it more easily in a bowl of similar-looking keys. The internal representations of search targets, which can be stored in different memory systems of the brain, have been of interest to scientists for nearly a century, but only recently have we begun to examine the nature of these memory representations and how they guide our perceptual attention and behavior.

Advances in neuroscience have considerably improved our knowledge about how information stored in working memory or previously laid down in long-term memory can guide future action. New behavioral paradigms combined with noninvasive neuromonitoring methods, such as electroencephalography (EEG) with its exquisite temporal resolution, have provided us with a window into the neural dynamics of attentional guidance processes as they rapidly unfold over time. The opportunity to visualize the dynamics of the memory mechanisms guiding attention has opened up an entirely new realm of theoretically important, empirical hypotheses about the nature of the cognitive mechanisms guiding attention. In addition to electrophysiological measurements of brain activity, the field of memory-guided attention may benefit from a new class of neuroscience tools that offer the possibility of directly modulating neural activity in a noninvasive and reversible manner. Such tools promise the unique opportunity to establish causal relations between the brain, cognitive processes, and behavior and to more rigorously address questions about the nature of goal-driven behavior.

In this chapter, we focus on the neuromodulation method of transcranial direct current stimulation (tDCS). We discuss how tDCS has been used in conjunction with electrophysiological measurements of human brain activity to examine the memory systems underlying the control of attention during the analysis of complex visual scenes. We begin with a brief overview of the major theories of memory-guided attention. Then we discuss the electrophysiological signatures in human EEG that provide the correlative evidence for these theories. This is followed by a brief discussion on tDCS and its purported mechanisms of action. Next, we consider in some detail how tDCS has helped clarify the dynamic interplay among working memory and long-term memory in guiding visual search. Finally, we discuss the translational potential of tDCS and its ability to temporarily reverse attentional impairments by modulating faulty memory representations in schizophrenia.

2 Memory-Guided Attention: Theory and Electrophysiological Evidence

Intuitively, we know that we can pay attention to only a small part of what we see at any given time. Since there are often important consequences for what we pay attention to, identifying relevant inputs from the environment is critical. Current theories describe attention as an interplay between factors that make an input stand out against others (the bottom-up, stimulus-driven capture of attention) and factors that allow the volitional focus on inputs relevant for current task demands (top-down control and guidance of attention) [1–3]. Here, we discuss some of these top-down factors that guide our attention.

Theoretical accounts of attention have sought to explain how top-down factors influence the selection of one input over others. As Desimone and Duncan [4] suggest, "objects in the visual field compete for representation, analysis, or control." In an influential computational theory of visual attention [5, 6], Bundesen and colleagues propose how this competition could be solved in favor of one input over others. This critical role is accomplished by the memory systems of the brain. Representations of a target object in these memory systems can provide "templates" to the attentional system describing what to search for in the environment. In this role, memory systems provide top-down control of information to the attention systems. These templates are eventually used to categorize inputs as relevant targets or irrelevant distractors [5, 6]. Maintenance of an internal template to match inputs in order to identify them as targets has been a prevailing feature in many theoretical and descriptive accounts of visual search (e.g. [4, 7–9]). In the brain, these representations are thought to provide a biasing signal that feeds the neurons engaged in visual perception, increasing their sensitivity for detecting target features of interest [4, 6, 9].

The question that naturally follows is how are these templates maintained within our cognitive makeup? The predominant view implicates working memory in this process. When searching for a target object in a cluttered scene, an active representation of the target is maintained in working memory. These representations provide biasing signals to perceptual areas. To experimentally validate this hypothesis, variations of the memory-guided visual search paradigm have been used across laboratories (see Fig. 1a for an example). In these tasks, participants are required to search for a target in an array of non-target distractors. However, before the search array is presented, participants are cued with the identity of the upcoming search target. During the time interval between cue and search array presentation, the cued target is thought to be actively maintained in working memory. That is, because participants are completely informed beforehand about what the target looks like, they can maintain a representation of the target in
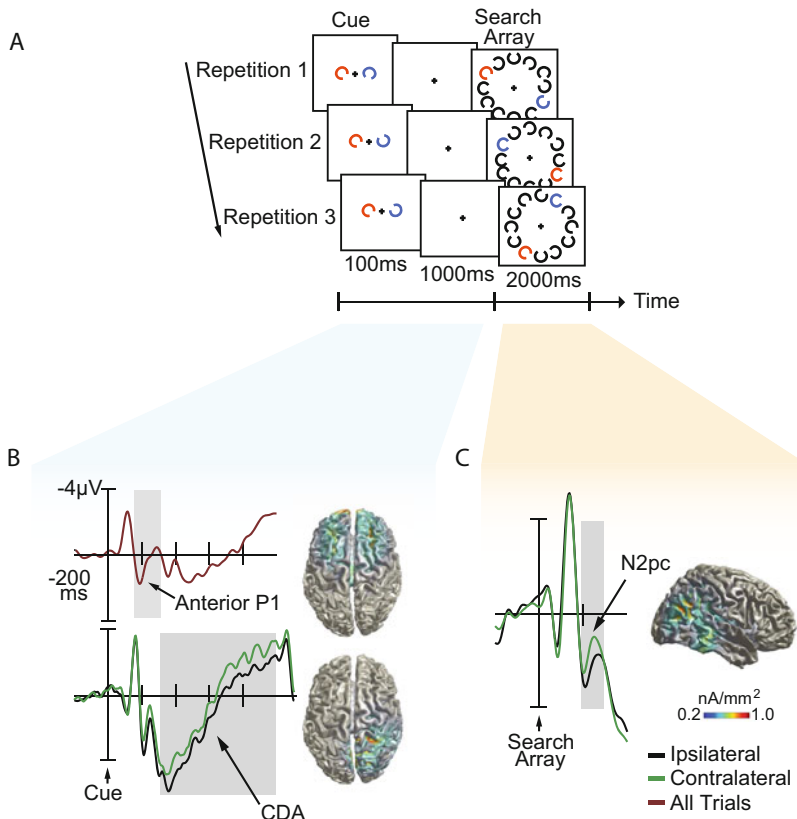
Fig. 1 Memory-guided visual search paradigm and the ERP components used to study working memory, long-term memory, and attentional focus. (**a**) Task-relevant cue (red) is presented indicating the target that should be searched for in the search array. A task-irrelevant cue (blue) is also presented to balance visual input across hemifields. Following a delay period, the search array is presented, and the participant indicates whether the target is present in the array or not. The cue could remain fixed across runs of three to seven trials. (**b**) During the delay period between presentation of cue and search array, memory representations of the cue can be observed using electrophysiology. Working memory involvement is observed using the CDA (bottom panel), while long-term memory can be indexed using the anterior P1 (top panel). Both representations have distinct spatial and temporal profiles, with anterior P1 appearing early relative to the CDA (gray shaded areas), and the former having a bilateral frontal topography while the latter is localized to the contralateral posterior sites. (**c**) Both memory representations improve attentional focus which is measured using the N2-posterior-contralateral potential. The N2pc is evident after the presentation of the search array suggesting a completely independent temporal profile

working memory to provide a biasing signal to facilitate target detection and speed behavioral responses. Thus, working memory can be an appropriate store for maintaining such templates.

Indeed, extensive work in cognitive psychology has found reliable evidence for the role of working memory representations in guiding attention. When a representation is held in working memory, participants are quicker to attend to objects that match

the representation than those which do not [10–17]. This tuning of attention is often measured as changes in reaction times or how long it takes to react to a target when some representation is within memory versus when it is not. If a representation is maintained in working memory, attention is likely to be drawn to the matching objects. However, a parallel body of work has also suggested that simply keeping a representation in working memory is not enough to automatically attract attention. Such representations do not always capture attention and can even be strategically used to guide attention away from potential distractors [18–23]. Further, working memory representations can differentially affect target selection based on current task goals [16, 17], task difficulty and demands [24–27], magnitude of rewards [28], and state of the representation within working memory [29, 30]. Such evidence agrees with more recent additions to the theories of visual attention which propose that upstream executive control mechanisms can provide directions on how working memory representations should guide attention [6, 31]. Together, these studies have further expanded the initial proposition that representations in working memory guide attention, by suggesting that the exact manifestation could differ across different environmental conditions.

With recognition of this complexity, the need for supplementing behavioral evidence with established neural measures becomes necessary. The original theoretical models made explicit proposals on neuronal modulation by memory contents [4]. This strengthens the need to determine neural correlates of working memory in attention. The first set of neural evidence in favor of working memory-guided attention came from studies in nonhuman primate electrophysiology. Chelazzi and colleagues observed sustained firing in the inferotemporal cortex during maintenance of the cued target representation prior to visual search [32, 33]. Firing activity even after the offset of visual input suggests that an internal representation of the cue is maintained to eventually select the appropriate target and suppress attention to distractors. Thus, at least in nonhuman primates, information maintenance in working memory could be reflected in sustained firing patterns in the brain. This provides a potential neural measure to examine the contribution of working memory in nonhuman primates, but a noninvasive measure is more appropriate for studying the phenomenon in humans.

Supporting evidence from human studies was made possible with the discovery of an event-related potential (ERP) observed when a representation is maintained in working memory. ERPs are systematic voltage deflections evident in averaged EEG segments time-locked with respect to stimulus or response events. When storing an object presented on one half of the visual field, the average voltage at electrodes on the back of the head (posterior), opposite to the side where the cue was presented (contralateral),

becomes more negative compared to the corresponding electrodes on the same side of the target (ipsilateral) [34]. Subtracting the potentials from the contralateral and ipsilateral sites provides a measure called the "contralateral delay activity," or CDA, as it is observed during the delay period of working memory tasks, mirroring the sustained activity pattern of inferotemporal neurons in primates (see the bottom panel of Fig. 1b for an example). The effect emerges approximately 300 ms after the presentation of the object. A large body of work has demonstrated the CDA to be a reliable signature of information maintenance in working memory. The CDA tracks the quantity of objects represented in working memory, increasing in amplitude up to each individual's visual working memory capacity [35–37]. It is sensitive to the quality or precision of the stored object representations [38] and to various features of stored objects, such as color [35, 39], orientation [36, 39], or shape [37, 40]. The CDA does not only track retention of previously displayed items but also reflects online processing of concurrently visible items as discussed in a preceding chapter by Balaban and Luria [41]. The CDA occurs even when the information stored in memory needs to be compared with objects that can appear anywhere in the visual field [28, 42–47], making it an ideal tool for studying the role of working memory in attentional guidance during visual search in humans.

To test the role of working memory in guiding attention using the CDA, variations of the cued visual search paradigm are typically used. In this paradigm, on each trial, a target-cue array is followed by a complex search array of objects (Fig. 1a). The cue informs participants of the identity of the target prior to search. Thus, the cue can be maintained in working memory to guide attention during search. Importantly, EEG can be acquired as participants perform this task, and the voltage fluctuations in response to the cue and search array can be later analyzed. Consistent with the view that attentional templates are maintained in visual working memory, the cue-elicited CDA has been observed (Fig. 1b, bottom panel) to continue until search is performed and to correlate with later search performance, with higher CDA amplitudes predictive of faster search reaction times [42, 43]. Immediately following the search array, a second ERP component can be measured called the N2-posterior-contralateral or N2pc (Fig. 1c), a well-validated and reliable index of the deployment of covert visual attention [48–51]. The N2pc has been measured in a number of studies in conjunction with the CDA to provide further evidence that working memory mechanisms can direct perceptual attention under various circumstances [28, 44, 45, 52–54]. The results from these studies show that ERPs can be used to directly measure the visual working memory representations that proactively drive the attention-demanding search process, when targets switch from moment to moment, as is typically the case in the real world.

While our environment is often dynamic and search demands frequently change, we also come across situations that are similar to earlier experiences. If such experiences are repeatedly and consistently encountered, we learn and adapt our behavior to perform required actions more efficiently, skillfully, and automatically. Researchers studying learning and skill acquisition have proposed theoretical models to explain how behavior becomes automatized with increasing experience [55–59]. In Logan's instance theory of attention and memory [56], each encounter with a given object leaves a trace or an "instance" in memory. As more instances are accumulated over time, they increasingly influence the choice among various behavioral options such that one option becomes more biased, leading to faster selection of that choice. Similar speeding of performance due to attentional tuning has long been observed in the field of visual search when search targets repeat trial after trial [60–63]. Thus, it is possible that even the search process can be automatized if the search environment remains consistent over time. In a way, we can *learn* to guide our attention automatically in relatively stable environments.

We know that visual working memory representations benefit attentional search in dynamic environments. But, are working memory representations equally important when performing search in consistent environments? When working memory is filled to capacity by information irrelevant for the search process, one might expect visual search to worsen. This is because the limited working memory resources can no longer be leveraged to maintain active target representations to guide the search process. In dynamic environments where search demands change from moment to moment, Woodman and colleagues [64] observed precisely this effect. In their study, participants performed an orthogonal demanding task along with memory-guided visual search. The second task demanded working memory resources, leaving little available for maintaining an active cue representation for the search. Consequently, if the cues changed from trial to trial, participants became worse at maintaining those cue representations, and their search performance suffered. However, if the cue remained consistent for a series of consecutive three to seven trials (called "runs"; Fig. 1a), the lack of working memory resources had no effect on search performance. That is, search can be performed equally well regardless of whether working memory is available or not as long as one is searching for the same target over and over again. Using electrophysiology, Carlisle and colleagues [43] observed that the CDA amplitude in response to the cues systematically decreases if the cue identity remains fixed during a run of trials, even though search performance progressively improves. This result again suggests that the need for maintaining a representation in working memory reduces over time in consistent environments. Since search

performance is unaffected, these data suggest that visual search can be aided by some source other than working memory.

Despite the prevailing theoretical view that working memory representations of target objects provide top-down control of attention as we search for these objects in cluttered visual scenes [4–7, 29], a more current alternative view, though not mutually exclusive, is that long-term memory representations play a critical role in guiding attention [45, 56, 65–74]. The incorporation of long-term memory into the mechanisms that tune visual attention has the advantages of both freeing up limited resources from working memory and leveraging the virtually unlimited capacity of long-term memory [75, 76], which enables the storage of a large number of items without incurring costs on behavior [65]. This perspective has strong real-world significance, as the guidance of attention during everyday activities often relies on past experiences without explicit cues. Thus, when environments are stable, attention may be aided by long-term memory in lieu of the working memory system, which is more important when environments are dynamic or unpredictable.

Electrophysiology has again been tremendously useful to address the hypothesis that long-term memory is taking over the role of attentional guidance from working memory in consistent environments. To examine how search behavior becomes rapidly automatized, researchers have employed an additional ERP measure indexing long-term memory called the anterior P1, in addition to the CDA component indexing visual working memory. The anterior P1 or P170 is a product of the long-term recognition memory literature using visual memoranda [77–79], in which modulation of this early frontal positivity has been demonstrated to predict the magnitude of behavioral priming effects across protracted memory intervals (i.e., hundreds of stimuli in the past) [80]. Although the anterior P1 is a positive component, it becomes increasingly more negative as encounters with a stimulus accumulate traces in long-term memory [28, 45, 79] (see the top panel of Fig. 1b for an example). As a result, the anterior P1 is generally thought to reflect the successful buildup of information in long-term memory on the basis of stimulus familiarity [79–82]. Given the different spatial and temporal profiles of the anterior P1 (frontal; 150–200 ms after stimulus onset) and the CDA (posterior; 300 ms onward after stimulus onset), both ERP components can be independently measured, thereby giving simultaneous measures of working memory and long-term memory.

If the hypothesis is correct that long-term memory takes over the control of attention from working memory during the tuning of visual attention, then the automation of attentional performance should derive from a decline in attentional templates in working memory, indexed by decreasing CDA amplitudes, and a rise in attentional templates in long-term memory, indexed by increasing

anterior P1 negativity. Indeed, these patterns of CDA and anterior P1 effects were observed by Woodman and colleagues [45] using data from Carlisle et al. [43]. Using the cued visual search task with runs of trials in which the same target was repeatedly cued, participants showed an increase in negative anterior P1 amplitudes, a decrease in CDA amplitudes, and faster reaction times, as they continued to search for the same target object over runs of trials. The results suggest that the tuning of attention was accomplished by the transitioning of target representations guiding attention from working memory to long-term memory. These data provide a prime example of how control of attention can be construed as a dynamic process among multiple memory systems in line with theoretical proposals emphasizing a role for mechanisms of long-term memory [45, 56, 65–74] and executive control [31, 70] in the tuning of perceptual attention.

Subsequent studies have further investigated the dynamic interplay between the memory systems that direct attention when participants analyze complex scenes for target objects. First, the co-occurrence of mounting anterior P1 negativity and declining CDA amplitudes during attentional tuning has been replicated in several studies using simple and more complex stimuli [47, 53]. Second, we now also know that anterior P1 amplitudes continue to change over longer time scales of learning, while the trends of CDA amplitude modulation do not change over time. This suggests that the two memory systems are at least partially independent with non-overlapping roles in guiding attention [53]. Third, it has been found that even after working memory relinquishes control when the targets of search become increasingly familiar, its resources can be recruited under situations of heightened cognitive control [28, 52]. Although the precise role of the anterior P1 is under debate (see [47]), and its modulations have yet to be as thoroughly investigated as the CDA, the linkage between long-term memory and the anterior P1 seems encouraging. Further, the negatively correlated changes in anterior P1 and CDA suggest a transition of representations from working memory to long-term memory, with the role of attentional guidance switching between the two.

We have gained some insight into the memory mechanisms that control attention using theories from cognitive psychology and various electrophysiological tools. The literature outlined here has shown that the strength of working memory representations, as indexed by the CDA, is predictive of attentional behavior and how repetitive visual search comes to rely less on working memory, potentially transferring control to long-term memory in order to guide attention. However, in the field of human memory-guided attention, the body of evidence to date has been largely correlative in nature. That is, our inferences derive from relating changes in behavior to changes in neural activity according to

experimental manipulations of cognitive demands. It is true that visual search performance has been associated with changes in the CDA and anterior P1, but we do not yet know whether these changes are mechanistically causing behavioral enhancements. Further, the nature of the anterior P1 and its relationship to long-term memory attentional control has yet to be sufficiently characterized. Thus, stronger evidence is needed to determine how these electrophysiological signals interrelate and affect search performance.

3 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) has gained increasing popularity among scientists in recent years as a noninvasive neuromodulation technique that can provide an opportunity to obtain causal insight into how human brain activity relates to cognitive processing and behavior, with implications for the development of therapeutic interventions for clinical populations [83]. The approach is safe, well tolerated, inexpensive, portable, and straightforward to administer [84], which are partly the reasons for its growing popularity. TDCS involves the noninvasive application of a low-intensity and sustained direct electrical current with the goal of modulating neuronal excitability in a causal and reversible manner. Conventionally, two relatively large electrodes (5 × 5 cm) are used with an appropriate electrolyte buffer (e.g., conductive gel, paste, or saline) applied between electrodes and the surface of the scalp. The electrode from which current enters the body is designated the anode, and the electrode from which current exits the body is designated the cathode. Classic in vivo animal studies have shown that neuronal excitability tends to increase nearest the inward current flow of the anode and decrease nearest the outward current flow of the cathode [85–89]. More current work showing anodal/cathodal stimulation leads to somatic depolarization/hyperpolarization, and increase/decrease in firing rate [90, 91] further supports the sliding-scale rationale that the anode excites and the cathode inhibits, which, although oversimplified, remains a reasonable first approximation for introducing how differences in tDCS polarity generally influence the brain. Thus, application of a weak current has the potential to modify how excitable a cortical tissue of interest is in a polarity-dependent manner, allowing researchers to obtain bidirectional control over brain activity and behavior [92]. Using computational models that estimate how the applied current should flow through the brain, we can fine tune stimulation parameters, such as the location and intensity values of the anodal and cathodal electrodes, to maximize the effect on a given brain region while minimizing impact on nearby regions [93]. Further, improved neuromodulation methods, such as high-definition tDCS (HD-tDCS), which use an array of smaller

electrodes (e.g., 10 mm in diameter) in carefully designed montages have been shown to stimulate one brain region or a network of regions with higher spatial resolution and longer-lasting effects compared to conventional tDCS [94].

The applied direct current interacts with the physiology of neurons and other cells in the brain [95–97]. Unlike other brain stimulation techniques, such as transcranial magnetic stimulation (TMS), tDCS does not cause direct spiking or firing of neurons. A conventional tDCS experiment involves applying between 1 and 2 mA current using a regular 9-V battery. Most of the applied current is filtered out by the skull, scalp, and intermediate layers which protect the brain [98]. The remaining current produces a weak electrical potential gradient typically less than 1 V/m [99, 100], which, by itself, is not sufficient to cause neurons to directly fire [90, 98]. Instead, the beneficial effects of tDCS that outlast the stimulation duration happen through gradual, cumulative changes in neuronal membrane potential [88]. Although this implies that effects of tDCS take minutes to develop and are not as immediate as compared to TMS effects, tDCS has been shown to exert a surprising degree of temporal precision by influencing specific electrophysiological mechanisms that are as brief as 100 ms during a 1–5 s flow of information processing [101].

The low-intensity electrical current used in typical tDCS studies confers benefits to participant comfort and safety and to the effectiveness of sham control procedures. TDCS is most commonly associated with only minor side effects, such as slight itching sensations under electrodes observed, as the current ramps up and initially spreads over the scalp [84, 102]. In order to control for these side effects, an "active" stimulation session is often coupled with a sham stimulation session (analogous to a placebo). Participants are generally kept blind to the stimulation condition they undergo in a given session. Of note, the experimenter can also be kept blind to the stimulation condition which greatly facilitates the use of tDCS for randomized controlled designs. The most common type of sham design involves brief periods of ramping up of the current before switching it off completely. This ramp-up period simulates the itching sensations experienced in the actual "active" stimulation condition. After the ramp-up, the current is ramped down and switched off for a period of time that matches the duration of the total stimulation in the active condition. As no current is being delivered, few neurophysiological effects are expected (however, see [103] for a review of mixed results). Toward the end of this period, the current is ramped up and down again to simulate the itching sensations observed at the end of an active stimulation session. Alternate designs involve continuous delivery of a current at the same site as in active stimulation but at much weaker intensity or application of a current with the same intensity but at a different site [103–107]. Newer designs that provide the same current intensity

but use a montage that effectively shunts the current within the scalp preventing it from reaching the brain have also been proposed [108]. Determining optimal sham controls is still an active area of tDCS research, but the ease of designing sham controls and the tolerability of the side effects during stimulation make tDCS an attractive tool for neuromodulation.

Complex biophysical mechanisms potentially underlie the effects observed with tDCS. As the current moves through the brain tissue, it affects the membrane potential of neurons in its path. This changes the flux of ions across the neuronal membranes, changing the neurons' likelihood of firing [84, 109–111]. Prolonged changes in the membrane potential can modify the efficacy of neurotransmitter receptors, such as NMDA, which leads to changes in the overall excitability of the tissue [111]. As excitability changes, small modulations are observed in the firing rates which get amplified due to the intrinsic connectivity across neurons in the cortical networks, leading to the macroscopic effects observed in behavior [91]. Much work remains to be done on the biophysical basis of tDCS, but we know that a variety of neurotransmitter systems are potentially implicated including GABA, glutamate, dopamine, serotonin, and acetylcholine [112–114] suggesting that tDCS broadly affects a variety of networks. Thus, tDCS is potentially a powerful tool to modulate intrinsic brain activity through both electrophysiological and chemical changes.

Various avenues of research are currently in progress to maximize the utility of tDCS. For developing better montages and fine-tuning stimulation parameters, the biophysical mechanisms have to be precisely elucidated. In this regard, examination of in vivo and in vitro models of applied electric field on neural tissue is a major area of investigation [115]. Special emphasis is also being given to merge tDCS with neuroimaging techniques such as fMRI and EEG, with other stimulation methods such as TMS, and with structural connectivity measurements obtained from diffusion imaging. Doing so provides a window to observe the macroscopic effects in neuronal functioning and broad, network-based changes in brain states due to stimulation [116–121]. A major body of work uses tDCS to modulate brain networks that are hypothesized to underlie a specific cognitive function such as attentional allocation, learning, and memory [120, 122]. Another active area of work examines how tDCS, with its neuromodulatory abilities, can be used as a therapeutic intervention to correct for deficits in neuropsychiatric disease [123]. In the following sections, we build on these areas of research, discussing recent multimodal evidence obtained via tDCS in combination with EEG about memory-guided attention in healthy population and in people with schizophrenia.

4   Visual Attention Improved in Healthy Young Adults by Modulating Long-Term Memory Electrophysiology with tDCS

The ability to manipulate neural processes using transcranial stimulation has important implications for studying cognition, in general, and memory-guided attention, in particular. We have seen that modulation of electrophysiological signals indexing working memory and long-term memory is associated with enhanced attentional performance. Transcranial stimulation allows us to examine this relationship more stringently by modifying the neural processes directly. We can dissect how multiple control mechanisms converge, diverge, or compete to direct attention by studying which mechanisms are most differentially affected when we externally modulate attention.

A growing body of work shows evidence that tDCS can be used to transiently improve attentional performance (see [124, 125] for a review). Given that both dorsal and ventral attentional networks span a variety of brain areas [126], researchers have targeted various nodes of these networks to enhance attention, including dorsolateral prefrontal cortex (DLPFC) [127, 128], inferior frontal cortex [105], and posterior parietal cortex (PPC) [129, 130]. However, few studies have taken advantage of such converging evidence of attentional enhancement with brain stimulation to study top-down attentional guidance.

An earlier study using TMS tested how attention is captured by items that either match active working memory representations or match items that are perceptually familiar due to prior exposure [131]. The authors observed that activating visual cortex with TMS differentially affected the two forms of attentional capture. This suggests that the two representations influence attention differently – an important finding that supports multiple sources of attentional control. In another recent study, TMS was performed over DLPFC and PPC, and it was found that activating these regions leads to greater attentional capture by working memory representations [132]. These studies add to growing causal evidence that memory representations lead to different attentional states which can be demarcated in the brain. However, concurrent measurements of working memory and long-term memory would be necessary in order to examine the dynamics of their interactions.

Reinhart and Woodman [53] tested whether representations in working memory and long-term memory can be modified by tDCS to guide attention. In an earlier study, they observed that performing anodal stimulation over the medial frontal cortex improved target detection [92]. Medial frontal cortex is not commonly thought of as a region involved in the canonical attentional network of frontoparietal structures. However, medial frontal cortex is not a unitary structure. It is a broad categorization of various functional areas such as the

anterior cingulate cortex (ACC), the supplementary motor area (SMA), and the pre-supplementary motor area (pre-SMA). The cingulate cortex is considered a part of a wider cingulo-opercular network that shows functional connectivity with the attentional network during perceptual search [133]. This area also performs core cognitive control functions, including specifying task sets or rules, and the making and monitoring of choices [134–140]. Due to this performance monitoring role, the ACC has also been considered a part of an anterior attention system influencing recruitment of attention [141]. The pre-SMA and SMA have also been shown to perform performance monitoring [142, 143], indicating their potential involvement in attentional control. Therefore, attentional control could be modified by broadly targeting the medial frontal cortex which could improve detection performance [92].

The positioning of the medial frontal cortex makes it relatively inaccessible for tDCS to directly target. However, using current flow models, the authors [53] were able to confirm that by placing the anode over the FCz site in the international 10–20 convention and placing the cathode over the right cheek, current could be maximally distributed over the pre-SMA, the SMA, and the fronto-medial surface of the brain including the ACC. Therefore, such a stimulation montage that broadly targets various nodes within the medial frontal cortex could influence the control of which top-down signals need to be sent to the downstream visual areas to guide attention.

Based on this evidence, Reinhart and Woodman [53] targeted medial frontal cortex as the site of anodal stimulation during memory-guided visual search. The same paradigm was previously used to test both working memory and long-term memory contributions by repeatedly looking for the same target for a series of trials [43]. Specifically, participants searched for a target among a bilateral array of distractors (Fig. 1a). The target identity was informed prior to search onset and would remain constant for three to seven consecutive trials. Earlier studies observed reduction in the CDA amplitudes and increasing anterior P1 negativity across these short bursts of learning trials, suggesting that the control of attention shifted from working memory to long-term memory [28, 45]. By combining tDCS with these electrophysiological signals, the authors examined whether attentional enhancements brought about by medial-frontal stimulation were accompanied by changes in the CDA or anterior P1 or both. It is possible that exciting the medial frontal cortex leads to improved working memory representations providing stronger downstream attentional control. If that is the case, then the reduction in the CDA amplitudes might disappear or even reverse. Alternatively, if the behavioral enhancement happens due to increasing contribution from long-term memory, anterior P1 amplitudes would become exceedingly negative, without much change in the CDA.

As expected, attentional tuning was observed as participants repeatedly searched for the same target across the short runs of trials in the baseline (sham) condition. Stimulation of the medial frontal cortex enhanced this effect even further. In fact, attentional performance became so efficient that the time taken to search for the target reached floor levels within the first two repetitions. This effect was supported by an electrophysiological correlate of attentional focus. With stimulation, the N2pc component in response to the search target reached its highest amplitudes within the first two repetitions, indicating that modulation of medial frontal cortex could significantly enhance attentional allocation. However, the crucial question was whether stimulation improved the working memory representation making the search process more efficient or whether the stimulation caused participants to rely on a stronger long-term memory representation.

Comparing the CDA amplitudes between sham and stimulation conditions can test whether working memory representations changed as a consequence of stimulation. In the sham condition, working memory indexed by the CDA was found to reduce with repeated target search in line with previous studies. However, there was no evidence that stimulation affected this rate of change of the CDA with repetition. The authors tested this effect in two experiments where participants were asked to remember and look for simple shapes (Landolt-Cs) or real-world objects. Neither experiment showed evidence that stimulation affected the natural modulation of the CDA with repetition. This suggests that the medial-frontal stimulation-induced improvements in visual search were not due to improved representations in working memory.

Although evidence using the CDA indicated that working memory representations remained unaffected following tDCS, long-term memory representations may have been driving the attentional benefits. As the participants engaged in multiple instances of searching for the same target, these instances could contribute to a greater buildup of target representation in long-term memory [55, 56]. Thus, behavioral improvements can happen due to changes in long-term memory instead of relying on active working memory. Since anterior P1 can index the buildup in the long-term memory, its amplitude might become more negative with repetitive search during stimulation. This is precisely what the authors observed. With stimulation, it took less repetitions for anterior P1 to reach its maximum amplitudes (highest negativity) than in the sham condition. In fact, anterior P1 amplitudes peaked within the first two repetitions, paralleling behavioral and N2pc observations. The change in the amplitude of anterior P1 across repetitions correlated with the change in reaction times across repetitions during stimulation across all participants. Further, these results were consistent across search for simple shapes and real-world objects. These results suggest that when looking for the same target repeatedly, exciting the medial frontal cortex caused

long-term memory representations to rapidly take over the control of attention without affecting working memory.

Similar evidence of enhanced long-term memory aiding attention was evident at even more protracted time scales. The runs of three to seven trials where the search target remained constant were repeated throughout the experiment. We have already discussed how reaction times progressively decreased within each run, with simultaneous decreases in the CDA and increases in anterior P1 negativity. As runs are repeated, offering more opportunity to learn the identity of a previously encountered target, learning effects could accumulate throughout the experiment. If learning-induced changes in anterior P1 underlie improvements in attention, then learning at even longer time scales such as the time course of the experiment should be reflected in anterior P1 amplitudes and behavioral performance. In order to examine this, the authors looked at performance and ERP amplitudes for the same runs during the first third, middle third, and last third of the experiment. The authors observed that even without stimulation, reaction times at the beginning of the runs progressively reduced across the early, middle, and late phases of the experiment. Anterior P1 amplitudes similarly became more negative potentially reflecting greater local consolidation of the target item in long-term memory over the 3-h time course of the experiment. The pattern of CDA amplitudes within a run, however, did not vary across the duration of the experiment. Thus, visual search improved with repetition throughout the experiment not because of a better use of working memory representations but potentially through increasing consolidation in long-term memory. Anodal stimulation over the medial frontal cortex led to even faster reaction times and greater attentional tuning over the course of the experiment. Anterior P1 amplitudes became even more negative even though the CDA amplitudes remained unaffected. These results imply that visual search efficiency could be improved with stimulation and were potentially brought about by greater reliance on long-term memory. Of note, stimulation was performed for only 20 min which was still enough to improve representations in long-term memory and enhance attentional performance for nearly 3 h. Therefore, stimulation could provide behavioral benefits that outlast its duration if the appropriate neuronal networks are targeted.

To our knowledge, this is the only study so far testing simultaneous contributions of working memory and long-term memory in attentional guidance using tDCS. The study provides additional evidence that the contributions from one type of memory system could be preferentially enhanced without affecting the other, suggesting the presence of independent memory guidance mechanisms that likely produce different downstream effects in the sensory regions, as proposed by Soto and colleagues [131].

The study was informative in various aspects. First, the study suggests that stimulation-induced benefits in attentional allocation can happen due to rapid recruitment of long-term memory for guiding attention. Second, it lends further support to the idea of multiple memory systems guiding attention [70] since stimulation enhanced long-term memory without changing the role of working memory in guiding attention compared to baseline. Third, performing stimulation is advantageous since it provides preliminary evidence for the putative origins of the anterior P1 ERP component. Much work is needed to determine whether anterior P1 is a definitive reflection of long-term memory or how its response to familiarity is dependent on the nature of inputs and task requirements. Identifying the sources of anterior P1, as potentially indicated by this study to include medial frontal cortex, might be a good starting point. Fourth, the study suggests that top-down control can be relegated to long-term memory rapidly – within the first two repetitions of repeating the same search behavior. This potentially suggests newer avenues for theories of automaticity as under the right neural conditions (enhanced excitability) the transition to long-term memory can happen rapidly without much need for repetition of instances of search. Finally, using tDCS and observing its effects allow us to determine which of the two memory guidance mechanisms under consideration are best available for manipulation. Under situations where attention is sub-optimal, identification of the prime locus of selection guidance presents itself as a potential target for manipulation to improve any deficits, as will be discussed further in the following section.

5 Identifying and Remediating Memory-Guided Attentional Deficits in Schizophrenia with tDCS

Impairments in cognition are prevalent in various neuropsychiatric disorders [144, 145]. Cognitive impairments often precede and are predictive of later functional disability, such as the mild cognitive impairment observed before the onset of Alzheimer's disease [146] or cognitive symptoms prior to the onset of psychosis in schizophrenia [147]. These impairments remain a defining feature throughout the progression of the disorder. Therefore, identifying the sources of cognitive deficits and finding ways to slow, stop, or reverse these impairments are major goals of psychiatry and translational neuroscience.

Realizing this objective generally requires linking various domains of experimental and theoretical neuroscience. Within cognitive neuroscience, theoretical frameworks and their associated experimental paradigms can be developed, and their validity can first be tested in healthy human samples, observing transient modulations in cognitive functioning with respect to baseline. These

human-validated interventions can then be transferred to a patient population, in order to bring the level of cognitive functioning closer to the baseline levels of healthy participants. However, determining a theoretical framework that can be empirically validated in healthy individuals consistently is a difficult feat in itself [148]. Here, we discuss how a framework developed to study memory-guided attention, with supporting theoretical, behavioral, and electrophysiological evidence, can be translated to study cognitive dysfunction and remediation in schizophrenia.

Schizophrenia is a debilitating brain disorder, characterized by complex combinations of positive, negative, and cognitive symptoms that show considerable variability across individuals. Its pathological origins and treatment options are a matter of interest, debate, and profound implications. Despite the variability, cognitive impairments, especially those related to attention, are considered "core" pathophysiological signatures of schizophrenia [148]. In this view, despite the variability of symptoms across patients, deficits in certain basic cognitive processes like attention would be consistently observed throughout the disease progression but might remain uncaptured in conventional neuropsychiatric examinations [148–150]. Since the subtleties of attentional processes are routinely quantified in cognitive neuroscience, we can adapt frameworks from cognitive neuroscience to examine attentional deficits in schizophrenia.

Top-down control of attention during visual search is one framework from cognitive neuroscience found to be impaired in schizophrenia [151]. What is not known for certain, however, is the source of this impairment. The theoretical motivation for how attentional deficits play out in visual search follows from our previous discussion on models of learning and skill acquisition. Cognitive models of schizophrenia suggest that faulty internally generated predictions cause various symptoms due to mismatch between unreliable predictions and the incoming perceptual input [148, 152, 153]. Memory representations of previous experiences are a crucial source of these predictions. If representations are not stored in memory or if they are inaccessible, various cognitive symptoms could arise [148]. At the same time, the top-down control of attention during visual search could be unfavorably affected. According to theoretical models of learning and memory [55, 56], repeated encounters of an object should lead to a greater number of instances being stored in long-term memory. In the absence of any deficits, after searching for the same object repeatedly, attention can be automatically guided by representations of that object in long-term memory. However, if long-term memory representations are impaired, they cannot properly guide attention. In order to perform visual search successfully, schizophrenia patients would have to consistently rely on their working memory resources. Every instance of visual search, in a way, is a

new search in itself, having little benefit from previous instances of the same search.

This deficit in the ability of long-term memory to guide attention in schizophrenia was noted in a recent study by Reinhart and colleagues [54]. We now know that memory-guided visual search paradigms when used in conjunction with electrophysiology can be used to distinguish the contributions of working memory and long-term memory in attentional guidance in healthy individuals [28, 45, 47, 52, 53]. In their study with schizophrenia patients, Reinhart and colleagues [54] examined whether the contribution of working memory and long-term memory, as indexed by the CDA and anterior P1, respectively, was different between healthy people and people with schizophrenia. For healthy participants, if the target identity for visual search is fixed for a set of consecutive trials, attention appears to increasingly rely on long-term memory representations and less on working memory representations. This is evidenced by increasing negativity of anterior P1 and reduction in the CDA amplitudes. Reinhart et al. found that schizophrenia patients did not exhibit a reduction in CDA amplitudes despite maintenance of the target identity over a series of consecutive trials. In fact, the patients exhibited even greater CDA amplitudes at baseline relative to healthy controls, and these amplitudes did not change with repetitive search. This demonstrates that schizophrenia patients engage more working memory resources to maintain the same target representations as healthy individuals. Moreover, the anterior P1 amplitude did not change over time unlike the increasing negativity observed in healthy controls. Therefore, prior instances of searching for the same target did not lead to a gradual transfer of attentional control to long-term memory. Instead, every search was like a new search causing the patients to rely on their limited working memory resources. This is perhaps why the CDA amplitudes did not reduce over time, unlike healthy controls. These results support the hypothesis that attentional deficits in schizophrenia could stem from an inability to perform a successful transition from working memory to long-term memory to guide attention, consistent with the well-established structural and functional alterations in long-term memory brain regions such as the hippocampus in schizophrenia [154, 155].

Given research showing how medial-frontal tDCS can be used to preferentially enhance the contribution of long-term memory in attentional guidance in healthy young adults [53], it is possible that a similar stimulation protocol could temporarily reverse the attentional deficits in patients with schizophrenia. Indeed, following 20 min of anodal tDCS over medial frontal cortex, Reinhart and colleagues [54] observed that schizophrenia patients exhibited behavioral and electrophysiological patterns that were indistinguishable from healthy controls at baseline. After stimulation, schizophrenia patients showed faster search times, reduced CDA

amplitudes, and increasingly negative anterior P1 amplitudes as a function of target repetitions. Stimulation also improved attentional focus in schizophrenia patients as their N2pc amplitudes went up. This suggests that even downstream attentional selection mechanisms can be improved if deficits in guidance are corrected. Overall, these results imply that 20 min of medial-frontal stimulation was enough to transiently improve attentional performance in people with schizophrenia.

The pattern of results provides a compelling framework of attentional dysfunction in schizophrenia. Attentional abnormalities could arise due to inefficiencies in working memory and an inability to transfer the control between working memory and long-term memory representations in consistent environments. While healthy individuals can successfully transfer control to long-term memory, schizophrenia patients have to continue to rely on the resource-limited working memory throughout. Since patients require greater working memory resources to maintain a given representation, the inefficiency of working memory affects attentional performance. Increased excitability of the medial frontal cortex may correct for the deficits in the long-term memory system that would have otherwise taken over the process of attentional guidance or may modify cognitive control mechanisms that mediate among different memory subsystems in order to execute task demands. More work will be needed to establish the robustness of these effects and validate these hypotheses further.

While other recent studies have looked at the benefits of tDCS on working memory enhancement ([156, 157], but see [158]), no other study has yet examined working memory and long-term memory together, specifically in the context of attentional guidance. Further, even though tDCS has been used in a variety of other neuropsychiatric disorders (see [159, 160] for a review), its use in ameliorating attentional deficits due to impairments in top-down control needs more research in schizophrenia as well as other illnesses. Here, we have discussed in detail the recent evidence that tDCS can transiently remedy such impairments in schizophrenia and can even provide mechanistic understanding to the causes of these impairments. Such line of work, still in its infancy, can have important translational implications going forward for various neuropsychiatric disorders.

6 Conclusions and Future Directions

It is intriguing how we direct our attention to find something of interest and relevant in a complex environment. Over the years, we have gained considerable insight into the various memory systems that can store object representations that serve as a template to guide attention [45, 70]. While theoretical proposals on this matter

go back a century [161], we discussed empirical evidence for memory-guided attentional allocation following advancements in cognitive psychology and electrophysiology in the recent decades, and we believe we are now in a position to determine the causal relationships between the phenomena of memory-guided attention and its neural substrates with the advent of noninvasive neuromodulation techniques such as tDCS. With the recent use of tDCS in examining memory-guiding attention, we have gained insight into how long-term memory-related neural dynamics drive improved attention, independent of working memory top-down control. Further, the locus of attentional deficits in schizophrenia was identified in the transition between working memory and long-term memory, and tDCS was found to transiently reverse these deficits. Thus, with tDCS we can test how different memory systems contribute and interact to provide top-down control and guide attention during the analysis of complex visual scenes.

Despite these advances, there is much work to be done. Determining the action mechanisms of tDCS is a major frontier to cross in order to interpret its effects and design better experiments to answer subtle questions. As a noninvasive neuromodulation technique, it is difficult to precisely determine the effects of tDCS on physiology directly. The efforts have primarily centered on in vitro and in vivo stimulation in animal models [115] although a growing body of work uses neuroimaging in humans to observe network-level changes in neuronal functioning and linking them with what we know from animal models [162]. More recently, using human cadavers as a model, scientists have determined that conventionally applied tDCS is quite weak raising concerns about the purported focality and efficacy of stimulation [98]. The fact that we do not completely understand how tDCS affects the underlying tissue in the living human brain, what stimulation parameters are most effective for modulating cognitive processes, and the heterogeneity of cognitive paradigms tested with tDCS might account for some of the observed variability across tDCS studies that have led to contradictory results [163]. Scientists now argue for more integrated experimental designs which leverage information from anatomy and physiology to develop computational models of induced electric field gradients in the brain and of the consequent behavioral effects [98, 164–166] to determine more focal and effective stimulation parameters and protocols. Given that effects of most tDCS designs are limited to the cortex, newer stimulation tools are being developed in animal models which can target deeper, subcortical structures [167], and these designs are currently being adapted for humans. Thus, we can examine the interaction among these memory systems more stringently, as our designs of tDCS and understanding of its mechanisms advance.

Another growing consensus in neuroscience is that large-scale, coordinated activity across populations of neurons underlies

cognition [168]. While we discussed the putative ERP measures associated with working memory and long-term memory, a large body of work suggests that patterns of rhythmic, oscillatory activity and their interactions, as observed in EEG and magnetoencephalography (MEG), are also associated with these cognitive phenomena. For example, activity in the alpha frequency band (8–12 Hz) [169–171] and interactions between theta and gamma bands [107, 172–174] have been shown to index contents of working memory. Theta (4–8 Hz) and beta (12–30 Hz) oscillations, among others, have been widely implicated in long-term memory consolidation [175–177]. As oscillations are observed across various spatial scales of neuronal investigation, such phenomena can be more reliably tied to neuronal physiology improving their validity and interpretability compared with ERP components [178]. Thus, scientists are now interested in the effects of tDCS beyond simple excitation and inhibition of a given region, examining how they specifically impact brain oscillations. Examining EEG before and after tDCS can show the stimulation-induced changes in activity across various frequency bands [179]. Recently, mathematical models applied to MEG data have also been used to examine changes in oscillatory activity during tDCS [180]. Using principles similar to tDCS, a growing body of work directly modulates these oscillatory activity patterns, entraining a neuronal population at a certain frequency using transcranial alternating current stimulation (tACS) or modulating the interactions among oscillatory activity patterns across networks [107, 181–186]. Understanding how these transcranial stimulation methods modulate global activity patterns and linking them with changes occurring at a single neuron and synapse level will be crucial in determining their efficacy for scientific and translational objectives. Moving forward, we are hopeful that innovative multimodal approaches will allow us to more definitively test, and potential unify, major theories of attention, learning, and skill acquisition [55–59] and ultimately advance a more robust understanding of human goal-directed cognition and action.

References

1. Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3(3):201

2. Wolfe JM, Cave KR, Franzel SL (1989) Guided search: an alternative to the feature integration model for visual search. J Exp Psychol Hum Percept Perform 15(3):419

3. Wolfe JM (1994) Guided search 2.0 a revised model of visual search. Psychon Bull Rev 1 (2):202–238

4. Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Annu Rev Neurosci 18(1):193–222

5. Bundesen C (1990) A theory of visual attention. Psychol Rev 97(4):523

6. Bundesen C, Habekost T, Kyllingsbæk S (2005) A neural theory of visual attention: bridging cognition and neurophysiology. Psychol Rev 112(2):291

7. Duncan J, Humphreys GW (1989) Visual search and stimulus similarity. Psychol Rev 96(3):433

8. Theeuwes J (1993) Visual selective attention: a theoretical analysis. Acta Psychol (Amst) 83 (2):93–154

9. Hamker FH (2004) A dynamic model of how feature cues guide spatial attention. Vision Res 44(5):501–521

10. Downing PE (2000) Interactions between visual working memory and selective attention. Psychol Sci 11:467–473

11. Soto D et al (2005) Early, involuntary top-down guidance of attention from working memory. J Exp Psychol Hum Percept Perform 31(2):248

12. Soto D, Humphreys GW, Rotshtein P (2007) Dissociating the neural mechanisms of memory-based guidance of visual selection. Proc Natl Acad Sci U S A 104 (43):17186–17191

13. Soto D et al (2008) Automatic guidance of attention from working memory. Trends Cogn Sci 12(9):342–348

14. Olivers CN (2009) What drives memory-driven attentional capture? The effects of memory type, display type, and search type. J Exp Psychol Hum Percept Perform 35 (5):1275

15. Olivers CN, Meijer F, Theeuwes J (2006) Feature-based memory-driven attentional capture: visual working memory content affects visual attention. J Exp Psychol Hum Percept Perform 32(5):1243

16. Carlisle NB, Woodman GF (2011) When memory is not enough: electrophysiological evidence for goal-dependent use of working memory representations in guiding visual attention. J Cogn Neurosci 23 (10):2650–2664

17. Carlisle NB, Woodman GF (2011) Automatic and strategic effects in the guidance of attention by working memory representations. Acta Psychol (Amst) 137(2):217–225

18. Downing P, Dodds C (2004) Competition in visual working memory for control of search. Vis Cogn 11(6):689–703

19. Woodman GF, Luck SJ (2007) Do the contents of visual working memory automatically influence attentional selection during visual search? J Exp Psychol Hum Percept Perform 33(2):363

20. Han SW, Kim MS (2009) Do the contents of working memory capture attention? Yes, but cognitive control matters. J Exp Psychol Hum Percept Perform 35(5):1292

21. Kiyonaga A, Egner T, Soto D (2012) Cognitive control over working memory biases of selection. Psychon Bull Rev 19(4):639–646

22. Houtkamp R, Roelfsema PR (2006) The effect of items in working memory on the deployment of attention and the eyes during visual search. J Exp Psychol Hum Percept Perform 32(2):423

23. Peters JC, Goebel R, Roelfsema PR (2009) Remembered but unused: the accessory items in working memory that do not guide attention. J Cogn Neurosci 21(6):1081–1091

24. Luria R, Vogel EK (2011) Visual search demands dictate reliance on working memory storage. J Neurosci 31(16):6199–6207

25. Dalvit S, Eimer M (2011) Memory-driven attentional capture is modulated by temporal task demands. Vis Cogn 19(2):145–153

26. Soto D, Humphreys GW (2008) Stressing the mind: the effect of cognitive load and articulatory suppression on attentional guidance from working memory. Percept Psychophys 70(5):924–934

27. Dombrowe I, Olivers CN, Donk M (2010) The time course of working memory effects on visual attention. Vis Cogn 18 (8):1089–1112

28. Reinhart RM, Woodman GF (2014) High stakes trigger the use of multiple memories to enhance the control of attention. Cereb Cortex 24(8):2022–2035

29. Olivers CN et al (2011) Different states in visual working memory: when it guides attention and when it does not. Trends Cogn Sci 15(7):327–334

30. van Moorselaar D, Theeuwes J, Olivers CN (2016) Learning changes the attentional status of prospective memories. Psychon Bull Rev 23(5):1483–1490

31. Logan GD, Gordon RD (2001) Executive control of visual attention in dual-task situations. Psychol Rev 108(2):393

32. Chelazzi L et al (1993) A neural basis for visual search in inferior temporal cortex. Nature 363(6427):345

33. Chelazzi L et al (1998) Responses of neurons in inferior temporal cortex during memory-guided visual search. J Neurophysiol 80 (6):2918–2940

34. Klaver P et al (1999) An event-related brain potential correlate of visual short-term memory. Neuroreport 10(10):2001–2005

35. Vogel EK, Machizawa MG (2004) Neural activity predicts individual differences in visual working memory capacity. Nature 428 (6984):748

36. Vogel EK, McCollough AW, Machizawa MG (2005) Neural measures reveal individual differences in controlling access to working memory. Nature 438(7067):500

37. Ikkai A, McCollough AW, Vogel EK (2010) Contralateral delay activity provides a neural measure of the number of representations in visual working memory. J Neurophysiol 103 (4):1963–1968

38. Machizawa MG, Goh CC, Driver J (2012) Human visual short-term memory precision can be varied at will when the number of retained items is low. Psychol Sci 23 (6):554–559

39. Woodman GF, Vogel EK (2008) Selective storage and maintenance of an object's features in visual working memory. Psychon Bull Rev 15(1):223–229

40. Luria R et al (2010) Visual short-term memory capacity for simple and complex objects. J Cogn Neurosci 22(3):496–512

41. Balaban H, Luria R (in press) Using the contralateral delay activity to study online processing of items still within view. In: Pollmann S (ed) Spatial learning and attention guidance, Neuromethods. Springer Nature, New York

42. Woodman GF, Arita JT (2011) Direct electrophysiological measurement of attentional templates in visual working memory. Psychol Sci 22(2):212–215

43. Carlisle NB et al (2011) Attentional templates in visual working memory. J Neurosci 31 (25):9315–9322

44. Reinhart RM, Carlisle NB, Woodman GF (2014) Visual working memory gives up attentional control early in learning: ruling out interhemispheric cancellation. Psychophysiology 51(8):800–804

45. Woodman GF, Carlisle NB, Reinhart RM (2013) Where do we store the memory representations that guide attention? J Vis 13 (3):1–1

46. Gunseli E, Meeter M, Olivers CN (2014) Is a search template an ordinary working memory? Comparing electrophysiological markers of working memory maintenance for visual search and recognition. Neuropsychologia 60:29–38

47. Gunseli E, Olivers CN, Meeter M (2014) Effects of search difficulty on the selection, maintenance, and learning of attentional templates. J Cogn Neurosci 26(9):2042–2054

48. Eimer M (1996) The N2pc component as an indicator of attentional selectivity. Electroencephalogr Clin Neurophysiol 99(3):225–234

49. Kiss M, Van Velzen J, Eimer M (2008) The N2pc component and its links to attention shifts and spatially selective visual processing. Psychophysiology 45(2):240–249

50. Luck SJ, Kappenman ES (2011) The Oxford handbook of event-related potential components. Oxford University Press, Oxford

51. Luck SJ (2014) An introduction to the event-related potential technique. MIT Press, Cambridge

52. Reinhart RM, McClenahan LJ, Woodman GF (2016) Attention's accelerator. Psychol Sci 27 (6):790–798

53. Reinhart RM, Woodman GF (2015) Enhancing long-term memory with stimulation tunes visual attention in one trial. Proc Natl Acad Sci U S A 112(2):625–630

54. Reinhart RM, Park S, Woodman GF (2018) Localization and elimination of attentional dysfunction in schizophrenia during visual search. Schizophr Bull 45:96–105

55. Logan GD (1988) Toward an instance theory of automatization. Psychol Rev 95(4):492

56. Logan GD (2002) An instance theory of attention and memory. Psychol Rev 109 (2):376

57. Anderson JR (1982) Acquisition of cognitive skill. Psychol Rev 89(4):369

58. Anderson JR (2000) Learning and memory: an integrated approach. Wiley, Hoboken

59. Rickard TC (1997) Bending the power law: a CMPL theory of strategy shifts and the automatization of cognitive skills. J Exp Psychol Gen 126(3):288

60. Schneider W, Shiffrin RM (1977) Controlled and automatic human information processing: I. Detection, search, and attention. Psychol Rev 84(1):1

61. Shiffrin RM, Schneider W (1977) Controlled and automatic human information processing: II. Perceptual learning, automatic attending and a general theory. Psychol Rev 84(2):127

62. Neisser U (1963) Decision-time without reaction-time: experiments in visual scanning. Am J Psychol 76(3):376–385

63. Nickerson RS (1966) Response times with a memory-dependent decision task. J Exp Psychol 72(5):761

64. Woodman GF et al (2007) The role of working memory representations in the control of attention. Cereb Cortex 17(suppl_1): i118–i124

65. Wolfe JM (2012) Saved by a log: how do humans perform hybrid visual and memory search? Psychol Sci 23(7):698–703

66. Moores E et al (2003) Associative knowledge controls deployment of visual selective attention. Nat Neurosci 6(2):182

67. Chun MM (2000) Contextual cueing of visual attention. Trends Cogn Sci 4 (5):170–178

68. Summerfield JJ et al (2006) Orienting attention based on long-term memory experience. Neuron 49(6):905–916

69. Stokes MG et al (2012) Long-term memory prepares neural activity for perception. Proc Natl Acad Sci U S A 109(6):E360–E367

70. Hutchinson JB, Turk-Browne NB (2012) Memory-guided attention: control from multiple memory systems. Trends Cogn Sci 16 (12):576–579

71. Võ MLH, Wolfe JM (2012) When does repeated search in scenes involve memory? Looking at versus looking for objects in scenes. J Exp Psychol Hum Percept Perform 38(1):23

72. Rosen ML et al (2017) Cortical and subcortical contributions to long-term memory-guided visuospatial attention. Cereb Cortex 28(8):2935–2947

73. Rosen ML et al (2015) Influences of long-term memory-guided attention and stimulus-guided attention on visuospatial representations within human intraparietal sulcus. J Neurosci 35(32):11358–11363

74. Rosen ML, Stern CE, Somers DC (2014) Long-term memory guidance of visuospatial attention in a change-detection paradigm. Front Psychol 5:266

75. Brady TF et al (2008) Visual long-term memory has a massive storage capacity for object details. Proc Natl Acad Sci U S A 105 (38):14325–14329

76. Standing L (1973) Learning 10000 pictures. Q J Exp Psychol 25(2):207–222

77. Danker JF et al (2008) Characterizing the ERP old–new effect in a short-term memory task. Psychophysiology 45(5):784–793

78. Paller KA, Lucas HD, Voss JL (2012) Assuming too much from 'familiar' brain potentials. Trends Cogn Sci 16(6):313–315

79. Voss JL, Schendan HE, Paller KA (2010) Finding meaning in novel geometric shapes influences electrophysiological correlates of repetition and dissociates perceptual and conceptual priming. Neuroimage 49 (3):2879–2889

80. Tsivilis D, Otten LJ, Rugg MD (2001) Context effects on the neural correlates of recognition memory: an electrophysiological study. Neuron 31(3):497–505

81. Duarte A et al (2004) Dissociable neural correlates for familiarity and recollection during the encoding and retrieval of pictures. Brain Res Cogn Brain Res 18(3):255–272

82. Friedman D (2007) ERP studies of recognition memory: differential effects of familiarity, recollection, and episodic priming. New Res Cogn Sci:188

83. Reinhart RM et al (2017) Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. Atten Percept Psychophys 79(1):3–23

84. Bikson M et al (2016) Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 9(5):641–661

85. Bindman LJ, Lippold OCJ, Redfearn JWT (1962) Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. Nature 196 (4854):584

86. Creutzfeldt OD, Fromm GH, Kapp H (1962) Influence of transcortical dc currents on cortical neuronal activity. Exp Neurol 5 (6):436–452

87. Gartside IB (1968) Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. Nature 220(5165):383

88. Purpura DP, McMurtry JG (1965) Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 28(1):166–185

89. Terzuolo CA, Bullock TH (1956) Measurement of imposed voltage gradient adequate to modulate neuronal firing. Proc Natl Acad Sci U S A 42(9):687

90. Radman T et al (2009) Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul 2(4):215–228

91. Reato D et al (2010) Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci 30(45):15067–15079

92. Reinhart RM, Woodman GF (2014) Causal control of medial–frontal cortex governs electrophysiological and behavioral indices of performance monitoring and learning. J Neurosci 34(12):4214–4227

93. Bikson M, Rahman A, Datta A (2012) Computational models of transcranial direct current stimulation. Clin EEG Neurosci 43 (3):176–183

94. Kuo HI et al (2013) Comparing cortical plasticity induced by conventional and high-definition 4×1 ring tDCS: a neurophysiological study. Brain Stimul 6(4):644–648

95. Monai H et al (2016) Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun 7:11100

96. Ruohonen J, Karhu J (2012) tDCS possibly stimulates glial cells. Clin Neurophysiol 123 (10):2006–2009

97. Gellner AK, Reis J, Fritsch B (2016) Glia: a neglected player in non-invasive direct current brain stimulation. Front Cell Neurosci 10:188

98. Vöröslakos M et al (2018) Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 9 (1):483

99. Datta A et al (2009) Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2(4):201–207

100. Ruffini G et al (2013) Transcranial current brain stimulation (tCS): models and technologies. IEEE Trans Neural Syst Rehabil Eng 21(3):333–345

101. Reinhart RM, Woodman GF (2015) The surprising temporal specificity of direct-current stimulation. Trends Neurosci 38 (8):459–461

102. Poreisz C et al (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 72(4–6):208–214

103. Fonteneau C et al (2019) Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul. https://doi.org/10.1016/j.brs.2018.12.977

104. Boggio PS et al (2008) Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Depend 92(1–3):55–60

105. Coffman BA, Trumbo MC, Clark VP (2012) Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. BMC Neurosci 13(1):108

106. Bikson M et al (2018) Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul 11(3):465–480

107. Reinhart RMG, Nguyen JA (2019) Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci. https://doi.org/10.1038/s41593-019-0371-x

108. Richardson JD et al (2014) Toward development of sham protocols for high-definition transcranial direct current stimulation (HD-tDCS). NeuroRegulation 1(1):62–72

109. Liebetanz D et al (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125 (10):2238–2247

110. Nitsche MA et al (2002) Modulation of cortical excitability by transcranial direct current stimulation. Nervenarzt 73(4):332–335

111. Nitsche MA et al (2003) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553(1):293–301

112. Stagg CJ et al (2009) Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci 29 (16):5202–5206

113. Clark VP et al (2011) Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a 1H magnetic resonance spectroscopy study. Neurosci Lett 500(1):67–71

114. Medeiros LF et al (2012) Neurobiological effects of transcranial direct current stimulation: a review. Front Psych 3:110

115. Pelletier SJ, Cicchetti F (2015) Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. Int J Neuropsychopharmacol 18(2):pyu047

116. Callan DE et al (2016) Simultaneous tDCS-fMRI identifies resting state networks correlated with visual search enhancement. Front Hum Neurosci 10:72

117. Schestatsky P, Morales-Quezada L, Fregni F (2013) Simultaneous EEG monitoring during transcranial direct current stimulation. J Vis Exp 76:50426

118. Lauro LJR et al (2014) TDCS increases cortical excitability: direct evidence from TMS–EEG. Cortex 58:99–111

119. Roy A, Baxter B, He B (2014) High-definition transcranial direct current stimulation induces both acute and persistent changes in broadband cortical synchronization: a simultaneous tDCS–EEG study. IEEE Trans Biomed Eng 61(7):1967–1978

120. Santarnecchi E et al (2015) Enhancing cognition using transcranial electrical stimulation. Curr Opin Behav Sci 4:171–178

121. Krause MR et al (2017) Transcranial direct current stimulation facilitates associative learning and alters functional connectivity in the primate brain. Curr Biol 27 (20):3086–3096

122. Filmer HL et al (2014) Applications of transcranial direct current stimulation for

understanding brain function. Trends Neurosci 37(12):742–753

123. Kuo MF, Paulus W, Nitsche MA (2014) Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 85:948–960

124. Coffman BA, Clark VP, Parasuraman R (2014) Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage 85:895–908

125. Reteig LC et al (2017) Transcranial electrical stimulation as a tool to enhance attention. J Cogn Enhanc 1(1):10–25

126. Moore T, Zirnsak M (2017) Neural mechanisms of selective visual attention. Annu Rev Psychol 68:47–72

127. Nelson JT et al (2014) Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 85:909–917

128. Clarke PJ et al (2014) The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: evidence from transcranial direct current stimulation. Biol Psychiatry 76(12):946–952

129. Sparing R et al (2009) Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. Brain 132 (11):3011–3020

130. Moos K et al (2012) Modulation of top-down control of visual attention by cathodal tDCS over right IPS. J Neurosci 32 (46):16360–16368

131. Soto D, Llewelyn D, Silvanto J (2012) Distinct causal mechanisms of attentional guidance by working memory and repetition priming in early visual cortex. J Neurosci 32 (10):3447–3452

132. Wang M et al (2018) Evaluating the role of the dorsolateral prefrontal cortex and posterior parietal cortex in memory-guided attention with repetitive transcranial magnetic stimulation. Front Hum Neurosci 12:236

133. Sestieri C et al (2014) Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory. J Cogn Neurosci 26(3):551–568

134. Pardo JV et al (1990) The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci U S A 87(1):256–259

135. Dosenbach NU et al (2006) A core system for the implementation of task sets. Neuron 50 (5):799–812

136. Peterson BS et al (1999) An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. Biol Psychiatry 45(10):1237–1258

137. Benedict RH et al (2002) Covert auditory attention generates activation in the rostral/dorsal anterior cingulate cortex. J Cogn Neurosci 14(4):637–645

138. Margulies DS et al (2007) Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37(2):579–588

139. Johnston K et al (2007) Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching. Neuron 53(3):453–462

140. Rushworth MF et al (2007) Functional organization of the medial frontal cortex. Curr Opin Neurobiol 17(2):220–227

141. Posner MI, Dehaene S (1994) Attentional networks. Trends Neurosci 17(2):75–79

142. Bonini F et al (2014) Action monitoring and medial frontal cortex: leading role of supplementary motor area. Science 343 (6173):888–891

143. Scangos KW et al (2013) Performance monitoring by pre-supplementary and supplementary motor area during an arm movement countermanding task. J Neurophysiol 109:1928

144. Millan MJ et al (2012) Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 11(2):141

145. Trivedi JK (2006) Cognitive deficits in psychiatric disorders: current status. Indian J Psychiatry 48(1):10

146. Bozoki A et al (2001) Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. Arch Neurol 58(3):411–416

147. Bowie CR, Harvey PD (2006) Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr Dis Treat 2(4):531

148. Hemsley DR (2005) The development of a cognitive model of schizophrenia: placing it in context. Neurosci Biobehav Rev 29 (6):977–988

149. Barnett W, Mundt C (1992) Are latent thought disorders the core of negative schizophrenia? In: Phenomenology, language & schizophrenia. Springer, New York, pp 240–257

150. Huber G (1986) Psychiatrische Aspekte des Basisstörungskonzeptes. In: Schizophrene Basisstörungen. Springer, Berlin, pp 39–143

151. Gold JM et al (2007) Impaired top–down control of visual search in schizophrenia. Schizophr Res 94(1–3):148–155

152. Weiner I (2003) The "two-headed" latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. Psychopharmacology (Berl) 169 (3–4):257–297

153. Gray JA et al (1991) The neuropsychology of schizophrenia. Behav Brain Sci 14(1):1–20

154. Heckers S et al (1998) Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1 (4):318

155. Sigurdsson T et al (2010) Impaired hippocampal–prefrontal synchrony in a genetic mouse model of schizophrenia. Nature 464 (7289):763

156. Orlov ND et al (2017) Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul 10(3):560–566

157. Papazova I et al (2018) Improving working memory in schizophrenia: effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophr Res 202:203–209

158. Gomes JS et al (2018) Effects of transcranial direct current stimulation on working memory and negative symptoms in schizophrenia: a phase II randomized sham-controlled trial. Schizophr Res Cogn 12:20–28

159. Brunoni AR et al (2012) Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul 5(3):175–195

160. Kekic M et al (2016) A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. J Psychiatr Res 74:70–86

161. James W (1890) The principles of psychology. Holt, New York

162. Stagg CJ, Nitsche MA (2011) Physiological basis of transcranial direct current stimulation. Neuroscientist 17(1):37–53

163. Horvath JC, Forte JD, Carter O (2015) Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 8(3):535–550

164. Bestmann S, de Berker AO, Bonaiuto J (2015) Understanding the behavioural consequences of noninvasive brain stimulation. Trends Cogn Sci 19(1):13–20

165. Romei V, Thut G, Silvanto J (2016) Information-based approaches of noninvasive transcranial brain stimulation. Trends Neurosci 39(11):782–795

166. Widge AS (2018) Cross-species neuromodulation from high-intensity transcranial electrical stimulation. Trends Cogn Sci 22 (5):372–374

167. Grossman N et al (2017) Noninvasive deep brain stimulation via temporally interfering electric fields. Cell 169(6):1029–1041

168. Siegel M, Donner TH, Engel AK (2012) Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci 13(2):121

169. Jensen O et al (2002) Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. Cereb Cortex 12(8):877–882

170. Foster JJ et al (2015) The topography of alpha-band activity tracks the content of spatial working memory. J Neurophysiol 115 (1):168–177

171. Reinhart RM, Woodman GF (2014) Oscillatory coupling reveals the dynamic reorganization of large-scale neural networks as cognitive demands change. J Cogn Neurosci 26(1):175–188

172. Daume J et al (2017) Phase-amplitude coupling and long-range phase synchronization reveal frontotemporal interactions during visual working memory. J Neurosci 37 (2):313–322

173. Fell J, Axmacher N (2011) The role of phase synchronization in memory processes. Nat Rev Neurosci 12(2):105

174. Sarnthein J et al (1998) Synchronization between prefrontal and posterior association cortex during human working memory. Proc Natl Acad Sci U S A 95(12):7092–7096

175. Backus AR et al (2016) Hippocampal-prefrontal theta oscillations support memory integration. Curr Biol 26(4):450–457

176. Ketz NA, Jensen O, O'Reilly RC (2015) Thalamic pathways underlying prefrontal cortex–medial temporal lobe oscillatory interactions. Trends Neurosci 38(1):3–12

177. Griffiths B et al (2016) Brain oscillations track the formation of episodic memories in the real world. Neuroimage 143:256–266

178. Reinhart RM et al (2012) Homologous mechanisms of visuospatial working memory maintenance in macaque and human: properties and sources. J Neurosci 32(22):7711–7722

179. Polanía R, Nitsche MA, Paulus W (2011) Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp 32 (8):1236–1249

180. Soekadar SR et al (2013) In vivo assessment of human brain oscillations during application of transcranial electric currents. Nat Commun 4:2032

181. Herrmann CS et al (2013) Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 7:279

182. Antal A, Herrmann CS (2016) Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast 2016:1

183. Reato D et al (2013) Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Front Hum Neurosci 7:687

184. Reinhart RM (2017) Disruption and rescue of interareal theta phase coupling and adaptive behavior. Proc Natl Acad Sci U S A 114 (43):11542–11547

185. Helfrich RF et al (2014) Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol 12 (12):e1002031

186. Polanía R et al (2012) The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol 22 (14):1314–1318