Impaired Attention in Schizophrenia:
Insights from Electrophysiology and Noninvasive Brain Stimulation

By

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To my amazing Mom and Dad
for their infinite support and unconditional love.

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Contralateral delay activity (CDA)

Transcranial direct-current stimulation (tDCS)

Event-related potential (ERP)

Functional magnetic resonance imaging (fMRI)

Blood oxygen level dependent (BOLD)

CHAPTER 1

INTRODUCTION

The study of mental illness is one of the oldest branches of systematic inquiry, tracing back to ancient Egypt, India, and China, with a rich and fruitful history of achievement (Bloomfield, 1897; Zilborg and Henry, 1941; Huang and Ching, 1966) [1]. Viewed from a different perspective, the study of mental illness is quite young. Our modern understanding of psychiatric disorders comes from research enterprises that took shape at the turn of the 19th century and following World War II, when some of the leading ideas of the tradition were synthesized and developed, opening the way to what has proven to be highly productive inquiry.

That mental illness should have exercised such fascination over the years is not surprising. The study of acute schizophrenia, or what ancient scholars called madness, is one of the most severe mental disorders known, characterized by a host of spectacular symptoms, in which people interpret reality abnormally, often experiencing a combination of hallucinations, delusions, and extremely disordered thinking and

[1] Ethnographic research has shown that schizophrenia has existed in all human cultures, ranging from pre-literate agrarian communities to the most technologically advanced industrial societies of our day. The first records of psychotic symptomatology and schizophrenia-like features appear in ancient civilizations. For example, descriptions of psychosis or madness have been found in the ancient Egyptian Book of Hearts appearing prior to 2000 BC, the primary texts of Hinduism, such as *Atharva Veda* dating back to 1400 BC, and Chinese texts from 1000 BC, such as *The Yellow Emperor's Classic of Internal Medicine* (Bloomfield 1897; Zilborg and Henry 1941; Huang and Ching 1966). These writings demonstrate the prevalence of psychotic symptoms and attest to the robust longevity of this debilitating disorder.

behavior. Greek rationalists, such as Plato and Hippocrates, were particularly struck by such symptoms, and sought the first empirical explanations for the nature of psychosis [2], classification schemes for such disorders, and for a host of conceptual, ethical, metaphysical, social, and epistemological issues that arise in all aspects of psychiatry. There was also strong interest in mental illness because explorations of abnormal behavior and experience were thought to provide a unique window into the general understanding of the mind. For example, that perceptual abnormalities and false beliefs in a disorder like schizophrenia might shed new light on how fragile these processes are, and how easily they might go astray in the normal case. Thus, it has been quite natural that the topic of mental illness, and schizophrenia psychosis in particular, with its many mysteries, to have stimulated the curiosity of those who seek to understand their own nature and their place within the wider world.

Although the remarkable psychotic features of schizophrenia, such as hallucinations and delusions, have long captured the interest of scientists and philosophers, it is recognized today that the cognitive impairments of schizophrenia largely drive much of the disability, setting sharp limits on the real world social and occupational functioning of patients (Green, 1996; Green et al., 2000). Traditionally, significant cognitive impairment was thought to be evident only in elderly deteriorated patients with schizophrenia. However, over the past several decades, evidence has

[2] In the 5th and 4th centuries BC, rationalist theories of mental illness, forwarded first by Plato, began to hold sway. For example, in the *Dialogues* (Jowett, 1898), Plato argued that the foundation of mental disturbances is rooted in the relationship between the mind and body, with psychotic behaviors resulting from one's psychological constitution (or "soul"). See also the Greek physician Hippocrates, widely considered the father of modern medicine, who, like Plato, also dismissed the idea of demonic causation of psychosis. Building on the Greek tradition of rational and empirical explanations of nature and behavior, Hippocrates was the first to suggest that disorders related to confusion and madness originate entirely from the brain (Carlsson, 2001).

accumulated to challenge this view. It is now clear that marked cognitive impairment is, in fact, the norm and often pre-dates the illness (Cornblatt and Erlenmeyer-Kimling, 1985; Saykin et al., 1994; Rund, 1998; Davidson et al., 1999; Bilder et al., 2000).

Extensive research has formed a rich literature characterizing the prevalence, degree, and nature of the cognitive abnormalities in schizophrenia (Blanchard and Neale, 1994; Dickinson et al., 2004). Yet, our current understanding of the mechanisms underlying schizophrenia cognitive dysfunction remains quite shallow and incomplete. Further, the general need for such knowledge has only increased in urgency. This is demonstrated by several dramatic facts. First, it is recognized today that acute schizophrenia is the most disabling disorder known, surpassing multiple sclerosis, untreated AIDS, and cancer (Salomon et al., 2013). Second, more than 51 million worldwide are affected by schizophrenia, and the personal and societal costs exceed $62.7 billion per year in the United States alone (Wu et al., 2005). Third, there are currently no established biomarkers for the illness (Ritsner, 2009). And fourth, decades of research show that schizophrenia cognitive deficits are mostly unresponsive to antipsychotic medication, and there are no available medications that effectively treat this debilitating aspect of the illness (Abbott, 2010). The present research is motivated by these challenges to our scientific understanding and clinical care. In this dissertation, I will describe a program of research aimed at increasing our understanding of the disease mechanisms underlying cognitive dysfunction in schizophrenia, and I will show how I have begun to use methods from cognitive neuroscience to pursue an entirely new avenue for developing non-pharmacological intervention strategies for rescuing cognitive function in this devastating brain disorder.

Background

Attentional dysfunction: a hallmark cognitive impairment in schizophrenia

At the core of the cognitive impairment in schizophrenia is an attentional abnormality. Deficits in attention have been considered a central element of schizophrenia since the first clinical descriptions of the disorder (Kraepelin, 1896; Bleuler, 1911), and a large body of empirical research has documented a diversity of behavioral abnormalities that are thought to reflect impaired attention (Nuechterlein and Dawson, 1984). Historically, the attentional impairment in schizophrenia has been evidenced most dramatically in the widespread result that patients show slower manual reaction times (RTs) in discrimination tasks (Nuechterlein, 1977) and impaired performance on traditional psychometric measures of processing speed, such as Digit Symbol and Trailmaking (Heaton et al., 2001; Dickinson et al., 2004). In fact, RT slowing in patients has been so pervasive that Cancro et al. (1971) once classically referred to it as the "closest thing to a north star in schizophrenia research" (p. 352). More recently, it was shown that individuals who are genetically predisposed to schizophrenia have impaired attention even prior to the first psychotic episode (Cornblatt and Erlenmeyer-Kimling, 1985), and by the time patients experience their first episode of psychosis, attentional deficits are typically present and of moderate severity (Caspi et al., 2003). Shakow (1962), a pioneer of experimental psychopathology, described impaired attention as central to schizophrenia. A similar argument, a half

century later, was forwarded by Green (Green, 1996; Green et al., 2000), who concluded that the attentional abnormality in schizophrenia undermines the information processing and performance of patients on nearly every task, driving much of the functional disability in the illness. Indeed, attention has been at the forefront of our understanding of impaired cognition in schizophrenia throughout much of the history of schizophrenia research.

Despite the long-standing view that attention plays a fundamental role in schizophrenia cognitive impairment, pinpointing the disease mechanisms underlying the attentional dysfunction has remained an unresolved challenge. In part, this is due to the broad conceptualization of attention as a complex cognitive construct (Zubin, 1975). As a result, the large literature investigating impaired attention in schizophrenia has often used experimental paradigms and behavioral measures that conflate the multiple mechanisms involved in attention. For example, if behavioral responses are slow or inaccurate for a given target item, this could be due to a failure to direct attention to this item, or a failure to effectively process this item and filter out distractors once attention has been directed to the item. The situation is further complicated by the fact that, even when narrowly defined, attention serves to modulate and enhance the functioning of other cognitive systems (e.g., perception, response selection), and interact with executive control systems, making it difficult to isolate the role of impairments in attention from impairment in these other systems.

In the present dissertation, I will overcome numerous challenges facing the study of impaired attention in schizophrenia. First, I will adopt a framework for conceptualizing attention that derives directly from advances from the fields of cognitive psychology and

neuroscience, grounded in decades of theoretical and empirical work (Broadbent, 1957; Deutsch and Deutsch, 1963; Norman, 1968; Duncan and Humphreys, 1989; Bundesen, 1990; Wolfe, 1994; Cowan, 1995; Desimone and Duncan, 1995; Logan, 2002; Bundesen et al., 2005). In this framework, the general concept of attention is divided into two distinct constructs: *input selection*, the selection of task-relevant inputs for further processing, and *selection guidance*, the processes that guide input selection. Second, I will employ a novel paradigm, allowing me to isolate more clearly the nature of the attentional abnormalities in schizophrenia by focusing on separable electrophysiological components of attention: the multiple memory representations providing the top-down control of attention, and the implementation of attention itself. Finally, I will move beyond the use of correlational methods, and combine electrophysiological measurements of brain activity with noninvasive electrical stimulation to determine whether it is possible to change how patients control and use their attention. The results will provide the strongest tests to date of theories in schizophrenia cognitive dysfunction (Behrendt, 1998b; Fuller et al., 2006; Gold et al., 2007; Luck and Gold, 2008; Ragland et al., 2009; Lesh et al., 2011). The potential advance of this project will be new mechanistic insight into schizophrenia cognitive dysfunction, and groundwork for future therapeutic interventions for remediating cognitive impairment and related functional disability in neuropsychiatric disorders, such as schizophrenia.

In the follow sections, I will provide the relevant background information. Specifically, I will (1) unpack the theoretical constructs of input selection and selection guidance, (2) summarize the basic scientific findings that have led to the development

of the experimental paradigm and electrophysiological tools that I will use in my experiments, and (3) characterize the relevant literature on impaired attention in schizophrenia that has motivated the objectives of this project focused on elucidating the nature of the attentional dysfunction in schizophrenia.

Attention: Input selection versus selection guidance

Of all the tasks we perform, perhaps none is more important for the processing and performance of other tasks than attention. When we attend, we perceive. When we attend and perceive, we remember. When we attend, perceive, and remember, we learn. When we learn, we can act purposely and with forethought. When performing a task, we must, conversely, lessen the need for constant attention to some of its specific components, allowing those components to be carried out automatically, yet the very act of pushing these components into the back of our minds occurs only because we must attend to something else. In short, perceiving, thinking, learning, deciding, and acting require that we budget our attention.

So, what is attention? A search for a succinct definition need go no further than the famous quotation from William James (James, 1890). Attention is “the taking possession by the mind, in a clear and vivid form, of one out of what seem several simultaneously present objects or trains of thought. Focalization, concentration, consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others” (p. 381-382). This is certainly the modal formulation of attention in cognitive psychology and neuroscience. However, here I will refer to this

form of attention as *input selection* to emphasize that it involves giving a subset of inputs preferential access to a given cognitive process.

Input selection

The key to understanding input selection is to recognize that it functions mainly when multiple potential inputs from the environment compete for access to a process, whether that process is perception, working memory, or response selection. If this were not the case, there would be no need to select only one potential input. This idea was explained in the *biased competition theory* of Desimone and Duncan (Desimone and Duncan, 1995). According to this theory, inputs to a process compete with each other for further processing, and attention provides a bias signal that can allow a given input to win this competition, beating out other inputs that might be even more salient. For example, low-level sensory inputs in primary visual cortex provide the inputs to higher-level object recognition processes, and a dim object that is attended can win out over an unattended bright object for object recognition. However, when only one input is present, or when a highly salient input is the to-be-attended stimulus, no bias signal is needed to allow the relevant input to win the competition. Thus, input selection is most important when bottom-up salience is not sufficient to allow relevant inputs to win the competition for processing.

The classic spatial cuing paradigm has provided strong evidence for the role of selection in biasing the competition between inputs. In this paradigm, the effects of cue validity are usually much stronger when the target must be selected from an array of distractors than when the target is presented alone (Luck et al., 1996). Similarly, the

effects of attention at the single-cell level are stronger when a target and a distractor are presented simultaneously inside a given cell's receptive field (Moran and Desimone, 1985; Luck et al., 1997) and when the target needs to overcome the greater salience of the distractor (Reynolds et al., 1999).

Of note, input selection operates within different cognitive systems depending on the nature of the competition. When competition arises at the level of perception (e.g., in a cluttered group of visual objects), attention influences which items are perceived (Treisman, 1996). That is, when we attend, we perceive. When competition arises at the level of working memory (e.g., when there is enough time to perceive all objects but the number of objects exceeds the limits of working memory), attention affects which perceptual representations are stored in working memory (Vogel et al., 1998). That is, when we attend and perceive, we remember. When competition arises at the stimulus-response translation stage (e.g., when multiple responses must be made in a small amount of time), attention affects the prioritization of information at the stage of response selection (Pashler, 1994). That is, when we attend, perceive, and remember, we learn what behavior to execute in a given situation.

Direct empirical evidence for input selection in humans has come from electrophysiological studies focused on the N2pc (N2- posterior-contralateral) component of the event-related potential (ERP) waveform, an extensively studied and well-validated correlate of the focusing of visual attention (Luck and Hillyard, 1990; Luck et al., 1993). When subjects focus attention onto a target object in a bilateral stimulus array, the N2pc component is seen as a negative-going wave at contralateral electrode sites between 200 and 300 ms post-stimulus. Previous work has shown that the N2pc

component is likely generated in lateral occipitotemporal cortex (Hopf et al., 2000), or more specifically from the human homologues of monkey inferotemporal cortex and area V4 (Hopf et al., 2006). In addition, studies of functional similarities have provided evidence that the N2pc component is a human ERP homologue of attentional modulations of single-unit activity that have been observed in these same areas (Luck et al., 1997; Chelazzi et al., 1998; Chelazzi et al., 2001) as well as the frontal eye field (Woodman et al., 2007b; Cohen et al., 2009) in macaque monkeys.

An important feature of the N2pc component is that its contralateral scalp distribution allows it to be isolated from the rest of the ERP waveform, which is largely bilateral when bilateral stimulus displays are used. Specifically, as shown in **Figure 1**, the N2pc component can be extracted by presenting a lateralized target within a bilateral stimulus array and by calculating difference waves based on the data measured from a posterior electrode ipsilateral with respect to the lateralized target subtracted from data measured from a posterior electrode contralateral with respect to the lateralized target. This contralateral-minus-ipsilateral difference wave reflects only the lateralized N2pc component and successfully removes the many bilateral ERP components that would otherwise overlap with the N2pc. Thus, by presenting a lateralized target with a bilateral stimulus array it is possible to isolate the N2pc and measure its onset latency, yielding a highly precise means of measuring the quality of the attentional focus onto a target object (Woodman and Luck, 2003b, a). In the present dissertation, I will describe how I will use the N2pc to evaluate the integrity of input selection in patients with schizophrenia to help pinpoint the locus of the attentional impairment in this disorder.

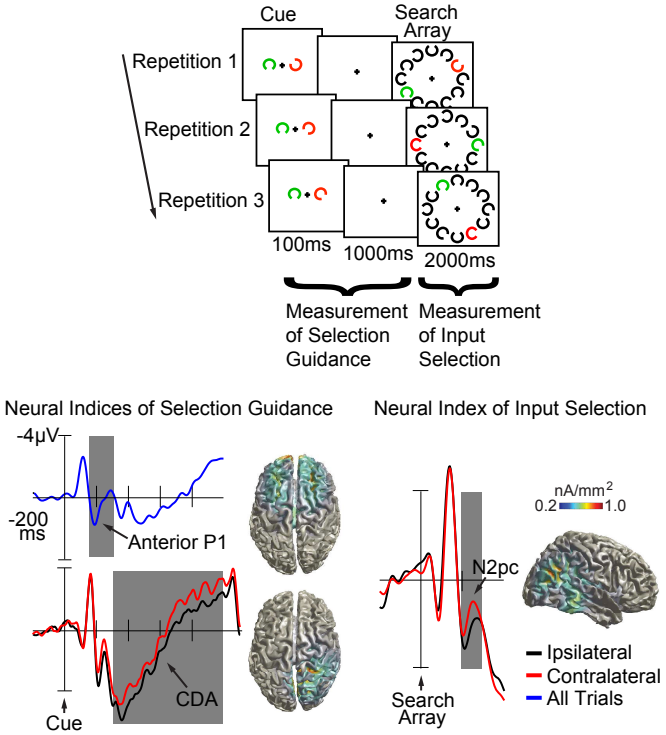

Figure 1. Memory guided search paradigm and neural indices of selection guidance and input selection. A cued visual search task, in which the task-relevant cue (red or green Landolt C) signals the shape of the target in the upcoming search array. Subjects search for the same target across a run of 3-7 trials (or target repetitions). Central fixation is maintained for the trial duration. Below are representative anterior P1, CDA, and N2pc waveforms from the first target repetition of the task, showing each component's distinctive temporal and spatial profile. This figure was modified from Reinhart and Woodman (2015a).

Selection guidance

It is important to distinguish between input selection and the control of input selection, which I will refer to as *selection guidance*. A clear description of executive control was offered by Logan and Gordon (2001), who defined executive processes as those processes whose outputs are the parameters that control the operation of other processes. For example, a categorization system could be set to classify an input in a variety of different ways. The input of “1” could be categorized as being an odd number, as being greater than zero, as rhyming with “done”, as being a vertically oriented shape, and so on and so forth. Control parameters are essential to determine which of these outputs will be provided by the categorization system. In this case, the input to the executive control system might be the instruction to make a rhyme judgment, and the output of the executive control system would be the parameters that cause the categorization system to make a rhyme judgment rather than a judgment based on magnitude, parity, curvature, and so on.

Input-selection processes are not executive control processes. For example, when a letter presented at a cued location is identified and a letter presented simultaneously at an uncued location is not identified, attention is operating to bias the competition between the two inputs and not between two rules. This kind of selection will happen even if the letter shown at the uncued location has never been related with a specific response. While input selection is not a form of top-down control, it does typically depend on controlled processing. In other words, executive control systems must set the parameters of the input-selection system so that it will select the task-relevant inputs. But, the difficult part of an input-selection task is the selection of the

relevant input and the suppression of the irrelevant inputs, not the activation of the correct rule (which could be quite prepotent, as in the case of peripheral cues).

In summary, executive processes convey control parameters to the input-selection system that determine what types of inputs should be selected. These parameters will cause attention to be focused onto a given input, which in turn causes a facilitation of processing for the attended input and a suppression of processing for the unattended inputs. One set of processes is used to identify the input that should be selected, and another set of processes is used to generate differential processing of the selected and unselected inputs. I refer to the first set of processes as selection guidance (or the control of attention), and the second set of processes as input selection (or the implementation of attention). Using the spotlight metaphor of attention, we can think of selection guidance as analogous to pointing the beam of light in the correct direction, whereas input selection would be analogous to the strength of the beam of light (**Figure 2**). In the next section, I will discuss how the control parameters of executive processes are carried to the input-selection system via different memory mechanisms.

The guidance of input selection by representations stored in working memory

For over a century, psychologists and neuroscientists have suggested that attention is controlled by the internal mental representations in memory (James, 1890; Pillsbury, 1908). Current theories of attention propose that the representations that we use to guide the selection of inputs in our environment are stored in working memory

(Duncan and Humphreys, 1989; Bundesen, 1990; Desimone and Duncan, 1995;

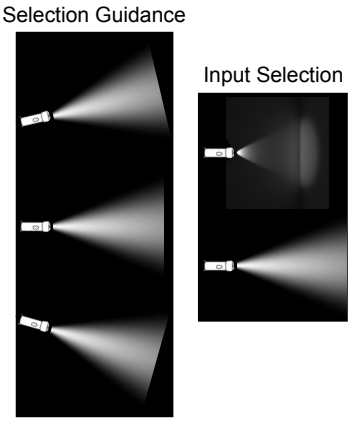

Figure 2. Spotlight metaphor of selection guidance and input selection. An illustration of the difference between selection guidance and input selection using the spotlight metaphor of attention. Here, selection guidance is analogous to pointing the beam of light, whereas input selection is analogous to the strength of the beam of light.

Bundesen et al., 2005). That is, the contents of working memory may provide a bias signal that influences the allocation of attention (Desimone and Duncan, 1995). For example, when the to-be-detected target changes from trial to trial in visual search, subjects store the identity of the target in working memory, which biases selection in favor of this object (Chelazzi et al., 1998; Woodman et al., 2007a). A rich body of work has now accumulated over the past 15 years providing empirical support for the hypothesis that representations in working memory are the source of top-down attentional control (Downing, 2000; Soto et al., 2005; Houtkamp and Roelfsema, 2006; Olivers et al., 2006; Soto and Humphreys, 2007; Soto et al., 2007; Woodman and Luck, 2007; Peters et al., 2008; Soto and Humphreys, 2008; Olivers, 2009; Carlisle and Woodman, 2011b, a; Dalvit and Eimer, 2011; Olivers and Eimer, 2011).

Direct evidence for target representations controlling attention in visual working memory has come from research using human electrophysiology. This work has shown that it is possible to track the representation of targets in visual working memory using a component of subjects' ERP waveforms. Specifically, when subjects are holding representations of objects in visual working memory, a sustained negative potential is observed over the hemisphere contralateral to the position of the objects in the visual field. This memory-related ERP component exploits the lateralization of the visual system, and as a result, is known as the contralateral delay activity (CDA) (Vogel and Machizawa, 2004; Vogel et al., 2005; Ikkai et al., 2010) [3]. This work shows that the CDA

[3] Like the precision of the N2pc to capture brain activity related to the focusing of attention, the precision of the CDA to capture visual working memory specific activity is also achieved via the contralateral control method (Gratton, 1998). Essentially, the idea here is to exploit the fact that the visual system is primarily organized in a contralateral fashion. For example, the subject fixates centrally and is presented with a bilateral display with equal amounts of stimuli in each hemifield. The subject is asked to remember or attend or make a decision about the stimuli in only one of these hemifields, and the activity of the process of interest can be isolated by examining the contralaterally specific activity with respect to

provides a measure of the objects represented in working memory, increasing in amplitude up to each individual's visual working memory capacity, provided the objects are task relevant and happen to be lateralized in the visual field when presented (Vogel and Machizawa, 2004; Vogel et al., 2005; Ikkai et al., 2010). Interestingly, the lateralized signature of the CDA is observed even though spatial location is not a task-relevant feature retained in memory. The CDA is observed when subjects need to remember the color (Vogel and Machizawa, 2004; Woodman and Vogel, 2008), orientation (Vogel et al., 2005; Woodman and Vogel, 2008), or shapes of objects (Luria et al., 2009; Ikkai et al., 2010) for an explicit, short-term memory task. The amplitude of the CDA also appears to be sensitive to the precision or quality of the object representations that are stored (Anderson et al., 2011; Machizawa et al., 2012).

The primary neuronal sources estimated to generate the CDA include frontal and parietal regions. The dorsal, posterior scalp topography of the CDA is generally consistent with a locus in the intraparietal sulcus. For example, several functional magnetic resonance imaging (fMRI) studies examining the blood oxygen level dependent (BOLD) response during visual working memory tasks have found that the intraparietal sulcus is strongly modulated by the number of items that are currently being held in memory, but reaches an asymptotic limit at approximately four items (Todd and Marois, 2004; Xu and Chun, 2006). Todd & Marois (2005) found that this intraparietal sulcus activity was sensitive to individual differences in memory capacity.

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the attended side of the display. The logic here is that most of the task-general activity (e.g., perceptual response, arousal, response preparation) will be equivalent for each hemisphere, and that the primary differences between the hemispheres will be the result of the process of interest.

Moreover, combining ERP recordings from macaque and humans, together with intracranial local field potentials from macaque, Reinhart et al. (2012) revealed a distributed neural network to generate the CDA. In particular, they found especially prefrontal areas (i.e., the frontal and supplementary eye fields) to exhibit close relationships, in terms of timing and activation levels, to memory-based behavioral performance, indicative of a contribution of these areas to the sustained surface CDA measureable at posterior electrode sites. Thus, it seems fairly unlikely that such a large and sustained ERP component is generated by a single cortical source, and is more likely the result of several coordinated sources of which frontal and parietal regions may play a significant role.

A number of recent studies have found that the CDA occurs when the information stored in memory needs to be compared to objects that can appear anywhere in the visual field (Carlisle et al., 2011; Woodman and Arita, 2011; Woodman et al., 2013; Gunseli et al., 2014; Reinhart et al., 2014; Reinhart and Woodman, 2014c, 2015b), demonstrating the utility of the CDA as a measure of target representations controlling attention in visual working memory. Specifically, as shown in **Figure 1**, when a lateralized cue is presented to a subject that indicates the target in an upcoming visual search array, it is observed that the cue elicits a CDA that continues through until the search array is presented (Woodman and Arita, 2011). In a further test of this idea, Carlisle et al. (2011) showed that when two possible targets were cued and presented in one hemifield, the amplitude of the CDA measured between the cue and the search array was twice as large as when subjects were cued to search for a single target. In addition, the amplitude of each subject's presearch CDA has been shown to predict

their search RT (Carlisle et al., 2011) or accuracy before search has even begun (Woodman and Arita, 2011), indicating that if subjects maintained a low quality representation or lost the target representation on a subset of trials, then their CDA would be smaller and their search less efficient. These findings have been replicated and extended (Gunseli et al., 2014; Reinhart et al., 2014; Reinhart and Woodman, 2014c, 2015b; Reinhart et al., 2016), and have helped establish the CDA as a direct measure of the fidelity of the target representations stored in visual working memory that are used to guide attention to task-relevant inputs in the environment.

The guidance of input selection by representations stored in long-term memory

Unlike modern theories of attention that have emphasized the importance of working memory in attentional control (Duncan and Humphreys, 1989; Bundesen, 1990; Desimone and Duncan, 1995; Bundesen et al., 2005), models of learning and skill acquisition have viewed long-term memory as the primary source for directing mechanisms of input selection (Anderson, 1982; Logan, 1988; Anderson, 2000; Logan, 2002). This proposal grows out of one of the most consistent findings in the visual search literature from the 1960s and 1970s, namely the observation that there are strong learning effects when subjects search complex scenes for the same target or set of targets trial after trial (Neisser, 1963; Nickerson, 1966; Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977). The theoretical understanding that developed from these empirical findings was that the representations providing top-down control over input selection rapidly transition between working memory and long-term memory as subjects

acquire skill and become more practiced on a task (Anderson, 1982; Logan, 1988; Rickard, 1997; Anderson, 2000; Logan, 2002), a view that has been integrated into some current theories of attention (Wolfe, 2012; Woodman et al., 2013).

To empirically evaluate the hypothesis that the representations controlling attention are transferred from working memory to long-term memory given sufficient practice on a task, researchers have used a unique set of ERP tools that independently measure the contributions from visual working memory and long-term memory. As discussed above, the CDA can be used to track the involvement of subjects' visual working memory representations. However, a separate component, called the anterior P1 or P170, has been shown to directly measure the accumulation of long-term memory representations. The anterior P1 is a frontocentral positivity observable during memory tasks using simple geometric shapes (Voss et al., 2010), and appears to reflect the accumulation of information that supports successful recognition via familiarity (Tsivilis et al., 2001; Duarte et al., 2004; Friedman, 2004; Diana et al., 2005). This waveform is more negative when a given stimulus has previously been stored in long-term memory and is encountered again. The CDA indexing visual working memory and the anterior P1 indexing long-term memory can be measured simultaneously during each trial of the visual search task shown in **Figure 1** with essentially no overlap between these ERPs due to differences in latency and scalp distribution (Woodman et al., 2013). Thus, by measuring these components simultaneously and tracking their dynamics on trial after trial during practice it has been possible to empirically establish how the representations from different memory stores contribute to controlling attention over a short period of learning.

As compared with the CDA and N2pc, less is known about the neuronal origins of the anterior P1. The characteristics of the anterior P1 are consistent with the characteristics of the neurocognitive processes indexed by similar potentials. In particular, vertex positive potentials (i.e., frontal-central, early positive potentials between 120 and 200 ms), which can be elicited selectively by certain categories of stimuli (e.g., faces or letterstrings relative to other objects), show temporal and spatial characteristics similar to the anterior P1 (Schendan et al., 1998; Rossion et al., 2003). Vertex positive potentials are accompanied by the N170, and these potentials, like the anterior P1, are modulated for old relative to new stimuli that are encountered in a variety of memory tasks. Research suggests that vertex positive potentials and the N170 may be generated from ventral occipitotemporal and fusiform cortices (Allison et al., 1999; Joyce and Rossion, 2005). However, the scalp distribution of the frontopolar anterior P1 is more consistent with an origin in anterior prefrontal cortex, and work combining electrical brain stimulation and recordings of the anterior P1 suggest that regions of medial-frontal cortex may play a significant role in anterior P1 production (Reinhart and Woodman, 2015b).

A number of experiments have now provided clear evidence indicating that the dominant source of controlled processing during learning shifts between the working and long-term memory systems (Carlisle et al., 2011; Woodman et al., 2013; Gunseli et al., 2014; Reinhart et al., 2014; Reinhart and Woodman, 2014c, 2015b), as predicted by theories of learning and automaticity (Anderson, 1982; Logan, 1988; Rickard, 1997; Anderson, 2000; Logan, 2002). In these experiments, subjects were cued on each trial to look for a specific target object while ERPs were recorded. The critical manipulation

was that intertrial target repetitions were built into the task. That is, across short runs of trials (typically three to seven trials long), subjects were cued to search for the same target object on trial after trial before the identity of the target changed and subjects had to begin searching for a new target object. At the start of these short bursts of learning, subjects were relatively slow in responding, and exhibited a relatively large CDA, indicating that the cued target controlling subsequent search was primarily represented in visual working memory. However, as subjects repeatedly searched for the same target object, their RTs became faster reflecting their attention becoming more finely tuned to the target objects across trials. During this period of attentional tuning (or learning), the CDA rapidly decreased in amplitude, exactly as expected if working memory was giving up attentional control. Importantly, while the CDA was disappearing, the anterior P1 was systematically growing in negative amplitude, indicating that subjects' were laying down a more enduring long-term memory of the cued object and these target representations in long-term memory were beginning to guide attention in the visual search task. That performance improvements (indexed by RT speeding) were accompanied by decreasing working memory contributions (indexed by the CDA) and increasingly long-term memory contributions (indexed by the anterior P1) is consistent with the known efficiencies associated with long-term memory-guided attention (e.g., Logan, 1988). These results also conform to the predictions from theories of learning and skill acquisition about how the control parameters that guide selection are encoded in memory representations that rapidly transition between working and long-term memory during learning.

The theoretical and empirical insights reviewed above provide the basis for the experiments conducted in the present study. Specifically, measuring the N2pc in conjunction with the CDA and anterior P1 offers a unique approach to distinguish between the top-down signals guiding attention (with the CDA and anterior P1) versus the implementation of attention to task-relevant items (with the N2pc). I will use these measures of the different aspects of attention to better determine the underlying nature of impaired attention in schizophrenia.

Impaired attention in schizophrenia: A closer look at the gaps in our knowledge

Abnormalities of attention form the core of cognitive symptoms in schizophrenia, (Shakow, 1962; Nuechterlein and Dawson, 1984; Green, 1996; Green et al., 2000), and have a long tradition in theories of cognitive dysfunction in the illness (Nuechterlein and Dawson, 1984). However, there are numerous empirical discrepancies in the literature on schizophrenia attentional dysfunction that have led to debate over its nature and revealed that our current understanding of the dysfunction remains largely incomplete. In this dissertation, I will attempt to reconcile these long-standing discrepancies and provide greater insight into the specific mechanisms underlying impaired attention in schizophrenia.

The history of the attentional impairment in schizophrenia stretches back to the first clinical descriptions of the illness. For example, Kraepelin (1896) noted that patients with schizophrenia commonly “lose both inclination and ability on their own initiative to keep their attention fixed for any length of time” (pp. 5-6). Bleuler (1911) stated “The

general tendency to fatigue in some cases also causes the rapid dwindling of attention (p. 69)." Similarly, Shakow (1962) described the inability to maintain a major task set, that is, to keep up a state of readiness to respond to an upcoming stimulus, as central to schizophrenia. More recently, Green, in reviewing the literature, concluded that attentional processing deficits are characteristic of schizophrenia, driving much of the functional disability in the illness (Green, 1996; Green et al., 2000). Thus, there has been robust historical continuity in emphasizing the importance of impaired attention in schizophrenia, starting with the earliest clinical descriptions and definitions of the disorder.

Empirical tests of the hypothesized attentional deficits in schizophrenia have been reliably demonstrated, consistent with the history of intuition and clinical observations in the field. However, the precise mechanisms driving these impairments are unclear and heavily debated. A case in point is the large body of evidence for impaired attention in schizophrenia using continuous performance tasks, in which objects are presented at a constant rate, typically one per second, and interleaved target objects require a response. Because these tasks demand continuous focus rather than short bursts of attentional effort, performance on these tasks has face validity as manipulating selection-guidance processes. Patients with schizophrenia and their relatives display consistently lower target detection and more errors of commission on these tasks relative to control subjects (Wang et al.; Orzack and Kornetsky, 1966; Wohlberg and Kornetsky, 1973; Rutschmann et al., 1977; Nuechterlein, 1983; Cornblatt et al., 1989; Obiols et al., 1992; Pandurangi et al., 1994; Pigache, 1996; Buchanan et

al., 1997; Ito et al., 1997; Chen et al., 1998; Seidman et al., 1998; Egan et al., 2000; Jones et al., 2001; Liu et al., 2006; Tsuang et al., 2006; Birkett et al., 2007).

In most cases, impairment on continuous performance tasks has been interpreted as a deficit in the control of attention (or selection guidance). However, this view ignores the potential contribution of other processes, such as the adequacy of perception and input selection. Second, this interpretation does not recognize that different memory systems mediate the accurate guidance of selection, which may be disproportionately contributing to the behavioral impairment. Third, inferences from the continuous performance task results are based on behavioral measures, which are indices of the output of all of the computations performed during the task, and are thus incapable of disentangling the influence of the various sub-processes engaged during the task leading up to the behavior response. Although impairments have been reliably observed in several versions of the continuous performance tasks, it is unclear what specific selection-guidance processes are disrupted, or whether these impairments reflect a deficit in controlling attention at all.

One piece of unambiguous evidence of a deficit in selection guidance in patients relative to controls would be a demonstration that patients display a stronger decrease in target detection over time. This would capture the spirit of the construct by showing that the holding of attention over time, specifically, leads to problems, as opposed to suboptimal functioning of other processes at any given moment. None of the above-cited studies identified such an outcome, although only 4 out of the 20 studies reported testing for it, and the short task times of less than 10 minutes may have prohibited behavioral decrements over time. There are a few studies of this with perceptually

difficult visual continuous performance tasks, around 10 minutes in length (Nestor et al., 1990; Mass et al., 2000; Park et al., 2011) and with a 5-minute auditory versions of the task (Pigache, 1999). A trend effect was also seen by Nuechterlein (1983). Overall, however, these studies are massively outnumbered by reports using the same or similar versions of the continuous performance task that did not find a larger performance decrease over time in patients, yet it is unclear how many of these studies actually tested for it. The great lack of evidence of such a finding in patients led Nuechterlein et al. (1994) to suggest, “although the vulnerability-linked deficit in information processing is revealed in a task that demands sustained attention, the critical deficit might not be in sustained attention per se.” Similarly, based on the consistent absence of a decline in continuous performance task behavior over time, Cornblatt and Keilp (1994) concluded that a dysfunctional selection-guidance mechanism is not the critical deficit in patients. Still, deficits of patients on the continuous performance task continue to be construed as attentional control deficits, and conflict over this matter has greatly slowed progress for our understanding of impaired cognition in schizophrenia.

Similar to selection-guidance deficits, there has been equally great empirical ambiguity and controversy over the deficits of input selection in schizophrenia. Several studies have used visual search or similar experimental tasks to examine input selection in patients, yet none of them have definitively addressed the question of whether impaired input selection underlies the attentional abnormality in schizophrenia. For example, Lieb et al. (1994) used a texture discrimination task to investigate input selection and selection guidance in patients and concluded that deficits in visual information processing in such patients were confined to the input-selection process.

However, RTs of healthy subjects in this task, which Lieb et al. (1994) hypothesized would reflect the input-selection process, were greater than 700 ms. Such long RTs are usually taken as indicating serial, controlled processing, rather than parallel, automatic processing. Carr et al. (1998a, b) used a visual search task to determine whether patients with schizophrenia showed deficits in input-selection processing and concluded that their results provided no firm evidence of any deficits. However, a close inspection of their RT functions (Carr et al., 1998a) (Fig. 1, p. 157), shows that the slopes of the healthy control subjects in the feature search task were near zero in the target-present trials but clearly larger than zero in the target-absent trials, suggesting that their feature task may have been performed in a serial manner even by the healthy subjects and was inadequate for investigating the input-selection process. Alain et al. (2002) used a visual search task and ERPs to investigate performance during single feature and feature conjunction detection in patients with schizophrenia, concluding that patients have deficits not in single feature processing, but in integrating visual features. However, they did not show differences in slope between patients and healthy subjects on the feature search tasks and the conjunction search tasks. A problem common to previous studies (e.g., Mori et al., 1996) has been an inadequate examination of the experimental tasks. Further studies are clearly required to assess the integrity of input selection, as distinct from selection guidance, in patients with schizophrenia.

Given the conflict over the attentional impairment in the schizophrenia literature, it is worth considering what exact processes of attention are in fact disrupted in this disorder. The contributions of the present dissertation research in answering this critical question are three-fold. First, to overcome confusion in the literature focused on

attentional impairments in schizophrenia, I will conceptually fractionate the complex set of operations of attention into their component parts. Specifically, I will draw on decades of theoretical understanding from the cognitive psychology of attention, which divides the construct of attention into selection-guidance and input-selection processes. Second, studies of attention in schizophrenia typically rely on behavior as the single outcome measure, yet we know a subject's response is the product of many complex computations, and thus performance alone is a highly underspecified and course-gained metric of attention. To overcome this, I will use ERP tools combined with a novel behavioral paradigm that allows for the measurement of the distinct components of attentional processes, including the different memory representations controlling attention and the implementation of attention itself. Of note, no study to date has examined the memory representations guiding input selection in patients with schizophrenia, underscoring the novelty of the present research. Third, most studies in the schizophrenia literature use correlational methods, in which researchers relate the modulations of behavior and neural activity with the manipulations of the stimulus demands in a task. Despite the usefulness of this approach, a more robust understanding of the attentional dysfunction in schizophrenia requires studies that afford causal control over the brain and behavior. In this proposal, I will move beyond correlational results and use a causal neuroscientific technique to gain greater understanding of the processes underlying the attentional abnormality in schizophrenia.

Understanding the nature of the attentional dysfunction in schizophrenia would impact the mental health of many patients with this debilitating disorder. By better understanding the nature of the disorder, it should be possible to better treat the

underlying deficits. For example, if it turns out that the attentional dysfunction in schizophrenia is due to underlying memory problems, then treating this cognitive deficit would be more similar to the treatment of memory disorders. However, if the attentional dysfunction is accounted for with a model in which the focusing of attention itself is abnormal, then this means that the deficits are in the sensory information processing streams themselves. The largest potential translational impact of this research is in the development of noninvasive electrical stimulation to directly treat the cognitive deficits that we observe. It is possible that the experiments of this project could translate into drug-free, therapeutic interventions in the short term.

Objectives

Here, I will combine visual search tasks, electrophysiological responses of the brain, and noninvasive electrical stimulation to test specific hypotheses regarding the nature of attention in healthy people and people with schizophrenia. Visual search tasks are one of the most common attention-demanding tasks in our lives. When we look for our keys in our office, obstacles on the roadway, or an apple at the grocery store, we are performing visual search (Wolfe, 2003). When we are preparing to look for a specific object in our environment, we activate memory representations of the target we are about to search for in visual working memory and long-term memory (Woodman et al., 2013), and use these representations to guide the deployment of our attention to relevant inputs in our environment. My electrophysiological analyses will focus on the relationships between visual working memory, long-term memory, and shifts of

perceptual attention while subjects analyze complex visual scenes for target objects. The ERP technique has exceptional temporal resolution allowing me to distinguish between these different loci of the deficits in the patients. In addition, decades of ERP research have established a set of measures that can be recorded simultaneously to determine the contributions of both visual working memory (i.e., the CDA) and long-term memory (i.e., the anterior P1) in the control of attention as well as the implementation of attention itself (i.e., the N2pc) (Luck and Kappenman, 2012). In this project, I will combine these ERP measures with noninvasive electrical brain stimulation to determine whether it is possible to change how subjects control and use attention during visual search. The primary research goals of this project are to develop a novel approach for understanding the nature of attention in the healthy brain, and to elucidate the disease mechanisms of schizophrenia attentional dysfunction. The broader goal of this research is to achieve concrete translational progress for developing a novel drug-free intervention to remediate cognitive deficits in patients with schizophrenia.

The aims of this dissertation are as follows:

Aim 1) I will use electrophysiology and noninvasive brain stimulation to understand the mechanisms of attention in the healthy brain.

The processes of selection guidance derive from cognitive control regions of medial-frontal cortex. I will test this hypothesis by noninvasively stimulating regions of medial-frontal cortex in healthy adults, and then examining the processes of selection guidance and input selection as subjects search for target objects in cluttered visual scenes. I predict that stimulation over medial-frontal

cortex will preferentially augment selection guidance with downstream effects on the focusing of attention and search behavior.

Aim 2) I will use a novel combination of electrophysiological tools and brain stimulation to understand the nature of impaired attention in schizophrenia.

a. Attentional dysfunction in patients with schizophrenia is due to abnormal selection guidance, not input selection. I will test these competing hypotheses by examining the visual working memory and long-term memory representations that control attention (i.e., selection guidance) and the implementation of attention (i.e., input selection) as patients analyze complex visual scenes for certain target objects. If impaired attention derives from selection-guidance abnormalities, patients will be unable to effectively transfer representations controlling attention from working memory to long-term memory. However, if impaired attention derives from input-selection abnormalities, patients will be unable to effectively focus attention during the efficient processing of complex scenes.

b. Dysfunctional processes of selection guidance in schizophrenia are due in part to an abnormality in the cognitive control regions of medial-frontal cortex. I will test this hypothesis by noninvasively stimulating regions of medial-frontal cortex in patients with schizophrenia, and then examining the processes of selection guidance and input selection as patients search for target objects in cluttered visual scenes. I predict that the stimulation will improve selection guidance with downstream effects on the focusing of attention and search behavior.

CHAPTER 2

UNDERSTANDING THE MECHANISMS OF ATTENTION IN THE HEALTHY BRAIN

Introduction

The cognitive and neural mechanisms that tune visual attention to select certain targets are not completely understood despite decades of intensive study (Wolfe and Horowitz, 2004; Gilbert and Li, 2013). Attention can clearly be tuned to certain object features (i.e., like tuning a radio to a specific station, also known as an attentional set), but how this occurs as we search for certain objects in our environment is still a matter of debate. The prevailing theoretical view is that working memory representations of target objects provide top-down control of attention as we perform visual search for these objects embedded in arrays of distractors (Duncan and Humphreys, 1989; Bundesen, 1990; Desimone and Duncan, 1995; Bundesen et al., 2005; Olivers et al., 2011). However, an alternative view is that long-term memory representations play a critical role in the top-down control of attention, enabling us to guide attention based on the more enduring representations of this memory store (Chun, 2000; Logan, 2002; Moores et al., 2003; Summerfield et al., 2006; Hutchinson and Turk-Browne, 2012; Stokes et al., 2012; Võ and Wolfe, 2012; Wolfe, 2012; Woodman et al., 2013). To distinguish between these competing theoretical perspectives, we used transcranial

direct-current stimulation (tDCS) to causally manipulate activity in the brain (Nitsche et al., 2008; Reinhart and Woodman, 2015a), and combined this causal manipulation of neural activity with electrophysiological measurements that are hypothesized to index the working memory and long-term memory representations that guide visual attention to task-relevant target objects.

To determine the nature of the working memory and long-term memory representations that control visual attention during search, we simultaneously measured two separate human event-related potentials (ERPs) (Carlisle et al., 2011; Woodman et al., 2013; Reinhart and Woodman, 2014c). The contralateral delay activity (or CDA) of subjects' ERPs provides a measure of the maintenance of target object representations in visual working memory (Vogel and Machizawa, 2004; Vogel et al., 2005). The CDA is a large negative waveform that is maximal over posterior cortex, contralateral to the position of a remembered item. This large amplitude lateralized negativity is observed even when nonspatial features are being remembered, and persists as information is held in working memory to perform a task. A separate component, termed the anterior P1, or P170, is hypothesized to measure the buildup of long-term memory representations. The anterior P1 is a positive waveform that is maximal over frontal cortex and becomes increasingly negative as exposures to a stimulus accumulate traces in long-term memory (Voss et al., 2010; Woodman et al., 2013; Reinhart and Woodman, 2014c). This component is thought to reflect the accumulation of information that supports successful recognition of a stimulus on the basis of familiarity (Tsivilis et al., 2001). For example, the anterior P1 amplitude can be used to predict subsequent recognition memory for a stimulus observed hundreds of stimuli in the past (i.e., across

minutes to hours of time (Tsivilis et al., 2001). We used simultaneous measurements of the CDA and anterior P1 to determine the role that working memory and long-term memory representations play in the tuning of attention following brain stimulation.

Our tDCS targeted the medial-frontal region in our first experiments (**Fig. 3A**) because anodal stimulation of this area results in rapid improvement of simple visual discriminations relative to baseline sham conditions (Reinhart and Woodman, 2014a). If it is possible to induce rapid improvements in the selection of targets among distractors as humans perform search, then the competing theories of visual attention would account for the accelerated tuning of attention in different ways. The theories that propose working memory representations provide top-down control of visual attention predict that the stimulation-induced improvement in visual search will be due to changes in the nature of the visual working memory representations indexed by the CDA component (see **Fig. 1**). Specifically, the CDA elicited by the target cue presented on each trial should increase in amplitude relative to sham conditions to explain the improvement of attentional selection during search. This is expected if working memory driven theories of attention are correct based on previous evidence that the CDA is larger on trials of a short-term memory task when performed correctly compared to incorrect trials (Vogel and Machizawa, 2004). In contrast, theories that propose long-term memory representations rapidly assume control of attention during visual search, predict that the stimulation-induced improvement will be due to changes in the long-term memory representations indexed by the anterior P1 elicited by the target cue presented on each trial. Specifically, we should see the anterior P1 exhibit a more negative potential as search improves following stimulation.

Each subject completed anodal and sham tDCS sessions on different days with order counterbalanced across subjects (N=18). Immediately after 20 minutes of tDCS over medial-frontal (Experiments 1 and 2) or right parietal regions of the head (Experiment 3) (see **Figs. 3A** and **8A** for current flow models and **tDCS modeling results** below for addition information), we recorded subjects' ERPs while they completed a visual search task. In this search task, the target was cued at the beginning of each trial (**Fig. 1**). The task-relevant cue signaled the identity of the target that could appear in the search array presented a second later. In Experiments 1 and 3 the targets and distractors were Landolt-C stimuli, and in Experiment 2 they were pictures of real-world objects. A task-irrelevant item was presented with each cue to balance the hemispheric visual input so that the lateralized ERPs that elicit the CDA could be unambiguously interpreted (Woodman, 2010). The key manipulation in this task was that the target remained the same for 3-7 consecutive trials (length of run randomized) before it was changed to a different object. These target repetitions allowed us to observe attentional tuning becoming more precise across trials.

Methods

Subjects

Fifty-four subjects (Experiment 1, N=18, 5 women, mean age ± SD, 21.9 ± 3.4; Experiment 2, N=18, 6 women, 21.2 ± 3.4; Experiment 3, N=18, 5 women, 23.2 ± 4.9) with normal color vision and normal or corrected-to-normal visual acuity gave their

informed written consent to participate in the study approved by the Vanderbilt University Institutional Review Board.

Stimuli

After anodal or sham tDCS, subjects performed a visual search task in which the target was cued on each trial (**Fig. 1, 5A**). Stimuli were viewed from 114 cm on a gray background (54.3 cd/m^2). A black fixation cross (<0.01 cd/m^2, 0.4 × 0.4° of visual angle) was visible throughout each trial. Cue stimuli were presented 2.2° to the left or right of the center of the monitor, and search stimuli were arranged similar to the number of locations on a clock face, 4.4° from the center of the monitor. In Experiments 1 and 3, the cue array contained 1 red (x = 0.612, y = 0.333, 15.1 cd/m^2) and 1 green (x = 0.281, y = 0.593, 45.3 cd/m^2) and the search array contained 1 red, 1 green, and 10 black distractor (<0.01 cd/m^2) Landolt-C stimuli (0.88° diameter, 0.13° thick, and 0.22° gap width), of 8 possible orientations (0°, 22.5°, 45°, 67.5°, 90°, 112.5°, 135°, 157.5°). In Experiment 2, the elements in the cue and search arrays were pictures of real-world objects (subtending 1.75 x 1.75 of visual angle) drawn from > 2600 categorically distinct images (Brady et al., 2008). The cue array contained 1 “dog” category image (out of 8 possible) and 1 “bird” category image (out of 8 possible), outlined in a red (x = 0.612, y = 0.333, 15.1 cd/m^2) or green circle (x = 0.281, y = 0.593, 45.3 cd/m^2; 0.13° thick, 2° diameter) to mark the task-relevant, real-world image with a unique color, and allow the cue stimuli to be free from perceptual confounds. The search array contained 1 “dog” category image, 1 “bird” category image, outlined in a red or green circle, and

10 inanimate black and white distractor images (out of 8 possible) outlined in black circles (<0.01 cd/m^2). These circles made it so that search could be completed within 2000 ms, without excessive saccadic eye movements, and the N2pc to the target image unambiguously measured. The target shape (Experiments 1 and 3) and circle outlining the real world target object (Experiment 2) could only appear in the task-relevant color. The task-relevant color in Experiments 1 and 3 (i.e., red or green) and the task-relevant real world object category in Experiment 2 (i.e., dog or bird) of the cue stimulus were determined prior to the start of each experiment, counterbalanced across subjects to rule out physical stimulus confounds (Woodman, 2010).

Trial and inter-trial structure

Each trial began with fixation (1200-1600 ms). Next, two cue stimuli were presented for 100 ms, followed by a 1000 ms interval during which we measured the CDA and anterior P1. Then, the search array was presented for 2000 ms. The inter-trial interval was 1200-1600 ms, randomly jittered with a rectangular distribution. In all experiments, a target was presented in half of the search arrays and matched the shape (Experiments 1 and 3) or picture (Experiment 2) of the task-relevant cue. Every search array contained an item that matched the color of the cue object (i.e., the possible target), but on target absent trials this object had a different shape. Subjects responded as quickly and accurately as possible to the search array by pressing one button on a handheld gamepad (Logitech Precision) with their right hand for target present, and a different button with their right hand for target absent.

Target presence (present or absent) and the target location, when present, were randomly selected on each trial. The same target was cued across a run of 3, 5 or 7 trials randomly varying in length, with the identity of the target randomly selected for each run without repetition in adjacent runs. Each subject completed 720 trials in each condition (sham and anodal).

Transcranial direct-current stimulation

We used tDCS because it is an effective, noninvasive technique for directly manipulating cortical brain activity by passing a weak electrical current through electrodes placed on the scalp. The tDCS was administered using a battery driven, constant current stimulator (Mind Alive Inc., Alberta, Canada) and pair of conductive rubber electrodes (active: 19.25 cm^2 reference: 52 cm^2). The electrodes were placed in saline-soaked synthetic sponges and held in place by a headband. The reference (or cathodal) electrode was placed on the center on the right cheek to avoid any confounding effects from other brain regions (Berryhill et al., 2010; Hsu et al., 2011; Tseng et al., 2012; Reinhart and Woodman, 2014a). Specifically, the cheek electrode was placed diagonally, 3 cm from the cheilion (lip corner at rest) along an imaginary line connecting the cheilion to the ipsilateral condylion (palpable when the jaw is moved) (**Fig. 3A**).

Current at the anodal electrode was applied for 20 minutes at 2.0 mA intensity over the medial-frontal region (site FCz, from the International 10-20 System) for Experiments 1-2, and over the right parietal region (site P2) for Experiment 3. Similar

stimulation protocols to the one we used here have produced effects on behavior and electrophysiology lasting up to 4.8 hrs (Reinhart and Woodman, 2014a). These enduring effects are believed to reflect the induction of cortical plasticity from anodal stimulation having depolarized the resting state cell membrane potentials, leading to increased neuronal excitability (Nitsche et al., 2008). A sham tDCS condition was administered following an identical procedure, but stimulation only lasted 30 seconds, ramping up and down at the beginning, middle, and end of the 20-minute period to simulate the periodic tingling sensation often endorsed by subjects on active testing days. Debriefing questions confirmed that subjects were blind to the presence of stimulation.

Electrophysiological recordings

The EEG was acquired (250 Hz sampling rate, 0.01-100 Hz band-pass filter) using an SA Instrumentation Amplifier from 21 tin electrodes, including 3 midline (Fz, Cz, Pz), 7 lateral pairs (F3/4, C3/4, P3/4, PO3/4, T3/4, T5/6, O1/2), and 2 nonstandard sites (OL, halfway between O1 and T5; and OR, halfway between O2 and T6), arrayed based on the International 10/20 System and embedded in an elastic cap (Electrocap International). The right mastoid electrode served as the online reference, and signals were re-referenced offline to the average of the left and the right mastoids (Nunez, 1981). The electrooculogram (EOG) was recorded using bipolar electrodes placed 1 cm lateral to the external canthi to measure horizontal eye movements and bipolar electrodes above and beneath the left eye to measure vertical eye movements and

blinks. Trials containing incorrect behavioral responses or ocular or myogenic artifacts were excluded. A two-step ocular artifact rejection method was implemented (Woodman and Luck, 2003a), resulting in the removal of 1 subject from Experiment 1, and 2 subjects from Experiment 3 for excessive eye movements (either > 25% of individual trials rejected or any residual systematic eye movement that resulted in HEOG voltage deflections > 3.2 μV, corresponding to an ocular deviation of ± 0.1°). **Figures 4E**, **6E**, **9F**, and **13C** illustrate the HEOG waveforms time locked to cue and search-array targets for left and right visual hemifields, for each stimulation condition, and for each experiment. Grand average waveforms were 35 Hz low-pass filtered for presentation purposes.

Data analysis

To understand the locus of the effects following our causal manipulation of the brain, we examined six distinct ERP components, each providing a neural measure of a different cognitive mechanism (Woodman, 2010). The contralateral delay activity (CDA) was measured at lateral posterior parietal, occipital, and temporal electrode sites (PO3/4, O1/2, OL/R, and T5/6) as the difference in mean amplitude between the ipsilateral and contralateral waveforms during 300–1000 ms after target cue onset (Vogel and Machizawa, 2004; Vogel et al., 2005; Woodman and Vogel, 2008; Carlisle et al., 2011; Woodman et al., 2013; Reinhart et al., 2014; Reinhart and Woodman, 2014c). The N2pc was measured at lateral occipital electrodes (OL/R) as the mean difference in amplitude between the ipsilateral and contralateral waveforms with respect to the color

of the search target during 200-300 ms following the onset of the search array (Woodman and Luck, 1999). The anterior P1 amplitude was measured at the frontocentral electrode site (Fz) during 170–300 ms following target cue onset (Voss et al., 2010; Woodman et al., 2013; Reinhart and Woodman, 2014c). We used a liberal measurement window to capture the entirety of this anterior P1 effect across all subjects, but confirmed that all of the findings reported are also significant using the more conservative measurement window of 170-200 ms post cue onset (all $p < 0.05$). The posterior P1 and N1 were measured from lateral occipital electrodes (OL/R) from 75 to 100 ms and 125 to 175 ms, respectively, after search array onset, quantified as mean amplitude (Luck and Hillyard, 1990). The lateralized readiness potential (or LRP) was measured from central lateral electrodes (C3/4) during the time window from -200 to 0 ms relative to correct response onset as contralateral-minus-ipsilateral waveforms with respect to the right hand used for the button-press responses (Smulders and Miller, 2012). The LRP amplitude was defined as mean amplitude in the window from LRP onset until response, and the LRP onset latency was defined as the time point at which the voltage reached 50% of the peak amplitude (Miller et al., 1998). All ERP components were baseline corrected 200 to 0 ms prior to the relevant stimulus-locking event, except for the LRP corrected 800 to 600 ms prior to response (Smulders and Miller, 2012).

We computed analyses of variance (ANOVAs) using the within-subjects factors of stimulation condition (anodal vs. sham), target repetition (1 vs. 2-4 vs. 5-7), and target color laterality (contralateral vs. ipsilateral) on RT and the amplitudes of the anterior P1, CDA, N2pc, posterior P1, N1, and LRP. Binning repetition trials increased

statistical power across same-target runs, allowing us to obtain robust measures of the components of interest, consistent with prior work (Voss et al., 2010; Woodman et al., 2013; Reinhart and Woodman, 2014c). Preplanned single degree of freedom contrasts were performed on the first two serial positions in a run of same-target trials to assess the speed of attentional tuning after a single instance of using a target for search. To correct for multiple comparisons, we used Fisher's Least Significant Difference (LSD) tests. P-values were adjusted using the Greenhouse-Geisser epsilon correction for nonsphericity when this assumption was violated (Jennings and Wood, 1976).

Current-flow model

To increase our precision in reasoning about the effects of tDCS in the brain, we computed a computational forward model of tDCS current flow. Our model of tDCS current flow was informed by previously established methods (De Lucia et al., 2007; Wagner et al., 2007; Sadleir et al., 2010; Bikson et al., 2012). This involved 1) magnetic resonance imaging (MRI) segmentation, 2) electrode placement, 3) generation of a finite element model and 4) computation. We used the Montreal Neurological Institute (MNI) T1-weighted MRI reference brain from the CURRY 6.0 multimodal neuroimaging software (Compumedics Neuroscan). A combination of automated and manual segmentation tools was used to obtain tissue masks, including Gaussian filters, and morphological and Boolean operations implemented in Matlab (MathWorks, Natick, MA). Unlike previous models using simple geometries (e.g. spheres), we exploited realistic volumetric head geometries with a numerical solver Finite Element Method, as

this procedure should capture realistic sulci and gyri anatomy of the cortical surface, improving the precision of our tDCS model. Volumetric mesh was generated from the segmented data (> 140,000 vertices, > 800,000 tetrahedral elements). Segmented compartments and their respective isotropic electrical conductivities (in S/m) included: skin (0.33), skull (0.0042), and brain (0.33). In short, the production of meshes is a process where each mask is divided into small contiguous elements, which allow the current flow to then be numerically computed.

Our forward computation using a finite element model was implemented in SCIRun (available as open source software: http://software.sci.utah.edu). We simulated current flow with a bipolar electrode configuration including the anode (19.25 cm^2) centered over FCz (Experiments 1-2) or P2 (Experiment 3), and the cathode (52 cm^2) centered over the right cheek between the zygomaticus major and the condylion. Current density corresponding to 2.0 mA total current was applied at the anodal electrode and ground was applied at the cathodal electrode.

To determine the distribution of electrical potential inside the human tissues, the Laplace equation

$$\vec{\nabla} \bullet (\sigma \vec{\nabla} \varphi) = 0$$

(φ: potential, σ: conductivity) was solved and the following boundary conditions were used. Inward current flow = J_n (normal current density) was applied to the exposed surface of the anode. The ground was applied to the exposed surface of the cathode. All other external surfaces were treated as insulated. Plots showing the path of electrical field magnitude through brain tissue were generated in Matlab. We chose to illustrate the solutions in units of electric field (V/m) because the electric field in the brain is

directly related to neuronal activation, and for varied resistivity, the electric field, unlike current density, provides sufficient information to predict activation. Lastly, although the steps in tDCS modeling are the same, differences in protocols across publications can result in meaningful differences in current flow solutions. Thus, it is important to stress that our tDCS model serves only as a working hypothesis for where the trajectory of electrical field passes through the brain given our specific tDCS montages.

Results

Experiment 1

Primary results

We found that anodal medial-frontal tDCS in Experiment 1 accelerated the rate of attentional tuning across trials as evidenced by the speed of behavior and attention-indexing ERPs elicited by the search arrays (**Fig. 3B-C**). First, in the baseline, sham condition we observed that subjects became faster at searching for the target across the same-target runs of trials, as shown by reaction time (RT) speeding ($F_{2,34}$ = 6.031, p = 0.007) (see **Figs. 4A-B** and the **Supplemental results** below for additional analyses of the sham condition and to verify the absence of effects on accuracy). However, following anodal stimulation subjects' RTs dramatically increased in speed, such that search RTs reached floor levels within a single trial. This striking causal aftereffect of anodal tDCS was evidenced by a stimulation condition x target repetition interaction on RTs ($F_{2,34}$ = 3.735, p = 0.042), with this RT effect being significant between the first two

trials of search for a particular Landolt C ($F_{1,17}$ = 6.204, p = 0.023), but no significant change thereafter (ps > 0.310). Additionally, by fitting these behavioral RT data with a logarithmic function to model the rate of improvement (Logan, 2002) we found that anodal tDCS significantly increased the rate parameters of RT speeding ($F_{1,17}$ = 5.097, p = 0.037).

Consistent with the interpretation that tDCS changed how attention selected the targets in the search arrays, we found that the N2pc component, an index of the deployment of covert attention to the possible target in a search array (Woodman and Luck, 1999), showed a pattern that mirrored the single-trial RT effects ($F_{1,17}$ = 4.792, p = 0.043) (see **Fig. 1C**, and **Fig. 4A** in **Supplemental results** below for N2pc waveforms). However, other ERP components indexing lower-level perceptual processing or late-stage response selection during search were unchanged by the tDCS (see **Table 1** and **Fig**. **4C-D** in the **Supplemental results** below). Our findings demonstrate that the brain stimulation only changed the deployment of visual attention to targets in the search arrays and did not change the operation of any other cognitive mechanism we could measure during the visual search task. Thus, by delivering electrical current over the medial-frontal area we were able to causally accelerate the speed with which subjects tuned their attention to select the task-relevant objects.

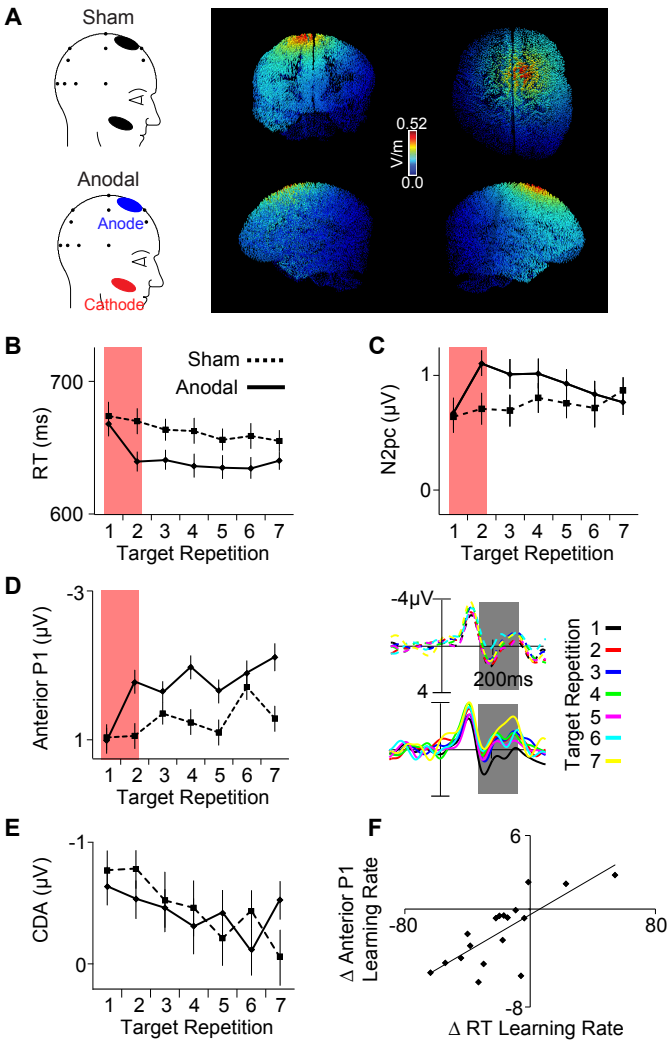

Figure 3. Transcranial direct-current stimulation (tDCS) montage and model targeting medial-frontal regions, and the primary results from Experiment 1. A. To the left is the tDCS montage with frontocentral midline anode paired with a right cheek cathode for sham and anodal stimulation conditions. To the right is the modeled distribution of electrical current projected onto top, frontal, and lateral views of a 3D reconstruction of the cortical surface. This montage was used in Experiments 1, 2, and 4 to manipulate regions of medial-frontal cortex. Mean RTs (**B**), N2pc amplitudes (**C**), anterior P1 amplitudes (**D**), and CDA amplitudes (**E**) shown across target repetitions for sham (dashed) and anodal (solid) conditions from Experiment 1. Error bars are ± 1 standard error of the mean. Red shading highlights dynamics across trials 1-2. Grand average event-related potential waveforms from the frontal midline electrode (Fz) synchronized to cue onset shown across target repetitions for sham (dashed) and anodal (solid) conditions. The measurement window of the anterior P1 is shaded in grey. **F**, The relationship between logarithmic rate parameters enhancements for mean anterior P1 amplitude and RT after anodal stimulation relative to sham.

To determine whether the tDCS-induced attentional improvements were caused by changes in working memory or long-term memory mechanisms of top-down control,

we examined the hypothesized neurophysiological signatures of visual working memory (i.e., the CDA) and long-term memory (i.e., the anterior P1) elicited by the target cues. Given the rapid tuning of attention following tDCS relative to sham, we might expect the flexible working memory system to underlie this effect. Contrary to this intuition, we found that the rapid, one-trial improvement in attentional tuning following medial-frontal tDCS was mirrored by changes in the hypothesized neural index of long-term memory, but left the hypothesized neural index of working memory unchanged (**Fig. 3D-E**). **Figure 3D** shows that the accelerated effects of attentional tuning caused by anodal stimulation were preceded by a rapid increase in negativity of the anterior P1 across same-target trials, mirroring the rapid, single-trial improvement in RT and the N2pc as the search array was analyzed. This was confirmed statistically by a significant stimulation condition x target repetition interaction on the anterior P1 amplitude ($F_{2,34}$ = 3.797, p = 0.049), and most dramatically between the first two trials of search ($F_{1,17}$ = 5.816, p = 0.027), with no significant pairwise changes in anterior P1 amplitude thereafter (ps > 0.707). Logarithmic model fits showed that the rate parameters of the anterior P1 significantly increased after anodal tDCS relative to the more gradual attentional tuning observed in the sham condition ($F_{1,17}$ = 5.502, p = 0.031, see **Supplemental results** below for anterior P1 analyses from the sham condition). Despite these causal changes in anterior P1 activity, neither the amplitude of the CDA ($F_{2,34}$ = 0.669, p = 0.437), nor its rate parameters ($F_{1,17}$ = 1.183, p = 0.292) significantly differed between stimulation conditions, showing the selectivity of medial-frontal tDCS on the hypothesized neural metric of long-term memory (see **Fig. 4B** and the **Supplemental results** belowfor CDA waveforms). We note that the absence of a

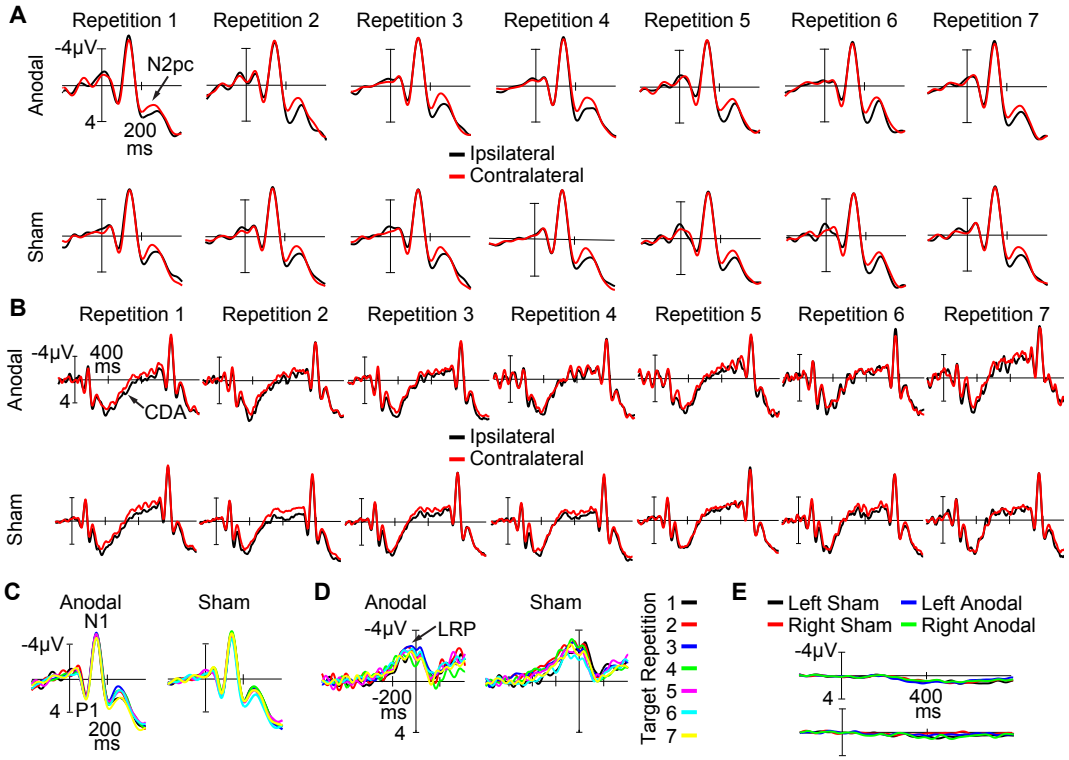

Figure 4. Sensory, response, attention, and working memory event-related potentials from Experiment 1. **A**. Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target color shown across repetitions 1-7 from anodal and sham tDCS conditions. **B**, Cue locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target shown across repetitions 1-7 from anodal and sham tDCS conditions. **C**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral with respect to target color location shown across target repetitions 1-7 from anodal and sham tDCS conditions. **D**, Response locked grand average difference waves (contralateral minus ipsilateral with respect to response hand) at central lateral sites (C3/C4) from correct trials shown across target repetitions 1-7 from anodal and sham tDCS conditions. **E**, Cue locked (top) and search array locked (bottom) horizontal electrooculogram (HEOG) waveforms for targets in the left and right visual hemifields and across tDCS conditions. Labels show the posterior P1, N1, lateralized readiness potential (LRP), N2pc, and contralateral delay activity (CDA).

stimulation induced CDA increase is not due to ceiling effects. The single target cue gave us ample room to measure such a boost of the CDA given that without brain

stimulation this memory load is far from eliciting ceiling amplitude levels for this component (Vogel and Machizawa, 2004).

If the better long-term memory representations indexed by the anterior P1 were the source of the improved search performance, then the size of the stimulation induced boost of the anterior P1 elicited by the cue should be predictive of the search performance that followed a second later. Consistent with the prediction, we found that an individual subject's anterior P1 amplitude change across the same-target runs following medial-frontal stimulation was highly predictive of the accelerated rates at which they searched through the visual search array that followed (r_{18} = 0.764, p = 0.0002) (**Fig. 3F**). Thus, the ERPs elicited by the target cues ruled out the working memory explanation of the rapid changes in attentional tuning we observed, and were consistent with the hypothesis that changes in the nature of the long-term memory representations that control attention were the source of this dramatic improvement.

Supplemental results

In the sham or baseline condition of Experiment 1, we observed evidence that attention became gradually tuned to the target object across the same-target runs of trials. As RTs became faster and N2pc amplitudes increased (**Fig. 4A**), CDA amplitudes systematically decreased ($F_{2,34}$ = 9.274, p = 0.001, **Fig 3E**, **Fig. 4B**) and anterior P1 amplitudes systematically increased ($F_{2,34}$ = 8.330, p = 0.006, **Fig 3D**) over trials in which subjects searched for the same target. Accuracy was at a mean of 96.6% correct across all trials types and did not differ across stimulation conditions or same-target runs (ps > 0.40). These findings conform to theories of learning and automaticity

(Logan, 2002), which propose that as task performance gradually improves, we rely less on working memory and increasingly on long-term memory representations to finely tune the processing of task-relevant information. Although these findings provide some support for the hypothesis that long-term memory representations play a role in controlling selection as the tuning of attention unfolds naturally, the key test of the working memory and long-term memory hypotheses of attentional control are in how they account for the rapid, one-trial improvements observed following tDCS.

In Experiment 1, we show that this gradual tuning of perceptual attention to simple objects can be enhanced after 20 minutes of brain stimulation over the medial-frontal region. We found that this enhancement in attentional control was caused by a selective influence on the hypothesized electrophysiological index of long-term memory (i.e., the anterior P1, see **Fig. 3D**) while leaving the electrophysiological index of working memory unchanged (**Fig. 3E**, **Fig. 4B**). To further test the specificity of the medial-frontal brain stimulation in Experiments 1 to affect only long-term memory driven attentional tuning, we examined other electrophysiological components known to index other cognitive mechanisms, including those associated with low-level perceptual processing and late-stage response selection. We found that medial-frontal tDCS did not have a significant affect on these ERP components, strengthening the interpretation that the improvements in attentional tuning that we observed following brain stimulation were due to the specific manipulation of information in long-term recognition memory.

Figure 4C-D shows the ERP components from Experiment 1 related to early perceptual processing (i.e., the posterior P1 and N1) elicited by the search array, and the ERP component related to response selection (i.e., the lateralized readiness

potential or LRP) preceding correct behavioral responses. There were no main effects of stimulation condition or target repetition, and no interaction between stimulation condition and target repetition on the amplitudes of the posterior P1, N1, or LRP (see **Table 1** for statistical results). Thus, changes in early perceptual and late response-stage processes could not account for the enhanced attentional control we observed following medial-frontal stimulation.

The effects of anodal stimulation reported in the present study were measured relative to the baseline sham condition in the same subjects. The within-subjects experimental design is considered one of the strongest approaches in brain stimulation research. However, to confirm our results, we also calculated between-subjects statistical tests. Specifically, we compared data from subjects who received anodal medial-frontal stimulation (i.e., Experiment 1, anodal condition) against the data from a separate group of subjects who received sham posterior parietal stimulation (i.e., Experiment 3, sham condition). We found that all of the behavioral and electrophysiological results from these between-subjects analyses replicated those obtained from our within-subjects analyses reported in the main paper. This included the single-trial enhancements in anterior P1 negativity ($F_{1,17}$ = 4.325, p = 0.050), N2pc amplitude ($F_{1,17}$ = 5.190, p = 0.036), and RT speed ($F_{1,17}$ = 7.742, p = 0.013), as well as the null findings of CDA amplitude ($F_{1,17}$ = 0.164, p = 0.690) following anodal medial-frontal stimulation relative to sham.

Experiment 1	Stimulation Condition	Target Repetition	Stimulation Condition x Target Repetition
posterior P1	$F_{1,17} = 0.795$, $p = 0.385$	$F_{2,34} = 0.619$, $p = 0.482$	$F_{2,34} = 0.021$, $p = 0.919$
N1	$F_{1,17} = 0.177$, $p = 0.679$	$F_{2,34} = 0.329$, $p = 0.589$	$F_{2,34} = 0.310$, $p = 0.597$
LRP	$F_{1,17} = 0.768$, $p = 0.393$	$F_{2,34} = 2.363$, $p = 0.116$	$F_{2,34} = 0.662$, $p = 0.458$
Experiment 2			
posterior P1	$F_{1,17} = 2.536$, $p = 0.130$	$F_{2,34} = 0.943$, $p = 0.355$	$F_{2,34} = 1.799$, $p = 0.196$
N1	$F_{1,17} = 0.062$, $p = 0.806$	$F_{2,34} = 0.182$, $p = 0.687$	$F_{2,34} = 0.009$, $p = 0.933$
LRP	$F_{1,17} = 0.748$, $p = 0.399$	$F_{2,34} = 0.752$, $p = 0.414$	$F_{2,34} = 1.765$, $p = 0.200$
Experiment 3			
posterior P1	$F_{1,17} = 3.988$, $p = 0.062$	$F_{2,34} = 2.138$, $p = 0.147$	$F_{2,34} = 0.293$, $p = 0.734$
N1	$F_{1,17} = 0.316$, $p = 0.582$	$F_{2,34} = 1.132$, $p = 0.305$	$F_{2,34} = 0.143$, $p = 0.773$
LRP	$F_{1,17} = 0.311$, $p = 0.585$	$F_{2,34} = 0.041$, $p = 0.930$	$F_{2,34} = 0.364$, $p = 0.643$

Table 1. Summary of statistical results on the amplitude of the posterior P1, N1, and LRP from Experiments 1-3.

Experiment 2

Primary results

In Experiment 2, we replicated the pattern of findings from Experiment 1 using a search task in which the targets and distractors were pictures of real-world objects. This demonstrates the robustness and reliability of the pattern of effects shown in Experiment 1. Specifically, brain stimulation resulted in attention being rapidly retuned to the new targets after one trial, as evidenced by RTs hitting the floor by the second trial in a run. Again, this change in RT was mirrored by stimulation changing the anterior P1, and not the CDA, consistent with accounts providing a role for long-term memory in the guidance of attention.

We asked whether our causal manipulation of long-term memory driven attentional tuning would generalize beyond simple geometric shapes to more complex objects. We designed Experiment 2 to be identical to Experiment 1 with the exception that Landolt-C stimuli were replaced with photographs of complex, real-world objects (**Fig. 5A**), and a new group of subjects was sampled (order of anodal and sham conditions counterbalanced, N=18).

In Experiment 2, we found that medial-frontal stimulation again caused selective enhancements in only the long-term memory activity elicited by the target cues, explaining the rapid improvement in the amplitude of the N2pc component elicited by the targets and the search RTs that followed (**Fig. 5B-E**). Relative to sham, the anodal stimulation accelerated RTs ($F_{2,34}$ = 4.232, p = 0.038), rapidly increased N2pc amplitude ($F_{2,34}$ = 4.168, p = 0.038) and anterior P1 amplitudes ($F_{2,34}$ = 4.106, p = 0.048), but had

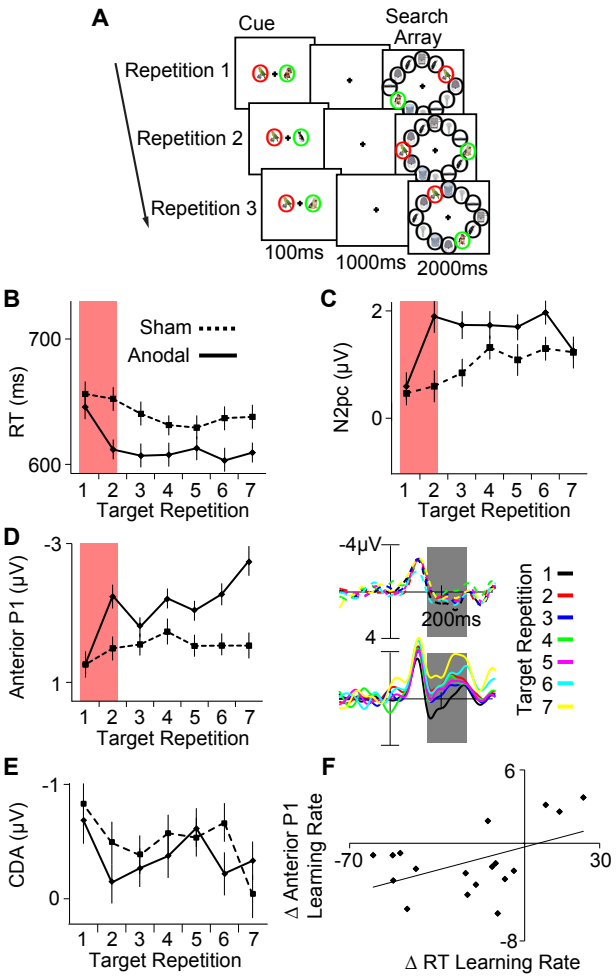

Figure 5. Task and priamary results from Experiment 2. **A**, The task in Experiment 2 was identical to that of Experiment 1 with the exception that Landolt-C stimuli were replaced with real-world objects. Mean RTs (**B**), N2pc amplitudes (**C**), anterior P1 amplitudes (**D**), and CDA amplitudes (**E**) shown across target repetitions for sham (dashed) and anodal (solid) conditions. Error bars are ± 1 standard error of the mean. Red shading high-lights dynamics across trials 1-2. Grand average ERP waveforms from the frontal midline electrode (Fz) locked to cue onset shown across target repetitions for sham (dashed) and anodal (solid) conditions. The measurement window of the anterior P1 is shaded in grey. **F**, The relationship between logarithmic rate parameters enhancements for mean anterior P1 amplitude and RT after anodal stimulation relative to sham.

no affect on the CDA ($F_{2,34}$ = 0.245, p = 0.758), which continued to decline in amplitude over same-target trials ($F_{2,34}$ = 6.695, p = 0.005), but at a rate that did not differ from the sham baseline ($F_{1,17}$ = 0.088 p = 0.770) (for N2pc and CDA waveforms see **Fig. 6A-B**).

Pairwise comparisons showed that the sharpest increase in attentional tuning for these real-world objects was between the first two trials as shown in search RT behavior ($F_{1,17}$ = 9.256 p = 0.007), N2pc amplitude ($F_{1,17}$ = 4.237, p = 0.050), and anterior P1 amplitude ($F_{1,17}$ = 10.540 p = 0.005). Accuracy was at a mean of 97.4% correct across all trials types and did not differ across stimulation conditions or same-target runs (ps > 0.35).

As in Experiment 1, we found that the rate of tDCS-mediated anterior P1 amplitude predicted the speed of an individual's improvement in search behavior after anodal stimulation (r_{18} = 0.489, p = 0.039) (**Fig. 5F**). As in Experiment 1, the medial-frontal effects were selective in that electrophysiological indices of low-level perceptual processing and late-stage response selection were not affected by stimulation (**Fig. 6C-D, Table 1**). This demonstrates that our findings can be replicated and extended to conditions in which subjects search for real-world objects. Like Experiment 1, our findings from Experiment 2 were consistent with the view that long-term memory representations can explain rapid changes in attentional tuning, not just the working memory representations that have been the focus of the dominant theories. Finally, one alternative explanation of the anterior P1 results is that this early frontal positivity is not as deeply linked to long-term memory processes as previously believed. The anterior P1's causal relationship with attentional improvements in the present study combined with previous research linking this component to long-term memory suggests that anterior P1 might play a role in the focusing of attention that activates representations maintained in long-term memory (Cowan, 1997). Future investigations using causal techniques such as tDCS will be necessary to test such rival hypotheses and better

determine the functional connection between the anterior P1 and mechanisms of selection guidance.

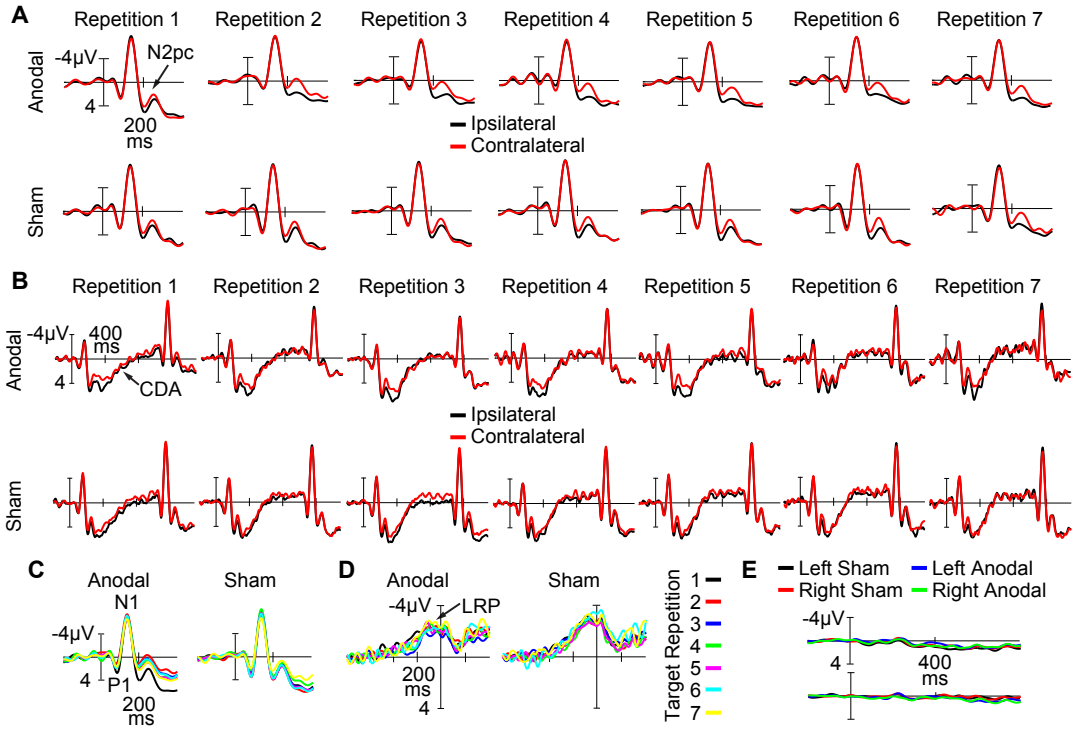

Figure 6. Sensory, response, attention, and working memory event-related potentials from Experiment 2. **A**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target color shown across repetitions 1-7 from anodal and sham tDCS conditions. **B**, Cue locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target shown across repetitions 1-7 from anodal and sham tDCS conditions. **C**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral with respect to target color location shown across target repetitions 1-7 from anodal and sham tDCS conditions. **D**, Response locked grand average difference waves (contralateral minus ipsilateral with respect to response hand) at central lateral sites (C3/C4) from correct trials shown across target repetitions 1-7 from anodal and sham tDCS conditions. **E**, Cue locked (top) and search array locked (bottom) horizontal electrooculogram (HEOG) waveforms for targets in the left and right visual hemifields and across tDCS conditions. Labels show the posterior P1, N1, lateralized readiness potential (LRP), N2pc, and contralateral delay activity (CDA).

Across session analyses of Experiments 1 and 2

Next, we sought to provide converging evidence for our conclusion that the stimulation was changing subjects' behavior by changing the nature of subjects' long-term memory, consistent with previously functional interpretations of the anterior P1. So far we have drawn conclusions using our analyses across the fairly short runs of same-target trials. However, we next looked at the learning that took place across the entire experimental session, lasting almost three hours. If our interpretation of the anterior P1 underlying accelerated attentional tuning is correct, then we should see that the anterior P1 is sensitive to the accumulative effects of learning across the entire experimental session and that these long-term effects change following stimulation. To assess the cumulative effects of learning across these long experimental sessions, we examined how behavior, the anterior P1, and CDA changed across the beginning, middle, and end of Experiments 1 and 2 (**Fig**. **7**). That is, we averaged the same-target runs together in the first third, second third, and final third of sessions across all of our subjects.

When we aggregated data across Experiments 1 and 2, we found that search RT and the anterior P1 were systematically modulated by the cumulative effects of learning across the full experimental session. **Figure 7** shows the results we observed across these long sessions. The RTs were slowest at the beginning of the experiment, when faced with a new target, but as subjects accumulated experience with the set of eight possible targets, we saw the RTs at the beginning of the same-target runs became progressively faster. An ANOVA with the factor of epoch (first third vs. second third vs. final third) revealed that RTs at the first target repetition in the runs of same-target trials

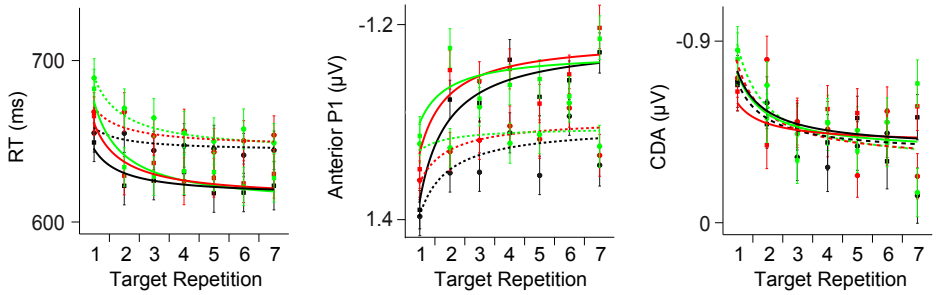

Figure 7. Within-session dynamics of Experiments 1-2. Mean RT, anterior P1 amplitude, and CDA amplitude as a function of target repetitions binned according to the first (black), middle (red), and last 1/3 of runs (green), collapsed across Experiments 1-2. Logarithmic model fits are shown for sham (dashed) and anodal (solid) tDCS conditions. Error bars are ± 1 standard error of the mean.

became increasingly faster as subjects gained more experience on the task ($F_{2,34}$ = 4.366, p = 0.038).

The accumulation of experience across the entire session that sped RT was mirrored by systematic changes in the amplitude of the anterior P1. The anterior P1 became progressively more negative across the experiments ($F_{2,34}$ = 6.241, p = 0.019), as we would expect if the magnitude of the negativity were indexing the quality (i.e., strength or number) of the long-term memories for these targets that accumulated across the entire experiments. The fact that the anterior P1 responded to cumulative learning effects in this manner is consistent with current functional interpretations of this component as reflecting processes related to long-term memory.

In contrast to these changes in anterior P1 and search RT, the accumulation of experience in these tasks did not systematically influence the amplitude of the CDA ($F_{2,34}$ = 0.713, p = 0.455), indicating that the role of working memory in updating the target at the beginning of the same-target runs does not change with protracted learning. For example, it is likely that working memory representations were reactivated to help reduce proactive interference from the target representations built up during the previous run of trials, consistent with influential theoretical proposals (Kane and Engle, 2002). Our medial-frontal tDCS boosted these learning effects measured with the anterior P1 and search RTs, while leaving the CDA unchanged, consistent with our interpretation of the findings across the shorter same-target runs. Thus, this cumulative learning across the entire experimental session allowed us to observe how the dynamics of the memory representations underlying the focusing of attention evolved over the long term. The results from the learning analysis conducted across the entire experimental session, and those obtained from the relatively short bursts of learning measured across the same-target runs of trials, converge on the conclusion that medial-

frontal stimulation changed visual search performance by influencing the nature of attentional guidance by long-term memory. These findings lend further support to the hypothesis that contributions from long-term memory are driving the causal boost of attentional tuning we observed following brain stimulation.

Experiment 3

Primary results

To determine whether the effects of Experiments 1 and 2 were specific to medial-frontal stimulation, in Experiment 3 we stimulated the posterior parietal region in a new group of subjects (order of anodal and sham conditions counterbalanced, N=18) (**Fig. 8A**). This region of the dorsal visual stream plays a role in memory (Eichenbaum and Cohen, 2001) and generating top-down attentional control signals (Corbetta and Shulman, 2002) so that it provides a useful contrast with our medial-frontal stimulation which influenced attentional selection by changing the long-term memory representations. We specifically targeted the right parietal region because previous studies show that disrupting activity in right parietal cortex can influence attentional selection (Beck et al., 2006; Tseng et al., 2010).

We found that, unlike medial-frontal stimulation, right parietal tDCS had no effect on the overall tuning of attention or the memory representations controlling search performance. **Figure 8B-E** shows the overlap between stimulation conditions for the RTs (no stimulation condition x target repetition interaction, $F_{2,34} = 0.029$, $p = 0.955$), the amplitudes of the N2pc ($F_{2,34} = 0.139$, $p = 0.807$), CDA ($F_{2,34} = 0.814$, $p = 0.439$), and

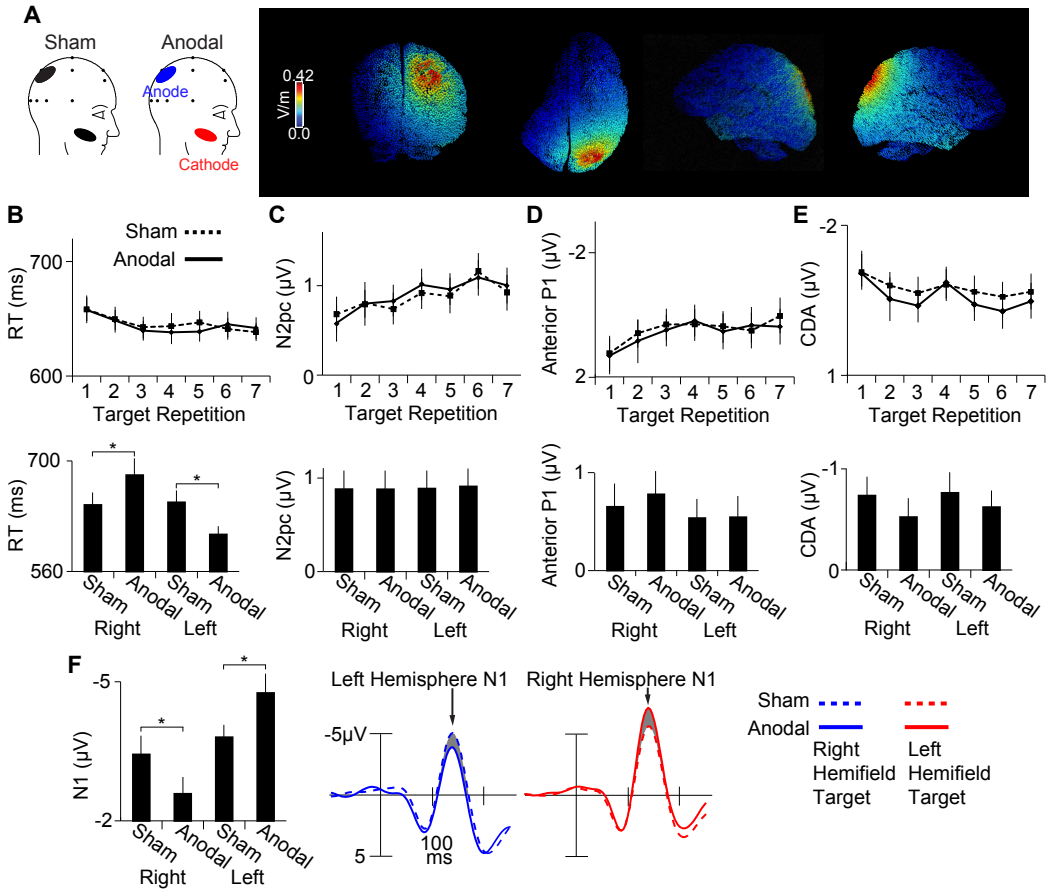

Figure 8. TDCS montage and model targeting right parietal regions, and the primary results from Experiment 3. **A**, To the left is the tDCS montage using a right lateral parietal anode paired with a right cheek cathode for sham and anodal stimulation conditions. To the right is the modeled distribution of electrical current projected onto top, rear, and lateral views of a 3D reconstruction of the cortical surface. This montage was used in Experiment 3 to manipulate regions of parietal cortex. Mean RTs (**B**), N2pc amplitudes (**C**), anterior P1 amplitudes (**D**), and CDA amplitudes (**E**) shown across taret repetitions for sham (dashed) and anodal (solid) conditions. Bar graphs show data collapsed across target repetitions for each stimulation condition based on whether the target color appeared in the left or right visual hemifield. Error bars are ± 1 standard error of the mean. **F**, Mean N1 amplitudes are illustrated as in **B-E**. The waveforms are search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral to right (blue) and left (red) hemifield target colors shown across sham (dashed) and anodal (solid) conditions.

anterior P1 ($F_{2,34}$ = 0.393, p = 0.663) across target repetitions. Because subjects again searched for the same target across the runs of trials in Experiment 3, we did observe main effects of target repetition on RTs ($F_{2,34}$ = 6.190, p = 0.015), and the amplitudes of

the N2pc ($F_{2,34}$ = 4.053, p = 0.045), CDA ($F_{2,34}$ = 5.292, p = 0.024), and anterior P1 ($F_{2,34}$ = 6.320, p = 0.006). These effects were due to the steady speeding of RTs, declining CDA amplitude, and increasing amplitudes of the anterior P1 and N2pc across same-target trials. The effects of target repetition indicate that the roles played by working memory and long-term memory in tuning attention across trials in the baseline sham condition were unchanged following right parietal stimulation (**Fig. 8B-E**, see also **Figs. 9D**, **10** in the **Supplemental results** below).

Given the lateralized application of tDCS in Experiment 3, we examined the data based on whether the target appeared in the left or right visual field. We found that parietal stimulation caused lateralized, bi-directional effects on search performance. Relative to sham, subjects were faster at searching for targets after anodal stimulation, but only on trials in which the target color appeared contralateral (i.e., in the left visual field) to the location of the stimulating electrode on the head (i.e., over the right hemisphere) (**Fig. 8B**). This was evidenced by a stimulation condition x target color laterality interaction on search RTs ($F_{1,17}$ = 12.098 p = 0.003), and a main effect of stimulation condition on contralateral search RTs ($F_{1,17}$ = 6.014 p = 0.025). In contrast, RTs were slower when target colors appeared ipsilateral (i.e., in the right visual hemifield) with respect to the location of tDCS ($F_{1,17}$ = 4.276 p = 0.054) (**Fig. 8B**). These results suggest that parietal stimulation facilitated and impeded overall search behavior depending on the location of the target in the visual field.

We found that the lateralized, bi-directional effects of parietal tDCS on search performance were caused by directly influencing perceptual processing, not changing the memory representations controlling attention. The amplitude of the posterior N1

component, a neural index of perceptual processing (Luck and Hillyard, 1990), was significantly modulated by stimulation condition and in a pattern mirroring that of the behavior (stimulation condition x target color laterality interaction: $F_{1,17}$ = 10.494 p = 0.005; stimulation condition main effects, contralateral: $F_{1,17}$ = 4.755 p = 0.044, ipsilateral $F_{1,17}$ = 4.573 p = 0.047) (**Fig. 8F**, see also **Fig. 9A** in the **Supplemental results** below). In contrast, our indices of the memory representations of the targets and of the deployment of attention were not significantly changed by tDCS (i.e., no stimulation condition x target color laterality interaction, N2pc $F_{1,17}$ = 0.041 p = 0.843; CDA $F_{1,17}$ = 0.107 p = 0.748; anterior P1 $F_{1,17}$ = 0.169 p = 0.686) (**Fig. 8C-E**, see also **9B-D** in the **Supplemental results** below).

In sum, our parietal stimulation protocol did not change the nature of the memory representations controlling attention, but directly influenced the perceptual processing of the objects in the search array. This was evidenced by lateralized changes in the early visual ERPs and the behavioral responses to the target colors contralateral versus ipsilateral to the stimulation. Thus, the effects observed in Experiments 1 and 2 are not a ubiquitous pattern observed following stimulation of any cognitive control structure. Instead, when we stimulated the posterior parietal region of the visual stream, we observed changes in early visual responses of the brain and similarly spatially mapped patterns of performance.

Supplemental results

The results from Experiment 3 provide evidence for the causal manipulation of perceptual processing via electrical stimulation over the parietal region. Our combined

results across Experiments 1-3 indicate a dissociation between parietal stimulation affecting perceptual processing and medial-frontal stimulation affecting top-down attentional control by long-term memory. Here we show additional plots of the waveforms and analyses to more fully flesh out our findings from Experiment 3.

Figure 9A shows the posterior P1 and N1 waveforms across target repetition sorted by stimulation condition (i.e., either anodal or sham) and by the location of the search target color (i.e., either in the left or right visual hemifield). These N1 components are identical to those shown in **Figure 8F**, but here we show the waveforms for each target repetition (see the main paper and **Table 1** for the statistical results). Note that, unlike the N1 component, the posterior P1 amplitude showed no significant stimulation condition x target color laterality interaction ($F_{1,17}$ = 0.104, p = 0.751), and no main effects of stimulation condition ($F_{1,17}$ = 0.004, p = 0.951) or target color laterality ($F_{1,17}$ = 0.400, p = 0.536), indicating that our parietal tDCS configuration had a selective influence on the N1 component related to the early perceptual processing of the visual search stimuli.

Figure 9B-C shows the CDA and N2pc waveforms from Experiment 3 sorted by stimulation condition and the location of the cue or search target in the visual field, respectively. Neither of these components were significantly changed by target laterality (N2pc $F_{1,17}$ = 0.025, p = 0.876; CDA $F_{1,17}$ = 0.356, p = 0.559) or stimulation condition (N2pc: $F_{1,17}$ = 0.031, p = 0.862; CDA $F_{1,17}$ = 1.916, p = 0.184) (see main results for additional statistical results). Similarly, the anterior P1 was not affected by target laterality ($F_{1,17}$ = 0.210, p = 0.653) or stimulation condition ($F_{1,17}$ = 0.126, p = 0.727) (see main results for additional statistical results) (**Fig**. **9D**). Accuracy was at a mean of

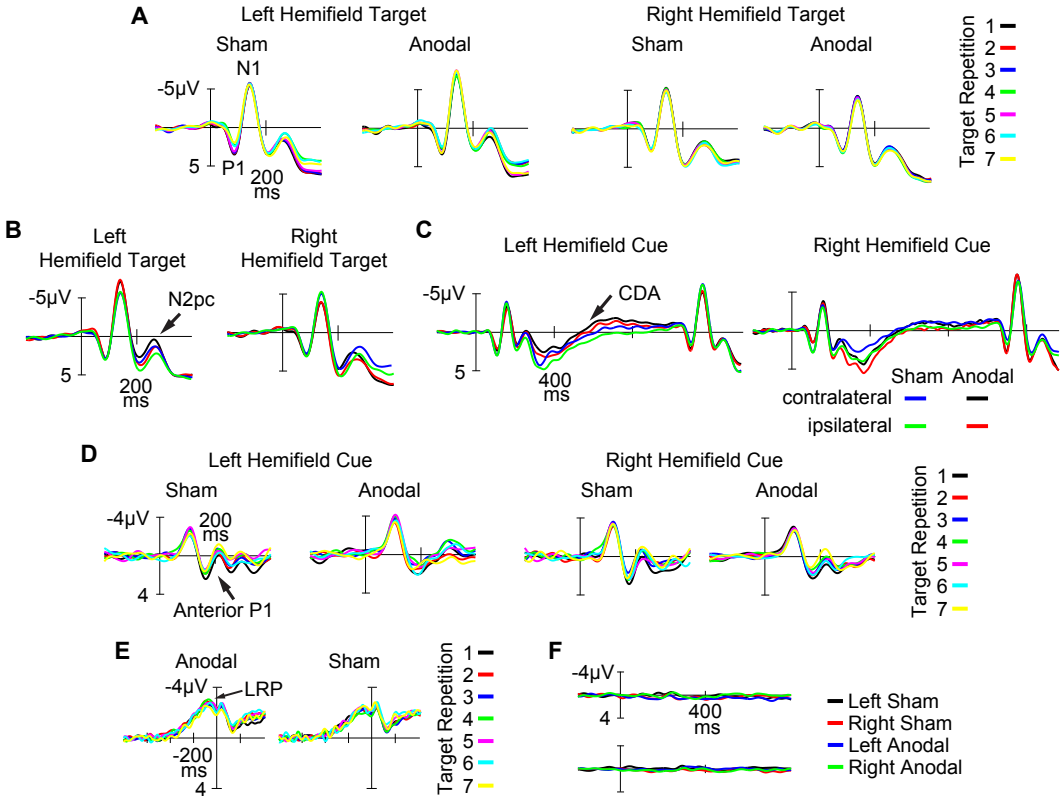

Figure 9. Sensory, attention, working memory, long-term memory, and response event-related potentials from Experiment 3. **A**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral to left and right hemifield target color locations shown across repetitions and tDCS conditions. **B**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral and ipsilateral with respect to left and right hemifield target color location shown for each tDCS condition and collapsed across target repetitions. **C**, Cue locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral and ipsilateral to the location of the target cue shown for each tDCS condition and collapsed across target repetitions. **D**, Cue locked grand average potentials at the frontal midline electrode (Fz) shown across target repetitions and sorted by left and right hemifield target cue location and tDCS condition. **E**, Response locked grand average difference waves (contralateral minus ipsilateral with respect to response hand) at central lateral sites (C3/C4) from correct trials shown across target repetitions and tDCS conditions. **F**, Cue locked (top) and search array locked (bottom) horizontal electrooculogram (HEOG) waveforms for targets in the left and right visual hemifields and across tDCS conditions. Labels show the posterior P1 and N1, the N2pc, CDA, anterior P1, and lateralized readiness potential (LRP).

98.2% correct across all trials types and did not differ across stimulation conditions or same-target runs (*ps* > 0.35). These results indicate our parietal stimulation protocol had no measurable influence on the cognitive mechanisms of covert attentional

selection (indexed by the N2pc), working memory (indexed by the CDA), or long-term memory (indexed by the anterior P1). Thus, changes in the early perceptual processing of the search stimuli (indexed by the posterior N1) were the source of the bi-directional effects we observed in search behavior following parietal tDCS.

As reported in the main results, the processes of input selection and attentional guidance did exhibit their characteristic modulations across same-target trials in Experiment 3, indicating their role in the tuning of attention that unfolds across trials of searching for the same object (Logan, 2002). Specifically, the waveforms in **Figures 9D** and **10** show a steady increase in the negativity of the anterior P1, decline in CDA amplitude, and increase in N2pc amplitude as subjects searched for the same target (see **Primary results** above for statistical results). Thus, despite the influence of parietal stimulation on subjects' perceptual processing of the search arrays, the deployment of attention and the memory representations providing top-down control of attention continued to function in a normal fashion, unchanged by the improvements and impairments we observed in perceptual processing and behavior following parietal tDCS.

As in Experiments 1-2, we examined the ERP component known to index motor preparation activity and response-stage processing (i.e., the LRP). **Figure 9E** shows the LRP waveforms for each target repetition and stimulation condition from Experiment 3. No significant results were found (see **Table 1**). This again underscores the conclusion that parietal stimulation had a selective impact on perceptual processing, in contrast to the effects of medial-frontal tDCS on the long-term memory representations providing top-down attentional control.

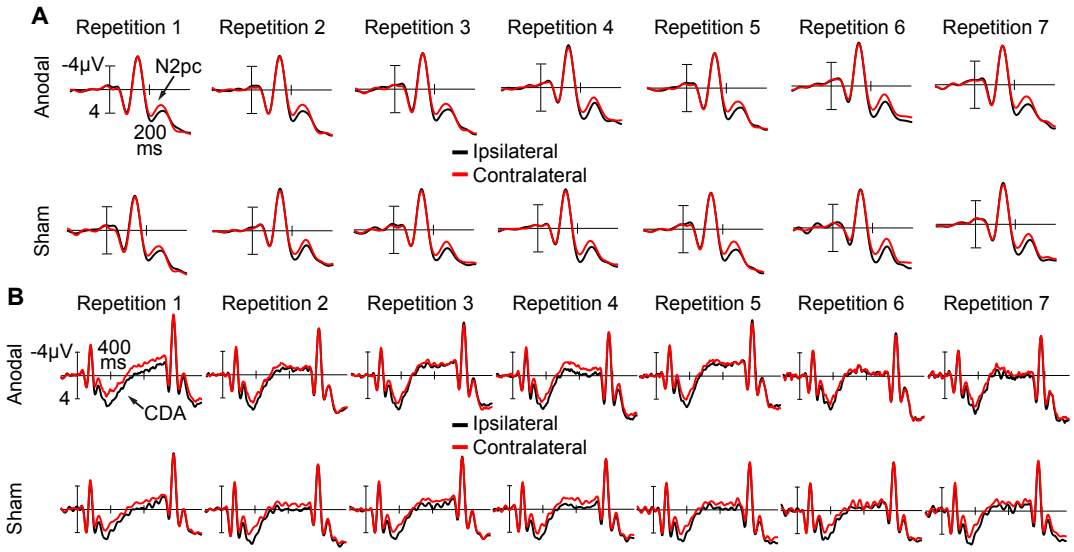

Figure 10. Attention and working memory event-related potentials from Experiment 3. **A**, Search array locked grand average potentials at lateral occipitotemporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target color shown across repetitions 1-7 from anodal and sham tDCS conditions. **B**, Cue locked grand average potentials at lateral occipito-temporal sites (OL/OR) contralateral (red) and ipsilateral (black) to the location of the target cue shown across repetitions 1-7 from anodal and sham tDCS conditions. Labels show the N2pc and contralateral delay activity (CDA).

tDCS modeling results

To visualize the brain areas affected by our tDCS manipulations we computed a forward computational model of the current flow. **Figure 3A** shows the pattern of current flow during anodal medial-frontal tDCS based on our stimulation protocol and standard estimates of underlying anatomy and tissue properties. Electrical fields were modeled as extending through the dorsal subdivision of the medial-frontal cortex, including areas such as the anterior cingulate cortex (ACC), supplementary motor area (SMA), and pre-supplementary motor area (pre-SMA). A higher intensity of current is likely to have influenced more dorsal or superficial areas of cortex, such as the SMA and pre-SMA. Due to the position of the cathodal electrode placed over the right cheek in our stimulation montage, to a lesser extent right dorsolateral cortex appeared to be implicated as well. Moreover, because of the highly interconnected nature of frontal cortex, we cannot rule out the possibility that tDCS induced neural activity in distally connected brain areas outside the regions of activation predicted by our model. Follow-up studies using neuroimaging techniques are needed to definitively identify the brain areas and associated networks responsible for the rapid changes in perceptual attention we observed following medial-frontal stimulation. However, here we rely on the qualitative predictions our modeling solution provides about the likely spatial distribution of the electrical field through the brain.

Figure 8A shows the model prediction of the current-flow pattern during tDCS using the P2 electrode position as the anodal site of stimulation paired with the cathodal electrode over the right cheek. The gravity center of the electrical field was situated in

the right hemisphere of the superior parietal lobule (Brodmann's areas 5 and 7). However, right lateralized extrastriate visual areas, such as the superior occipital gyrus (Brodmann area 19) also appeared to have been in the path of current flow. Future work will be necessary to more precisely determine the brain areas affected by this montage and the possibility of remote activations not captured by tDCS models.

Discussion

Our findings from Experiments 1 and 2, that stimulation over medial-frontal areas can rapidly improve attentional selection of targets, may seem surprising because the medial-frontal cortex is not commonly thought to be a crucial node in the network of regions that guide attention (Corbetta and Shulman, 2002; Buschman and Miller, 2007). This region is most frequently discussed as critical for the higher-level monitoring of task performance, response conflict, and prediction error (Brown and Braver, 2005; Shenhav et al., 2013). However, a variety of studies across species and methods have found connections between regions of medial-frontal cortex and both attention and memory processes. For example, human neuroimaging research shows that the cingulo-opercular network, including anterior cingulate and pre-supplementary cortex, is engaged during the implementation of a task set, visuospatial attention, and episodic memory (Dosenbach et al., 2006; Dosenbach et al., 2007; Sestieri et al., 2014). Second, studies using animal models show that attentional selectivity in the visual domain appears to reside in dorsomedial areas of prefrontal cortex (Dalley et al., 2004), such as the anterior cingulate gyrus. Third, both the dorsomedial and right dorsolateral

prefrontal cortices respond strongly in memory recognition tasks with specific activity bordering the anterior cingulate at or near Brodmann's areas 6, 8, and 32 (Wagner et al., 1998), including supplementary and pre-supplementary motor areas. The right dorsolateral prefrontal cortex, which also appeared to be in the path of our current-flow modeling, has been causally linked to human long-term memory processes (Rossi et al., 2001). Given the set of regions in this path, the specificity of our empirical observations is striking. However, future work is clearly needed to dissect the contribution of the group of medial-frontal and medial-prefrontal regions within the path of the current used here.

Our results present evidence from causal manipulations of the healthy human brain that suggest the rapid reconfiguration of the top-down control of visual attention can be carried out by long-term memory. This seems counterintuitive given that the active storage in working memory can strongly control attention (Chelazzi et al., 1993; Carlisle et al., 2011; Olivers et al., 2011), and that the dominant theories of attention focus exclusively on the role of working memory in guiding attention (Duncan and Humphreys, 1989; Bundesen, 1990; Desimone and Duncan, 1995; Bundesen et al., 2005). The present findings do not suggest that working memory representations do not control attention across the short term, indeed we observed the neural index of storage of the target in working memory that was concurrent with the large changes in the putative index of long-term memory. The critical implication of the present findings is that the rapid improvements in attentional control following brain stimulation were most closely related to our ERP measure of long-term memory and not working memory. This is surprising to us given that effects of long-term memory on attentional control are

typically observed in tasks in which improvements evolve slowly across protracted training (Chun and Jiang, 1998; Chun, 2000; Summerfield et al., 2006; Stokes et al., 2012; Võ and Wolfe, 2012; Wolfe, 2012) or even a lifetime of semantic associations (Moores et al., 2003). Here we show that the time course of improvement need not be diagnostic of the type of memory representation involved.

Our results can also be interpreted within theoretical models that take a broader view of top-down control and do not rely on a conceptual dichotomy between working memory and long-term memory processes that guide attention (Dosenbach et al., 2008). Neuroimaging research has identified multiple control mechanisms that configure downstream processing consistent with behavioral goals. Most relevant here is the network consisting of the anterior insula/frontal operculum and dorsal anterior cingulate cortex/medial superior frontal cortex. This network is thought to integrate information over relatively protracted, iterative timescales, similar to the dynamics and functional properties of the anterior P1. Further, the cingulo-operculer network carries various critical control signals, including the selection and maintenance of task goals and the making and monitoring of choices (Dosenbach et al., 2006; Johnston et al., 2006; Rushworth et al., 2007). It is possible that our medial-frontal stimulation activated functions within this control network, which are considered to encourage resilient performance, causing the improvements we observed in attentional control.

Finally, our findings provide evidence from novel causal manipulations of the human brain to support the slowly growing view that the nature of top-down attentional control involves the interplay of different types of memory representations (Pillsbury, 1908; Woodman and Chun, 2006; Chun and Turk-Browne, 2007; Hutchinson and Turk-

Browne, 2012; Woodman et al., 2013). Moving forward, we believe that such a view moves theories of attention nearly into register with models of learning, automaticity, and skill acquisition (Anderson, 1982; Rickard, 1997; Anderson, 2000; Logan, 2002). Ideally this will serve to unify, rather than further hyper-specialize, theories of information processing in the brain.

CHAPTER 3

UNDERSTANDING THE MECHANISMS OF IMPAIRED ATTENTION IN SCHIZOPHRENIA

Introduction

Scientists have argued that impairments in attention are a cardinal feature of schizophrenia cognitive dysfunction (McGhie and Chapman, 1961; Shakow, 1962), dating back to the earliest clinical definitions of the disorder (Kraepelin, 1896; Bleuler, 1911). Yet, the disease mechanisms underlying attentional dysfunction in schizophrenia remain elusive and heavily debated. One class of models proposes that the locus of the attentional dysfunction is in the control of perceptual selection (i.e., selection guidance) (Luck et al., 2006; Gold et al., 2007), whereas competing models propose the underlying cause is in the abnormal use of perceptual attention itself (i.e., input selection) (Hemsley, 1987, 1993, 2005). In the present work, I will use a novel behavioral paradigm and highly precise electrophysiological measurements of brain activity to characterize the integrity of the selection-guidance and input-selection processes underlying attentional dysfunction in schizophrenia. Then, I will determine whether the electrical brain stimulation protocol I have developed in Chapter 2 can

change how patients control and use their attention with the added possibility of temporarily rescuing cognitive function in the patients.

In the present study, I will build on my previous work with colleagues focused on the basic cognitive mechanisms that control attention to test cognitive models of schizophrenia (Woodman et al., 2013; Reinhart et al., 2014; Reinhart and Woodman, 2014b, c; Reinhart et al., 2015a; Reinhart and Woodman, 2015b; Reinhart et al., 2015b; Reinhart et al., 2015c; Reinhart et al., 2016). One prevailing model proposes that the variety of schizophrenia abnormalities derive from an alteration in the way new information is processed (Hemsley, 1987, 1993, 2005). This model claims that the locus of cognitive deficits lies not in a patient's ability to store representations in memory that drive attention, but rather in the rapid assessment of behaviorally relevant sensory input. A competing hypothesis emphasizes an abnormality in the guidance of attention, rather than attentional implementation (Luck et al., 2006; Gold et al., 2007). These models make different predictions about the nature of attentional dysfunction in schizophrenia. The memory-guided search paradigm developed in Experiment 1 of Chapter 2 (see **Fig. 1**) will allow me to test these competing predictions by focusing on separable components of top-down control. I will measure the visual working memory and long-term memory representations providing top-down control of attention with the CDA and anterior P1 elicited by the target cue, and the implementation of attention with the N2pc elicited by the search array. The Luck and Gold account predicts that patients will exhibit abnormal visual working memory and long-term memory attentional control and normal attentional deployment, the Hemsley account predicts the opposite.

There are several forms in which the precise selection-guidance abnormality in schizophrenia predicted by Luck and Gold could manifest itself. **Figure 11B** shows three different abnormal CDA and anterior P1 amplitude functions that I anticipate. For example, the ERP functions across subject groups may show different y-intercepts (**Fig. 11B**, black and red lines), reflecting that patients are using fewer (or weaker) overall visual working memory and long-term memory representations throughout the learning process (i.e., automating visual search behavior across runs of same-target trials). Alternatively, the slope and endpoint of the CDA and anterior P1 functions may significantly differ across subject groups (**Fig. 11B**, black and green lines). A flatter ERP amplitude slope in patients across trials searching for the same target object would indicate these subjects are transferring fewer (or weaker) target representations from visual working memory to long-term memory during learning. This outcome would also indicate that as a target is repeated, patients are maintaining more (or greater strength) representations that control attention in visual working memory with fewer (or weaker) accumulated in long-term memory. A third possibility is that the ERP amplitude functions reach their asymptotes slower in patients (**Fig. 11B**, black and cyan lines). This pattern of results would indicate that patients begin and end the learning process with a proportion of working memory and long-term memory representations similar to that of healthy subjects, however during learning patients rely on more (or stronger) working memory and less (or weaker) long-term memory, and transfer these representations at an abnormally slow rate (i.e., linear), unlike healthy subjects whose learning rate is best approximated with an exponential or power function (Woodman et al., 2013).

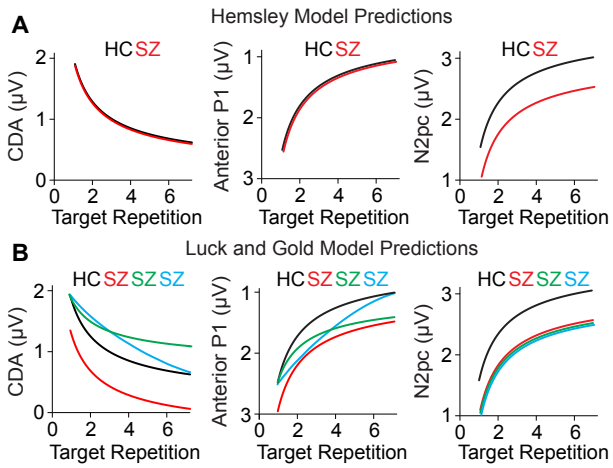

Figure 11. Experiment 4 predictions. CDA, anterior P1, and N2pc amplitudes in schizophrenia (SZ) and healthy control (HC) subjects based on the models of Hemsley (**A**) and Luck and Gold (**B**).

Methods

Subjects

Individuals who met the DSM-IV criteria for schizophrenia were recruited from outpatient psychiatric facilities in Nashville, Tennessee. Diagnoses were confirmed with structured clinical interviews (SCID-IV) (First et al., 1995). Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Two patients were medicated with typical antipsychotic drugs, fourteen patients were medicated with atypical antipsychotic drugs, and two patients with medicated with both typical and atypical antipsychotic drugs. The mean chlorpromazine dose equivalent was 311.08 mg/day (SD = 287.77). All subjects were screened to exclude substance use within the past 6 months, history of neurological disorders, history of head injury, inability to fixate, and excessive sleepiness. All subjects had normal color vision, and normal or corrected-to-normal visual acuity. All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid. Data were collected from 18 schizophrenia patients and 18 demographically matched healthy subjects. Subjects in each group were matched on age, gender, and handedness (see **Table 2**).

Stimuli and procedures

Table 2. Demographic Information

	Patients Mean (SD)	Control Mean (SD)	statistical test	*p*-value
Age, yrs	44.5 (9.07)	44.5 (8.98)	$t = 0.148$	0.88
Gender, *n*			$x^2 = 0.000$	1.00
Female	9	9		
Male	9	9		
Duration of Illness, yrs	21.1 (9.23)			
SAPS, total	14.9 (11.78)			
Hallucinations	1.6 (1.54)			
Bizarre Behavior	0.4 (0.70)			
Delusions	1.2 (1.48)			
Positive Formal TD	0.7 (1.16)			
SANS, total	35.9 (13.94)			
Affective Flattening	1.8 (0.95)			
Alogia	1.0 (1.06)			
Avolition Apathy	3.1 (1.32)			
Anhedonia Asociality	2.6 (1.41)			
Attention	1.24 (1.03)			
BPRS	20.5 (13.2)			

The $\chi 2$ value results from a Pearson's chi-squared test. The *t* value results from an independent two-tailed t-test. SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale

The stimuli and procedures in this experiment (i.e., Experiment 4) with patients with schizophrenia and matched controls were identical to those used in Experiment 1 described in Chapter 2. In brief, each subject received anodal and sham tDCS on different days, with order counterbalanced across subjects. Immediately following stimulation, subjects performed the memory-guided search task (**Fig. 1**), while we recorded their ERPs. In the task, each trial began with central fixation, followed by a target cue that signaled the shape that was to be searched for in the upcoming array of objects. The task-relevant object in the cue array was indicated by color (e.g., the red shape), with both red and green items presented to eliminate physical stimulus confounds (Woodman, 2010). Subjects were cued to search for the same target shape across a run of consecutive trials before the target changed to a new, randomly selected shape. Subjects responded to the item in the search array of the task-relevant color (e.g., red) as fast and accurately as they could on each trial by pressing one of two buttons on a gamepad. The analyses focused on the memory representations measured during the time interval between cue onset and search array onset, the deployment of attention measured following search array onset, and the RT and accuracy of subjects' manual button-press responses about whether the target was present or absent in the search array of objects. The repetition of the target objects (i.e., target repetitions) across 3-7 trials in a run was a critical feature of the task, allowing us to observe the dynamics of selection-guidance (i.e., indexed by the CDA and anterior P1) and input-selection (indexed by the N2pc) processes, and thereby test the competing model predictions of schizophrenia cognitive dysfunction.

We took several measures to ensure that information about the experiment did not lead to biasing of the results. First, all behavioral and electrophysiological testing was conducted in a sound-attenuated, electrically shielded booth to eliminate subject-experimenter interaction, in addition to minimizing sources of electrical noise. Second, subjects were blind to the presence of the stimulation. Blinding was confirmed through a series of debriefing questions. Specifically, after each testing day, we administered a safety questionnaire (Poreisz et al., 2007) and visual analog scale (Gandiga et al., 2006), which included questions regarding attention, concentration, mood, vision, headache, fatigue, and skin sensations under the tDCS electrodes. The scores from these ratings did not significantly differ by stimulation conditions for patients (*ts* < 0.310, *ps* > 0.760) or controls (*ts* < 0.842, *ps* > 0.410). In addition, all subjects were pointedly asked whether they could guess which testing day they had received active stimulation. Overall, both subject groups were equally below the chance level of detecting stimulation (i.e., 50%)(controls: hit rate 44.4%, false alarm rate 55.6%; patients: hit rate 50%, false alarm rate 50%).

Data analysis

All preprocessing, analysis, and current-flow modeling was identical to the methods conducted in Chapter 2, Experiment 1. Statistical analysis was also the same with the inclusion of the between-subjects ANOVA factor of subject group (patients vs. controls).

Results

Experiment 4

Primary results

We found that patients with schizophrenia exhibited marked impairments in the tuning of their attentional performance at baseline. **Figure 12A** (black lines) diagrams the results. First, relative to controls, patients showed an overall RT slowing in their visual search behavior, evidenced by a main effect of subject group on RT ($F_{1,17}$ = 18.567, $p < 0.01$). This result is consistent with the classic behavioral impairment widely observed in schizophrenia (Cancro et al., 1971; Reinhart et al., 2011). Critically, we found that patients were significantly impaired in their ability to rapidly tune their attention to targets embedded in the array of objects. This was demonstrated by the virtually flat RT function across target repetitions in patients (no main effect of target repetition, $F_{2,34}$ = 0.023, p = 0.966), relative to the acceleration of search RTs in controls (significant main effect of target repetition, $F_{2,34}$ = 4.082, p = 0.039). A significant subject group x target repetition interaction was observed ($F_{2,34}$ = 5.391, p = 0.015). Search accuracy was > 90% is both groups (mean percent correct, patients: 91.5%; controls: 94.8%) and did not differ between subject groups or target repetitions ($ps > 0.42$). These results reveal a clear impairment in the speed with which patients with schizophrenia tuned their visual attention to select the task-relevant objects in the visual scenes.

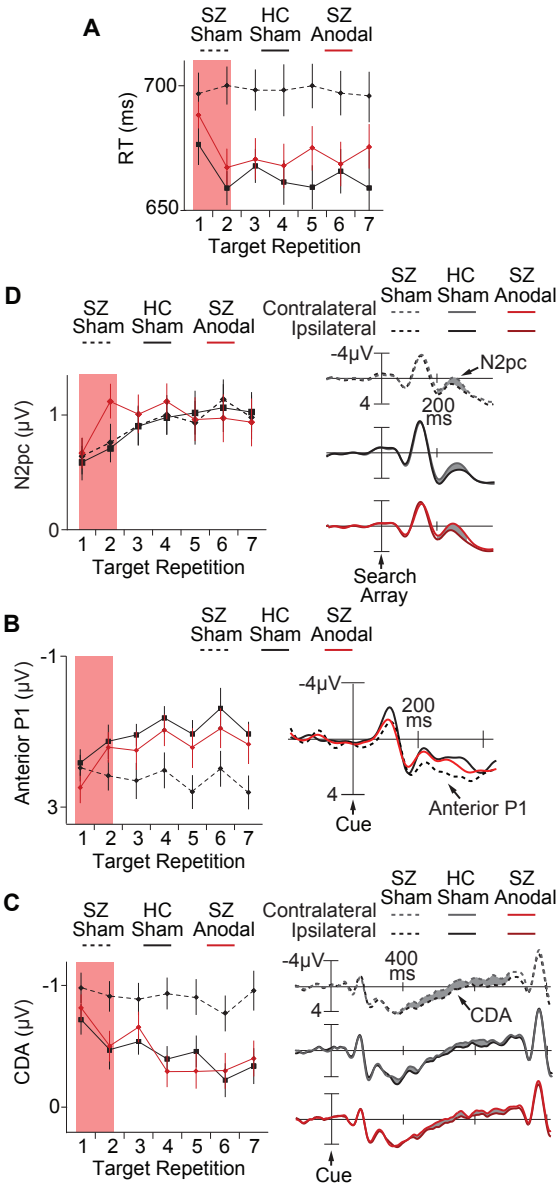

Figure 12. Primary results from Experiment 4. Mean RTs (**A**), anterior P1 amplitudes (**B**), CDA amplitudes (**C**), and N2pc amplitudes (**D**) shown across target repetitions in patients with schizohrenia (dashed, black) and healthy controls (solid, black) in the sham, baseline conditions and in patients with schizohprenia folowing active anodal stimulation (solid, red). Error bars are ± 1 standard error of the mean. Red shading highlights dynamics across trials 1-2. Grand average cue-locked event-related potential (ERPs) from the frontal midline electrode (Fz) averaged across target repetitions for each crticial condition (**B**). Grand average cue-locked ERPs at lateral occiptial sites (OL/OR) contralateral and ipsilateral to the location of the target cue averaged across target repetitions for each critical condition (**C**). Grand average search array-locked ERPs at lateral occiptial sites (OL/OR) contralateral and ipsilateral to the location of the target color averaged across target repetitions for each critical condition (**D**).

Approximately half a second before the behavioral response, subjects allocated their attention to the target in the search array. To discover whether an input-selection

mechanism was responsible for the attentional tuning deficit in the patients, as some models of schizophrenia dysfunction propose (Hemsley, 1987, 1993, 2005), we examined the neural signature of the focusing of covert visual attention (i.e. the N2pc). **Figure 12B** (black lines) show the results. Surprisingly, we found that the N2pc was fully intact in patients. Specifically, the N2pc amplitude function for patients was not different from that of controls in terms its y-intercept (i.e., amplitude at first target repetition) (no main effect of subject group, $F_{1,17} = 0.403$, $p = 0.534$), or its overall shape measured across the runs of same-target trials (no subject group x target repetition interaction, $F_{2,34} = 0.262$, $p = 0.769$). Both patients and controls showed gradually mounting N2pc components during learning, evidenced by significant main effects of target repetition on N2pc amplitude (patients: $F_{2,34} = 4.091$, $p = 0.030$; controls, $F_{2,34} = 3.700$, $p = 0.041$). These results demonstrate that the quality of covert attentional deployment in patients is not compromised, and thus cannot explain the dysfunctional tuning of visual attention that patients showed in their search behavior during learning. These findings provide evidence against the view that input selection is the primary source of attentional dysfunction in schizophrenia.

To test whether the attentional deficit in patients was due to changes in the memory mechanisms of top-down control, we assessed the neural signatures of visual working memory (i.e., the CDA) and long-term memory (i.e., the anterior P1) elicited by the target cues, appearing approximately 1 second before the search array. As illustrated in **Figure 12C-D** (black lines), we found that the patients' abnormal, unchanging speed of search behavior during learning matched their abnormal, unchanging CDA and anterior P1 amplitudes during learning. First, we observed y-

intercept differences in the CDA components between groups, suggesting that patients actually responded to the new search target by recruiting more (or higher strength) visual working memory representations relative to control subjects. Specifically, patients had larger CDA amplitude on the first target repetition for the storage of this single target item in memory (main effect of subject group, $F_{1,17} = 4.352$, $p = 0.050$). This was not true for the long-term memory representations indexed by anterior P1 (no main effect of subject group on anterior P1 amplitude at the first target repetition, $F_{1,17} = 0.004$, $p = 0.949$). Critically, in contrast to the standard, decreasing CDA ($F_{2,34} = 5.751$, $p = 0.012$) and increasing anterior P1 negativity ($F_{2,34} = 9.072$, $p = 0.002$) in controls, we observed severely blunted CDA ($F_{2,34} = 0.233$, $p = 0.683$) and anterior P1 ($F_{2,34} = 1.285$, $p = 0.288$) amplitude functions across same-target trials in the patients. Subject group x target repetition interactions on the amplitudes of the CDA ($F_{2,34} = 3.723$, $p = 0.037$) and anterior P1 ($F_{2,34} = 7.427$, $p = 0.005$) were significant (see **Discussion** for explanation of the unanticipated hyperactive CDA results). Thus, patients with schizophrenia showed multiple abnormalities in their neural dynamics related to the memory mechanisms used to control attention. These results are consistent with accounts proposing that attentional deficits in patients with schizophrenia arise, at least in part, from a disruption in the working to long-term memory transfer of the target representations involved in guiding attentional performance to relevant objects in clutter scenes.

Next, we asked whether anodal direct current noninvasively applied over the medial-frontal regions could change the selection-guidance abnormalities that we observed in patients at baseline. If medial-frontal stimulation can boost selection

guidance in patients as we have shown it can in healthy adults (see Experiments 1-2, Chapter 2), then it may be possible to enable patients to more effectively transfer target representations between memory systems, and improve how patients use their attention to select task-relevant objects from the search displays. However, it is also possible that the disease mechanisms in schizophrenia are resistant to the effects of such electrical stimulation, and that we will observe no significant stimulation-induced changes to the nature of selection-guidance processes, consistent with the null findings reported in tDCS studies investigating association learning and mental number line representation in schizophrenia (Vercammen et al., 2011; Ribolsi et al., 2013). Alternatively, given the complexity of the schizophrenia spectrum disorder, it is possible that medial-frontal tDCS could induce the opposite pattern of effects that we observed in healthy subjects, and cause further selection-guidance and behavioral impairments in the patients. The claim that the same electrical stimulation that provides cognitive enhancement to healthy people can cause cognitive impairment in patient populations is supported empirically by previous research. For example, bi-lateral tDCS over the dorsolateral prefrontal cortex can facilitate implicit learning in healthy subjects (Kincses et al., 2004) yet prevent implicit learning in patients with major depressive disorder (Brunonia et al., 2013).

We found that 20 minutes of direct current over medial-frontal cortex effectively recovered the ability of patients to tune their attention to task-relevant objects during visual search, such that the behavior of patients after anodal tDCS was indistinguishable from the behavior of controls after the sham tDCS. **Figure 12A** (red line) shows that after anodal stimulation patients exhibited significant attentional tuning,

demonstrated by a main effect of target repetition on search RT ($F_{2,34}$ = 4.366, p = 0.028). This behavioral change was a major improvement for patients compared to their search performance at baseline, the most prominent effects observed between the first two trials of search for a particular Landolt C (stimulation x target repetition interaction, $F_{1,17}$ = 5.377, p = 0.033). Further, the radical transformation of patients RT function following stimulation erased the discrepancy between patients' search efficiency and that of the controls at baseline (subject group x target repetition interaction, $F_{2,34}$ = 0.788, p = 0.462), with even greater overlap between subject groups across the first two trials in the same-target runs ($F_{1,17}$ = 0.282, p = 0.602). Search accuracy remained at relatively high levels (mean percent correct: patients, 93.1%; controls, 95.8%) and did not significantly change as a function of target repetition in the anodal condition or between stimulation conditions (ps > 0.57). Thus, 20 minutes of electrical stimulation over medial-frontal cortex was sufficient to temporarily eliminate the attentional tuning deficit in schizophrenia, allowing patients to successfully automate their visual search behavior like healthy control subjects.

The medial-frontal stimulation that normalized attentional tuning in patients with schizophrenia changed how these patients used their memory mechanisms to direct selection. **Figure 12B-D** (solid red versus black lines) shows that anodal stimulation reshaped the amplitude functions of the electrophysiological responses related to the guidance of selection by working memory (i.e., the CDA) and long-term memory (i.e., the anterior P1) representations, as well as input selection itself (i.e., the N2pc). In marked contrast to the flattened amplitude functions at baseline, anodal tDCS caused a rapid decline in CDA amplitude ($F_{2,34}$ = 8.394, p = 0.002) and sharp increase (more

negative) in anterior P1 amplitude ($F_{2,34}$ = 8.085, p = 0.008), as patients accumulated greater experience searching for the same target object. Mirroring the behavioral changes, the improvements in memory-related electrophysiology removed the between-group differences, such that the CDA and anterior P1 in patients after anodal stimulation no longer differed from these components in controls at baseline (CDA: subject group x target repetition, $F_{2,34}$ = 0.151, p = 0.796; anterior P1: subject group x target repetition, $F_{1,17}$ = 0.181, p = 0.827), including across the first two trials of the same-target runs (CDA: $F_{1,17}$ = 0.073, p = 0.791; anterior P1: $F_{1,17}$ = 1.824, p = 0.195). In addition, the stimulation-induced changes in memory-related ERPs led to a positive impact downstream on the focusing of attention, boosting N2pc amplitude between the first two target repetitions (stimulation x target repetition, $F_{1,17}$ = 4.848, p = 0.042) when the stimulation had its largest influence on behavior. However, other ERP components indexing lower-level perceptual processing or late-stage response selection during search remained unchanged by the tDCS (see **Fig**. **13** and **Table 3** in the **Supplemental results** below). Together, these results suggest that the processing efficiency following medial-frontal stimulation were caused by patients more effectively transitioning between sources of top-down control, offloading working memory representations while becoming more reliant on long-term memory to drive attentional selection.

Supplemental results

In the sham, baseline condition of Experiment 4, we found that patients with schizophrenia showed abnormalities in tuning attentional performance and that

abnormalities in the electrophysiological responses of the brain related to working and long-term memory mirrored these behavioral impairments. In the anodal stimulation condition, we found that patients' working and long-term memory electrophysiology could be modified leading to downstream improvements in attentional tuning measured by behavior and an ERP indexing input selection. Here, to further test the specificity of the electrophysiological findings, we examined additional ERP components known to index cognitive mechanisms related to sensory perceptual processing and late-stage response selection. We found that patients with schizophrenia exhibited significant impairments in these ERPs relative to healthy controls, but that medial-frontal tDCS had no effect on these components. These results reinforce the interpretation that the improvements in attentional tuning that we observed in patients with schizophrenia following brain stimulation were due to the specific manipulation of information transfer between memory systems important for controlling attention.

Figure 13A-B shows the ERP components from Experiment 4 related to early perceptual processing (i.e., the posterior P1 and N1) elicited by the search array, and the ERP component related to response selection (i.e., the lateralized readiness potential or LRP) preceding correct behavioral responses. We found main effects of subject group on the amplitudes of the posterior N1 and LRP (see **Table 3** for statistical results), consistent with previous research (Bruder et al., 1998; Mathalon et al., 2002; Butler et al., 2007; Luck et al., 2009; Cavus et al., 2012; Kappenman et al., 2012). However, critically, there were no main effects of stimulation condition or target repetition, and no interaction between stimulation condition and target repetition on the amplitudes of the posterior P1, N1, or LRP (see **Table 3**). Thus, changes in early

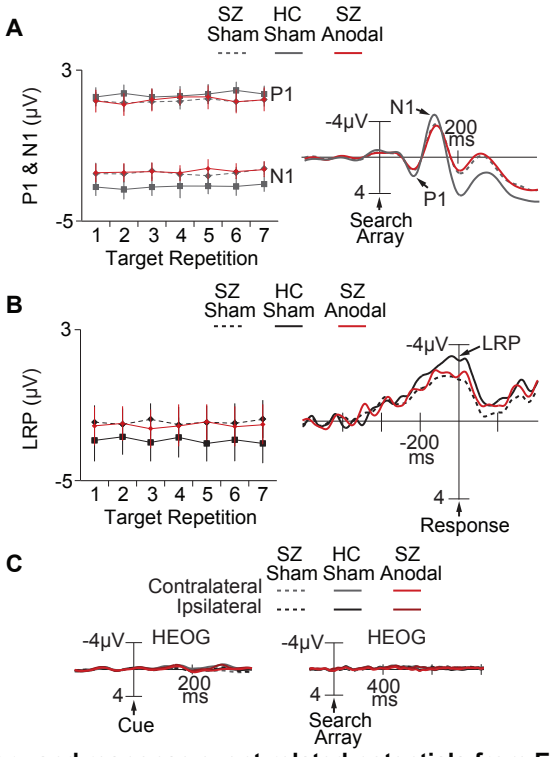

Figure 13. Sensory and response event-related potentials from Experiment 4. Mean posterior P1 and N1 amplitudes (**A**), LRP amplitudes (**B**), and horizontal EOG amplitudes (**C**) shown across target repetitions in patients with schizohrenia (dashed, black and grey) and healthy controls (solid, black and grey) in the sham, baseline conditions and in patients with schizophrenia following active anodal stimulation (solid, red). Error bars are ± 1 standard error of the mean. Grand average search array-locked ERPs at lateral occiptial sites (OL/OR) contralateral to the location of the target color averaged across target repetitions for each critical condition. Grand average response-locked differences waves (contralateral minus ipsilateral with respect to response hand) at central lateral sites (C3/C4) from correct trials averaged across target repetitions for each critical condition. Cue and search array-locked HEOG waveforms for targets in the left and right visual hemifields averaged across target repetitions for each condition.

perceptual and late response-stage processes could not account for the enhanced attentional control we observed following medial-frontal stimulation in patients with schizophrenia.

Experiment 4	Subject Group	Stimulation Condition	Target Repetition	Subject Group x Stimulation Condition
posterior P1	$F_{1,17} = 1.245$, $p = 0.280$	$F_{1,17} = 0.078$, $p = 0.784$	$F_{2,34} = 0.009$, $p = 0.975$	$F_{1,17} = 0.002$, $p = 0.969$
N1	$F_{1,17} = 6.067$, $p = 0.025$	$F_{1,17} = 0.012$, $p = 0.913$	$F_{2,34} = 0.264$, $p = 0.757$	$F_{1,17} = 0.045$, $p = 0.835$
LRP	$F_{1,17} = 6.983$, $p = 0.017$	$F_{1,17} = 0.080$, $p = 0.781$	$F_{2,34} = 0.758$, $p = 0.466$	$F_{1,17} = 0.040$, $p = 0.843$

Experiment 4	Subject Group x Target Repetition	Stimulation Condition x Target Repetition	Subject Group x Stimulation Condition x Target Repetition
posterior P1	$F_{2,34} = 0.035$ $p = 0.919$	$F_{2,34} = 0.042$, $p = 0.906$	$F_{2,34} = 0.011$ $p = 0.959$
N1	$F_{2,34} = 0.029$, $p = 0.934$	$F_{2,34} = 0.163$, $p = 0.795$	$F_{2,34} = 0.057$, $p = 0.919$
LRP	$F_{2,34} = 0.079$, $p = 0.862$	$F_{2,34} = 0.041$, $p = 0.911$	$F_{2,34} = 0.010$, $p = 0.971$

Table 3. Summary of statistical results on the amplitude of the posterior P1, N1, and LRP from Experiment 4.

Discussion

Our findings demonstrate that attentional performance deficits in schizophrenia are governed, in part, by dysfunctional memory representations of top-down control important for the efficient analysis of complex visual scenes. However, by stimulating over regions of medial-frontal cortex, we reconfigured selection-guidance mechanisms and enabled patients to rapidly improve attentional selection of targets.

Disease mechanisms of attentional tuning in schizophrenia

The quality of the baseline electrophysiology related to attentional control and selection in the patients with schizophrenia indicated an intriguing pattern of mechanistic abnormalities that inform our understanding of the pathophysiology of schizophrenia. We observed a number of effects suggesting the striking conclusion that the neural mechanisms that produce a given level of memory guided attentional control might not only be dysfunctional but also partially overactive. First, when confronted with a new search target, patients recruited abnormally large (or more) working memory representations, relative to controls. Second, during the short burst of learning to search for a new target, patients continued to recruit an unwarranted amount of working memory representations, while long-term memory recruitment stagnated and even slightly declined. The processing benefit of excessive working memory based control may have provided the boost in task accuracy that we observed to be unimpaired in patients relative to controls. However, the clear absence of a trade-off in the neural

dynamics related to working and long-term memory appeared to underlie the attentional performance deficits in the patients. These findings not only add to our knowledge of the neural deficits associated with schizophrenia pathophysiology, but also add to a growing body research proposing the radical new hypothesis that some disease mechanisms in schizophrenia can be characterized by abnormally hyperactive information processing (Whitfield-Gabrieli et al., 2009; Suh et al., 2013; Yoon et al., 2013; Ford et al., 2015; Kim et al., 2015), which some evidence has shown is predictive of the severity of schizophrenia psychosis (Yoon et al., 2013).

A closer look at the memory demands in the current experiment provides an explanation for the hyperactive use of processing resources in schizophrenia. The single item memory load requirement was likely much more difficult for patients than controls, consistent with previous work (Leonard et al., 2012; Luck et al., 2014). To compensate, patients may have called on additional top-down control and focus on this single memory representation to perform the task at a normal level of accuracy. This explanation conforms to previous fMRI studies measuring prefrontal BOLD signal during the performance of *N*-back tasks in patients with schizophrenia (Manoach, 2003). Specifically, patients showed increased BOLD activity at low loads (i.e., 1-back) relative to controls, but decreased BOLD activity relative to controls at high loads (i.e., 2- or 3-back). Thus, both patients and controls exhibit maximal prefrontal activation when they are at the peak of their behavioral performance, with patients peaking at lower loads than controls. From this perspective, an important future prediction is generated, namely, increasing the memory load of the target used to perform the upcoming search task should reverse the overall pattern of results by preferentially increasing CDA

amplitude in healthy subjects while having no further effect on the CDAs in patients with schizophrenia.

Not only did patients immediately respond in an abnormal fashion to the presentation of the first new search target, they also struggled to automate their ability to select the target over a run of learning trials. There is agreement in the literature that individuals with schizophrenia have diminished processing resources (Braff, 1981; Holzman, 1987; Nuechterlein, 1991; Asarnow et al., 1995; Harvey et al., 1996; Moriarty et al., 2003), and that the ability of patients to automate cognitive skills is more impaired than controls. However, the results in the present study provide a more nuanced picture of impaired automaticity in schizophrenia. Our electrophysiological findings suggest that the schizophrenia deficit in automating visual search (i.e., tuning attention) arose from a disruption in the interplay between working memory and long-term memory representations. Specifically, long-term memory representations guiding attention failed to be brought online, while working memory representations failed to be offloaded, as experience with searching for the target accrued. Based on previous work (Reinhart and Woodman, 2014c; Reinhart et al., 2016), working memory representations were likely used by the patients in a responsive manner to compensate for their inability to lay down new long-term memories of the searched-for-target. Unlike the healthy controls that effectively transitioned their representations between memory systems during learning, patients were stuck in continually recruiting oversized working memory representations for the task of finding a single target, as opposed to allowing the capacity unlimited long-term memory system to more efficiently drive top-down control. It is this reliance on capacity-limited working memory that may have blocked patients

from rapidly tuning their attentional performance. Overall, the results suggest that the transfer of information between memory mechanisms may play a critical role in the attentional impairment in schizophrenia.

Our electrophysiological findings also suggest a disconnect between attentional performance and the focusing of attention in patients with schizophrenia. That is, I anticipated that attentional tuning impairments in behavior would be preceded by either abnormalities in input selection (measured by the N2pc) (**Fig. 11A**), or abnormalities in both selection guidance (measured by the CDA and anterior P1) *and* input selection (measured by the N2pc). The logic of the latter prediction is that faulty processing upstream would negatively impact processing downstream (**Fig. 11B**). However, I found that the input-selection process indexed by the N2pc preceding the severe behavioral impairments in the patients was completely intact and statistically indistinguishable from controls.

The results showing isolated impairment in selection guidance in patients with schizophrenia can be explained by a disproportional abnormality in the multiple parallel visual processing streams of patients. The existence of parallel processing pathways is one of the most basic principles of the visual system (Milner and Goodale, 1995). The ventral pathway originates in primary visual cortex and extends along the ventral surface into the temporal cortex. This pathway has been associated with the generation of the N2pc (Hopf et al., 2000; Hopf et al., 2006). The dorsal pathway also arises from the primary visual cortex but continues along the dorsal surface into parietal cortex. This pathway has been associated with the production of the CDA (Perez and Vogel, 2012). The differential effects of schizophrenia on the N2pc and CDA are consistent with

evidence suggesting that patients have abnormalities in the dorsal, not ventral, visual processing stream. For example, studies have shown selective deficits in response to magnocellular-biased stimuli related to dorsal stream processing, but not parvocellular-biased stimuli related to ventral stream processing in schizophrenia (Martínez et al., 2008). Further, the magnocellular pathway is critical for visual processes such as motion discrimination (Tootell et al., 1995), face processing (Puce et al., 1995; Narumoto et al., 2000), and reading (Pugh et al., 1996; Booth et al., 2001), all of which have been shown to be impaired in schizophrenia (Chen et al., 1999; Manor et al., 1999; Chen et al., 2004; Herrmann et al., 2004; Revheim et al., 2006; Turetsky et al., 2007), indicating that the deficient responsiveness of the magnocellular pathway in patients may influence the operation of higher-order perceptual and cognitive systems. One of the unique contributions of the present experiment is its demonstration that the behavioral tuning deficit in patients with schizophrenia is accompanied by strikingly normal processing at a well-defined intermediate processing stage, and that this behavioral deficit is more likely attributable to abnormalities in dorsal stream function.

Normalizing disease mechanisms of attentional tuning in schizophrenia via exogenous modulation of cortical activity

The present study shows that direct current noninvasively applied to the heads of patients with schizophrenia can change how information transmission occurs between memory mechanisms that direct selection, leading to the successful normalization of impaired attentional performance in patients. Following the electrical stimulation over

medial-frontal cortex, the patients showed normal attentional tuning behavior, increasing efficiency of visual search speed for the target. Electrophysiological evidence showed that the patients' attentional performance was resolved due to the stimulation having changed the functioning of the memory representations engaged prior to the analysis of the search array. In contrast to the abnormal reloading of working memory representations we observed at baseline, after stimulation the patients quickly released working memory control over the guidance of attention, becoming less reliant on effortful executive processing. At the same time, we watched long-term memory spring into action from its previously static state, accumulating instances of the searched-for-target while behavior became rapidly automated. The end result was a boost to input selection and the formation of an attentional tuning curve, indistinguishable from that of healthy subjects.

One initially puzzling result across Experiments 1 and 4 is how the same electrical stimulation targeting medial-frontal cortex could cause slightly different effects in the patients with schizophrenia and healthy controls. In Experiment 4, anodal stimulation exerted clear effects on visual working memory representations indexed by the CDA in patients, while the same stimulation completely spared the CDA in the healthy subjects from Experiment 1. To confirm the validity of these results, we analyzed the healthy subjects' data from the anodal condition of Experiment 4. We found that all of the primary findings from Experiment 1 replicated. This included the critical stimulation condition x target repetition interactions on RT ($F_{2,34}$ = 4.231, p = 0.036), N2pc amplitude ($F_{2,34}$ = 4.530, p = 0.029) and anterior P1 amplitude ($F_{2,34}$ = 4.526, p = 0.030), but not CDA amplitude ($F_{2,34}$ = 0.219, p = 0.709), suggesting that

medial-frontal stimulation again caused preferential enhancements in only the long-term memory activity elicited by the target cues, explaining the rapid improvement in input selection and the tuning of search behavior. These results reinforce the conclusion that working memory activity indexed by the CDA responds differently to medial-frontal stimulation across healthy people and people with schizophrenia during memory-guided visual search.

One explanation for why the medial-frontal stimulation did not influence the CDA of healthy subjects is that the rate of CDA decline during learning was already at peak levels of efficiency, unlike patients whose hyperactive CDA amplitudes provided plenty of room for this component to be influenced by the stimulation. Based on this interpretation, the results can be understood in the following way. In the healthy brain, stimulation had a preferential influence over long-term memory representations, maximizing the tuning of attention in a single trial, whereas working memory, untouched by the stimulation, was already being offloaded by the brain at maximal speed. In contrast, for patients with schizophrenia, not only did the stimulation maximize long-term memory driven attention in one trial, the stimulation reduced the abnormally large working memory representations, which were more easily attenuated given their exaggerated nature. Importantly, this view leads to the testable prediction that medial-frontal stimulation can affect the CDA in the healthy brain when this component is above floor levels, as it was in patients with schizophrenia at baseline. Previous work has shown that high-reward cues induce greater recruitment of working memory representations indexed by CDA amplitude, without disturbing long-term memory representations indexed by the anterior P1 (Reinhart and Woodman, 2014c; Reinhart et

al., 2016). Thus, if the hypothesis is correct that the stimulation effects depend on the activity level of the components they can change, the reward-triggered CDA enhancement should be reduced in healthy subjects following electrical stimulation over medial-frontal cortex.

Another hypothesis is that the antipsychotic medication in the patients boosted their working memory representations at baseline, or allowed the anodal stimulation to uniquely influence working memory in patients but not controls. It is always challenging to rule out the possibility that differences in neural activity and behavior between patients and controls are a consequence of medications. However, it is possible to determine whether the different types of medications patients received could explain the individual differences among patients. We examined CDA, anterior P1, and N2pc amplitudes using ANOVAs with stimulation condition, target repetition, and drug group as factors, comparing those who were taking typical (n = 2) versus atypical antipsychotics (n = 14), those taking selective serotonin reuptake inhibitors (n = 7) versus those not (n = 11), those taking a benzodiazepine (n = 3) versus those who were not (n = 15), and those taking anti-parkinsonian drugs (n = 2) versus those not (n = 16). In none of these analyses did the main effect of drug group, or interactions between drug group and the other factors (i.e., stimulation condition and target repetition) approach significance (ps > 0.42). In addition, we computed chlorpromazine (CPZ) equivalents for each of the patients and examined the correlation between this measure and the primary outcome measures (i.e., RT, CDA, anterior P1, and N2pc across all repetitions and between target repetition 1 and 2). None of these correlations approached significance (ps > 0.31). Thus, there was no evidence that medications

influenced the present results, including those related to the exaggerated CDA at baseline or the preferential influence of stimulation on the CDA in the patients with schizophrenia.

In summary, the results of the present research conform to theories of schizophrenia dysfunction that cast the attentional impairment as fundamentally a selection-guidance abnormality. Our findings suggest that impaired attention in schizophrenia lies in how the control parameters are conveyed between memory systems that influence what types of inputs should be selected to achieve efficient information processing and behavior on a task. Further, we have discovered that passing electrical current over the medial-frontal regions of the head can temporarily rectify the transmission of these control parameters that are passed between memory mechanisms, resulting in the normalization of how patients with schizophrenia use their attention when analyzing their environment for task-relevant inputs. These findings should help integrate theories of schizophrenia attentional dysfunction with models of learning and memory (Anderson, 1982; Rickard, 1997; Anderson, 2000; Logan, 2002) and allow us to gain further mechanistic insight into the pathophysiology of schizophrenia.

CHAPTER 4

GENERAL DISCUSSION

The findings of this dissertation research take us a step closer to a full reconciliation of the controversy over the nature of impaired attention in schizophrenia, and lay important groundwork for future work in the field of schizophrenia research. One class of cognitive models of schizophrenia proposes that the variety of schizophrenia abnormalities of behavior and experience derive from an alteration in the rapid assessment of sensory input (Hemsley, 1987, 1993, 2005), whereas another class of theories claim that the locus of schizophrenia cognitive impairment lies in the controlled processing that guides selection of inputs from the environment (Luck et al., 2006; Gold et al., 2007). Both perspectives make explicit but opposing predictions regarding the nature of cognitive impairment in schizophrenia. To date, progress adjudicating between these rival perspectives has been thwarted by a variety of methodological and conceptual challenges that have plagued the field of schizophrenia research on attention. The experiments conducted in this dissertation aimed to provide new understanding by overcoming these challenges. This was accomplished by: 1) the separation of attention into selection-guidance and input-selection constructs, 2) the use of precise electrophysiological tools for probing the different processes of attention, in addition to behavioral metrics, 3) the design of an experimental paradigm allowing for

the simultaneous assessment of the multiple memory representations important for attentional control, and 4) the application of a novel neuroscientific technique for the causal manipulation of attention. The end result was new evidence in favor of a class of models that highlights the mnemonic basis of the attentional abnormality in schizophrenia, and concrete translational progress for the development of new strategies for the potential remediation of attentional deficits in patients with schizophrenia.

In Experiments 1-3, I combined noninvasive brain stimulation with electrophysiological measurements of brain activity to understand the basic mechanisms of attention in healthy individuals. I used a paradigm that allowed me to examine the tuning of visual attention as subjects repeatedly searched for the same target embedded in an array of distractors. To examine the processes underlying the attentional tuning phenomenon, I used independent measurements of brain activity that allowed me to distinguish between the visual working memory and long-term memory contributions in the guidance of attention, as well as the implementation of attention itself. The most relevant and striking set of results was that electrical stimulation aimed over regions of the medial-frontal cortex produced changes in the brain that rapidly accelerated the tuning of visual attention, causing subjects to reach floor levels of search performance in a single trial. Second, the electrophysiological data revealed that the boost in attention was due to the stimulation preferentially influencing long-term memory processes that direct mechanisms of selection. These findings provided support for theories that propose long-term memory plays a critical role in how attention is used in the healthy brain, and demonstrated the existence of a new technique for

boosting attention through the external modulation of neural activity, as opposed to the more familiar methods of training with visual input.

In Experiment 4, I tested the competing predictions of schizophrenia cognitive models, and determined whether the stimulation protocol that I developed on healthy individuals in Experiments 1-2 could effectively repair attentional deficits in schizophrenia. First, I employed the cued visual search task of Experiment 1 to evaluate the integrity of the tuning of attentional performance in schizophrenia. In this experiment, I also used the electrophysiological signatures of selection guidance and input selection to evaluate the integrity of the processes that support attentional tuning (or the lack thereof) in schizophrenia. I found a unique array of neural and behavioral abnormalities, suggesting deficits in the tuning of attentional behavior, hyperactive engagement of working memory representations of top-down control, and critically, a lack of information transmission between the mechanisms that guide selection to task-relevant inputs during learning. The results were generally supportive of models of schizophrenia that emphasize controlled processing as playing a major role in the cognitive impairment of the disorder. Second, by noninvasively stimulating over regions of the medial-frontal cortex I revealed that it is possible to improve attentional performance in patients with schizophrenia by changing how working memory and long-term memory tradeoff representations that control the efficient processing of visual scenes. The results provided unique causal evidence for selection-guidance models of schizophrenia, and offered a new avenue for developing drug-free, therapeutic interventions for patients with neuropsychiatric disorders, such as schizophrenia.

Our findings that revealed an over-engagement in visual working memory representations in patients are noteworthy because they are consistent with theoretical ideas implying that an overreliance on top-down factors can drive perceptual hallucinations in patients with schizophrenia (Behrendt, 1998a). For example, Grossberg (2000) suggested that strong top-down excitation can create conscious experiences in the absence of bottom-up information. In this way, conscious mental imagery can arise. Grossberg (2000) has proposed a mechanism by which this top-down excitation becomes chronically hyperactive, through which sensory expectations can generate conscious experiences (by the activation of mental images) that are not under a person's control (i.e., hallucinations). The hypothesis that people who tend have experience with hallucinations may be characterized by strong top-down expectations has been supported empirically by work investigating the role of semantic expectations on perception in nonclinical subjects (i.e., those without a psychiatric disorders or psychotic symptoms that need treatment) (Vercammen and Aleman, 2010). Future work will be important to determine whether the medial-frontal stimulation in the present study, which reduced the overactive visual working memory activity, can correspondingly reduce the aberrant top-down processing contributing to the experience of hallucinations in patients with schizophrenia.

The instance theory of attention and memory is the natural modeling framework in which to integrate and explain the current findings (Logan, 1988, 2002). Instance theory conceives of representations from working memory and long-term memory as runners racing towards a threshold with the cognitive process triggered once the threshold is crossed by the first runner. In the context of the present study, we can view

the deployment of attention to the task-relevant input in the visual search array as the process of interest. With a larger number of runners, the average finishing time will be faster assuming variability in the speed of the runner. Thus, instance theory predicts that when we have more representations in multiple memory stores converging to drive attention to the target objects in the scene, we will have more efficient processing of the target information.

My work in this dissertation extends the basic logic of instance theory to the realm of schizophrenia attentional dysfunction and the temporary normalization of this attentional deficit following brain stimulation. First, I propose that the severely inefficient target processing by patients with schizophrenia derives from a two-part abnormality: the perseveration on the failed strategy of using a single working memory runner to control attention, and the failure of additional runners from long-term memory to join the race in the drive to more efficiently select target objects from the scene. These proposals are supported by the baseline observations that the CDA remained abnormally elevated and the anterior P1 failed to gain in negative amplitude, as patients with schizophrenia acquired experience performing the task. Second, on instance-theoretic grounds, the delivery of direct current over medial-frontal regions appeared to completely rescue target processing efficiency in the patients by opening the gates to long-term memory runners, increasing the degree of overall running speed variability, shorten finishing times, and relieving the working memory runner from having to do all the racing. These claims are evidenced by the anodal stimulation observations that the CDA diminished in size in a normal fashion, while anterior P1 experienced a dramatic increase in negativity on the second encounter with a new target object, suggesting that

stimulation had established a long-term memory trace of the new object on the first trial. Future modeling simulations in conjunction with brain and behavioral data will be needed to determine that a cognitive model within the framework of instance theory can indeed predict the failures we observed in patients when trying to automate their visual search performance as well as the extraordinary recovery of this behavior caused by the electrical brain stimulation.

Integrating the current clinical findings within the modeling framework of instance theory learning and memory suggests the novel hypothesis that the cognitive symptoms of schizophrenia may be better understood in terms of memory representations, and better alleviated if patients could recruit the appropriate long-term memory representations. This perspective that emphasizes the mnemonic basis of impaired attention in schizophrenia is relevant to the growing neuroimaging literature examining the faulty memory systems in people with schizophrenia (Kraguljac et al., 2013). For example, the prefrontal cortex is the site of the most commonly reported fMRI activation abnormalities associated with impaired episodic long-term memory in schizophrenia (Ragland et al., 2001; Barch et al., 2002; Weiss et al., 2003; Ragland et al., 2004; Ragland et al., 2005), especially in the frontal pole, consistent with the patients' anterior P1 abnormalities the we observed at baseline in Experiment 4. Moreover, in the healthy brain, it is commonly observed that working memory and episodic long-term memory systems show overlapping fMRI activation patterns within areas, such as the prefrontal cortex, the dorsolateral cortex, and the dorsal anterior cingulate cortex (Cabeza and Nyberg, 2000; Duncan and Owen, 2000; Schacter et al., 2000; Nyberg et al., 2002; Nyberg et al., 2003), suggesting that working memory and long-term memory share

some basic processing components. This is interesting because these are regions likely in the path of the direct electrical current used in Experiments 1, 2, and 4, in which we observed marked changes in memory-guided attention after stimulation. Not surprisingly, these are the very areas that neuroimaging research of memory deficits in schizophrenia has found to be abnormal (Ranganath et al., 2008).

An alternative perspective is that the nature of impaired attention in schizophrenia is not based in memory representations per say, but rather in the recruitment of the memory representations via a cognitive control network. We know that patients with schizophrenia have deficits in the structure, connections, and activity of medial-frontal cortical regions during cognitive-control tasks (Tamminga et al., 2000; Sanders et al., 2002), and fMRI research demonstrates that the cognitive control network of medial-frontal cortex (e.g., the mid cingulate) plays an important role in the long-term memory guidance of visualspatial attention in the healthy brain (Rosen et al., 2015). Indeed, anatomical studies in nonhuman primates and connectivity studies in humans show that both the hippocampus and posterior parietal cortex make substantial connections with the mid-cingulate cortex (Baleydier and Mauguière, 1987; Vogt et al., 2006; Beckmann et al., 2009). The anatomy suggests that this region is well positioned to support the interactions between long-term memory and attention. Thus, it is conceivable that the electrical stimulation of the present study boosted control-related activity of medial-frontal cortex, which aids in the cooperation between long-term memory and attention systems.

Although the results in the present research suggest that the nature of the attentional impairment in schizophrenia is rooted not in the sensory information-

processing stream itself, but in the memory representations controlling selection (or the cognitive control network mediating between memory and selection systems as suggested above) future work is needed to better establish this conclusion. It is noteworthy that we found electrophysiological evidence for a sensory perceptual processing deficit in schizophrenia, consistent with previous studies (Bruder et al., 1998; Mathalon et al., 2002; Butler et al., 2007; Luck et al., 2009; Cavus et al., 2012; Kappenman et al., 2012). However, this deficit did not appear to underlie the impairment in attentional tuning in patients, given that changes in sensory function (as indexed by the posterior P1 and N1) did not accompany changes in the tuning of attentional performance. Nevertheless, to more definitely address the role of low-level sensory processing in schizophrenia, I have begun to explore the effects of using the stimulation protocol developed in Experiment 2 (Reinhart et al., in review), which I demonstrated can selectively augment basic sensory processing in a causal manner via the manipulation of neural activity in posterior visual cortex. In future work, by employing medial-frontal stimulation, to preferentially change sources of top-down control, together with posterior stimulation, to preferentially change perceptual function, there is real potential to establish a powerful double dissociation between the sites of stimulation and effects on the electrophysiological measures of top-down control and sensory processing in schizophrenia.

The present study has important implications for translating the findings from the laboratory into the real world. At present, the treatment of cognitive deficits is typically accomplished with pharmacological intervention (Lewis et al., 2008). For patients with schizophrenia, atypical antipsychotic drugs (e.g., clozapine, risperidone, olanzapine)

can improve some aspects of cognitive deficits (Leucht et al., 2013). However, the adverse side effects of medication (Elkis, 2007; Brunoni et al., 2008) creates demand for effective and noninvasive treatment options without the side effects. Accumulating evidence suggests that transcranial electrical stimulation methods may provide just such an alternative or adjunct approach (Brunoni et al., 2014). For example, N-methyl-D-aspartate (NMDA) receptor abnormality is associated with schizophrenia (Coyle, 2012; Kort et al., in review) and NMDA antagonists eliminate tDCS effects, whereas NMDA agonists improve tDCS effects (Nitsche et al., 2004b; Nitsche et al., 2004a). In addition, brain-derived neurotropic factor (BDNF)-dependent synaptic plasticity deficits are implicated in schizophrenia (Favalli et al., 2012), and research shows direct-current stimulation promotes this type of plasticity (Fritsch et al., 20). TDCS also shows promise in terms of its practical attributes, including cost-effectiveness, ease to use, portability, and safety. The potential use of tDCS in clinical applications for the treatment of neuropsychiatric disorders, such as schizophrenia, particularly refractory cases, is certainly a promising area for the literature to explore in upcoming years.

In summary, the current work has achieved three new discoveries. First, we have taken the first steps in developing two novel brain stimulation protocols in the healthy brain: one for the causal manipulation of attentional control, the other for the causal manipulation of sensory perceptual processing. Second, we have provided the first characterization of attentional tuning deficits in schizophrenia, and have shown how they trace back to dysfunctional memory representations of top-down control. Third, we have provided the first demonstration that impaired attentional tuning in schizophrenia can be temporarily normalized using noninvasive direct-current stimulation, and that this

improvement in attention was due to a change in how memory representations were being recruited in the service of efficient target processing of complex visual scenes. Overall, the results align best with theories that emphasize top-down control as primarily underlying the attentional dysfunction in schizophrenia, and challenge rival theories proposing the locus of the deficit lies in the use, not the control, of perceptual attention. The results offer mechanistic insight to the field of schizophrenia research, and point to a future in which noninvasive electrical stimulation may be a viable psychiatric treatment option.

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