Schizophrenia Bulletin vol. 45 no. 1 pp. 96–105, 2019
doi:10.1093/schbul/sby002
Advance Access publication February 6, 2018

Localization and Elimination of Attentional Dysfunction in Schizophrenia During Visual Search

Robert M. G. Reinhart*[,1], Sohee Park[2,3], and Geoffrey F. Woodman[2]

[1]Department of Psychological & Brain Sciences, Center for Systems Neuroscience, Center for Research in Sensory Communications and Neural Technology, Boston University, 677 Beacon Street, Rm 312, Boston, MA 02215; [2]Department of Psychology, Center for Integrative and Cognitive Neuroscience, Vanderbilt Vision Research Center, Vanderbilt University, Nashville, TN; [3]Kyung Hee University, Seoul, Korea

*To whom correspondence should be addressed; tel: 617-353-9481; e-mail: rmgr@bu.edu

Theories of the locus of visual selective attention dysfunction in schizophrenia propose that the deficits arise from either an inability to maintain working memory representations that guide attention, or difficulty focusing lower-level visual attention mechanisms. However, these theoretical accounts neglect the role of long-term memory representations in controlling attention. Here, we show that the control of visual attention is impaired in people with schizophrenia, and that this impairment is driven by an inability to shift top-down attentional control from working memory to long-term memory across practice. Next, we provide converging evidence for the source of attentional impairments in long-term memory by showing that noninvasive electrical stimulation of medial frontal cortex normalizes long-term memory related neural signatures and patients' behavior. Our findings suggest that long-term memory structures may be a source of impaired attentional selection in schizophrenia when visual attention is taxed during the processing of multi-object arrays.

Key words: medial frontal cortex/visual attention/working memory/long-term memory/transcranial direct-current stimulation

Introduction

Cognitive impairments predict disability and functional outcome in schizophrenia, one of the most debilitating health conditions.[1–3] More specifically, abnormal attention lies at the core of cognitive deficits[4,5] but it is unclear whether these deficits arise from an early deficit in focusing attention on task-relevant information (ie, the *input selection hypothesis*),[6–8] or a failure to maintain the target representation in visual working memory leads to the attentional deficits (ie, the *selection guidance hypothesis*).[9,10] Here, we propose a novel *long-term memory guidance hypothesis* that attributes attentional deficits in schizophrenia to an inability to transition from using working memory (WM) to using long-term memory (LTM) to control attention. This idea is consistent with evidence indicating that LTM is critical for the effective deployment of attention,[11,12] and the well-established structural and functional changes in LTM-related regions such as the hippocampus in schizophrenia.[13,14]

To test competing accounts of the cause of the attentional deficits in schizophrenia, we devised a cued visual search task that allowed us to examine the integrity of the memory mechanisms that control attention and the lower-level mechanisms for focusing attention (figure 1a). A target object was cued at the beginning of each trial signaling the identity of the target that could appear in the search array a second later. Then, the target remained the same for 3–7 consecutive trials before it was changed to a different object.

We used well-established electrophysiological indices to test each of the competing theoretical accounts (figure 1b). To test the input selection hypothesis, we used an electrophysiological marker of the focusing of covert attention on the task-relevant object in the search array. The N2 posterior-contralateral (N2pc) is a negative-going waveform maximal over posterior cortex, contralateral to the location toward which covert visual attention is shifted, and provides a measure of the focusing of attention.[15] Prior studies examining the N2pc in schizophrenia have yielded mixed results with one study reporting smaller N2pc amplitudes in patients relative to controls[16] whereas another study found no group differences.[9] To test the selection guidance hypothesis, we used the contralateral delay activity (or CDA), a negative waveform maximal over posterior cortex, contralateral to the position of a remembered item, providing a measure of the maintenance of target object representations in visual

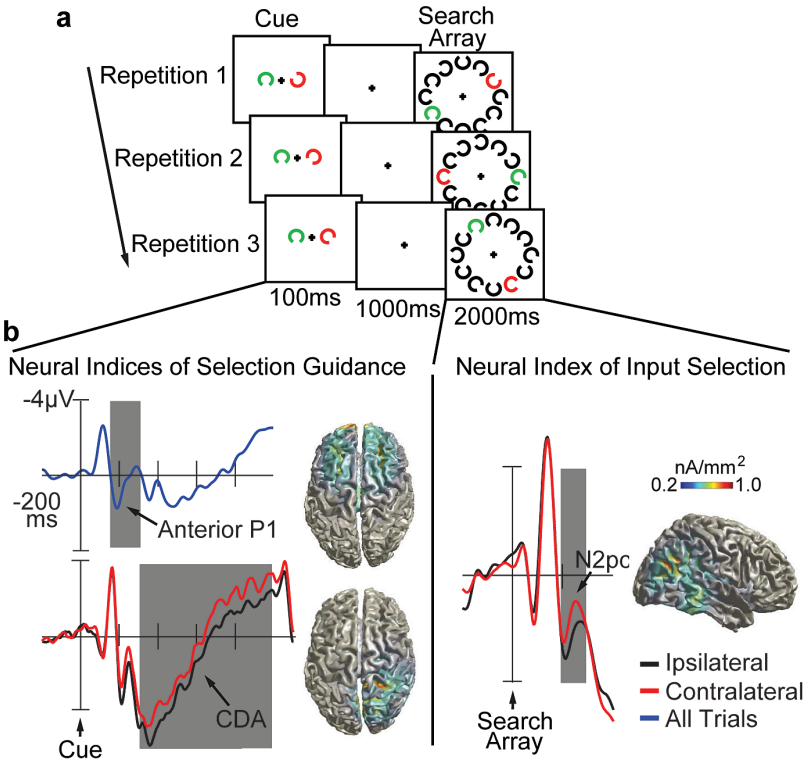

Fig. 1. (a) The cued visual search task, in which the task-relevant cue (red or green Landolt C, counterbalanced) signals the shape of the target in the upcoming search array (eg, looking for a green Landolt C with a gap down in the example). Subjects search for the same target across a run of 3–7 trials (or target repetitions). Central fixation is maintained for the trial duration. (b) Representative anterior P1, CDA, and N2pc waveforms showing each component's distinctive temporal and spatial profile.

WM.[17,18] The CDA amplitude is sensitive to various stimulus dimensions including color,[17,19] orientation,[18,19] and shape[20,21] as well as the precision or quality of the object representations that are stored.[22] CDA abnormalities have been linked to impaired visual WM in schizophrenia.[23] Finally, we tested our novel LTM guidance hypothesis. The anterior P1 is a positive waveform maximal over frontal cortex that becomes increasingly negative as encounters with specific stimuli accumulate traces in LTM.[11,24–26] The anterior P1 reflects a familiarity signal that builds up in LTM to support successful recognition, and can be used to predict recognition memory for a stimulus viewed hours in the past.[26] Additional evidence for the link between the anterior P1 and LTM comes from work showing that the amplitude of this component correlates with stimulus familiarity and previous encounters with a stimulus underlying recognition judgments.[26–29] To our knowledge, no studies have assessed the anterior P1 in schizophrenia. Together, these electrophysiological signatures provide a unique opportunity to simultaneously test rival theories of the mechanisms of attention in schizophrenia.

The input selection hypothesis predicts that impaired attention should stem from an abnormal front-end focusing of attention on possible targets in the search arrays, indexed by the N2pc, while the memory representations guiding attention (ie, the CDA, timelocked to the cue) should function normally. The selection guidance hypothesis predicts that impaired attention should stem from dysfunctional WM representations guiding attention indexed by the CDA timelocked to the cue. The LTM guidance hypothesis predicts that the LTM representations that control attention, indexed by the anterior P1 timelocked to the cue, should be disrupted. We tested these predictions in patients with schizophrenia and demographically matched healthy controls (table 1) performing the cued visual search task while we recorded their electroencephalogram (EEG).

Methods

Experiments 1 and 2 were run on the same group of patients so that we could use a within-subjects design to assess anodal transcranial direct-current stimulation (tDCS) effects, with order of the experiments counterbalanced across individuals to prevent confounds from learning or exposure to the other stimulation condition. To avoid expectancy and demand characteristic effects, in both experiments tDCS electrodes were placed, with the only difference being that sham stimulation was used in experiment 1 to induce the same itching and tingling experienced in experiment 2. After the 20 min of sham (experiment 1) or anodal stimulation (experiment 2) subjects began performing the cued visual search task while

Table 1. Demographic Information

	Patients Mean (SD)	Controls Mean (SD)	Statistical Test	*P*-Value
Age, years	44.5 (9.07)	44.5 (8.98)	$t = 0.148$	.88
Gender, *n*			$\chi^2 = 0.000$	1.00
Female	9	9		
Male	9	9		
Duration of illness, years	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)			

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

their event-related potentials (ERPs) were recorded (see supplementary methods for details).

Subjects

We first conducted a preliminary experiment to determine sample size by collecting data from 8 patients with schizophrenia. We conservatively merged mean difference and standard deviation values of behavioral and electrophysiological responses between anodal and sham tDCS conditions collapsed across target repetitions, and estimated Cohen's *d* effect sizes (RT: $d = 1.414$, anterior P1: $d = 0.933$, CDA: $d = 0.901$). We found that a sample size of 18 patients would be sufficient to detect an effect of similar magnitude with 80% power at the $P = .05$ significance level. Thus, data were collected from 18 patients with schizophrenia and 18 demographically matched healthy subjects in both experiments with order (experiment 1 vs 2) counterbalanced across subjects.

Subjects in each group were matched on age, gender, and handedness (table 1). Individuals who met the DSM-IV criteria for schizophrenia were recruited from outpatient psychiatric facilities in Nashville, TN. Diagnoses were confirmed with structured clinical interviews (SCID-IV).[30] Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS),[31] the Scale for the Assessment of Positive Symptoms (SAPS),[32] and the Scale for the Assessment of Negative Symptoms (SANS).[33] Two patients were medicated with typical antipsychotic drugs, 14 patients were medicated with atypical antipsychotic drugs, and 2 patients were medicated with both typical and atypical antipsychotic drugs. The mean chlorpromazine dose equivalent was 311.08 mg/day (SD = 287.77). Exclusion criteria were 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.

Stimuli

In both experiments, subjects performed a visual search task in which the target was cued on each trial (figure 1a). 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 locations on a clock face, 4.4° from the center of the monitor. 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°). The target shape could only appear in the task-relevant color. The task-relevant color of the cue stimulus was determined before the start of the experiment, counterbalanced across subjects to rule out physical stimulus confounds.[34]

Trial and Intertrial Structure

Each trial began with fixation (1200–1600 ms, duration jittered to prevent alpha entrainment). Next, 2 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,

during which we measured the N2pc. The intertrial interval was 1200–1600 ms, randomly jittered with a rectangular distribution. A target was presented in half of the search arrays and matched the shape of the task-relevant cue. Every search array contained an item that matched the color of the cue object (eg, the green item was the only possible target), but on target absent trials this object had a different shape. This allowed us to measure the N2pc to this possible target item on each trial. 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 (eg, an exact match between the shape of the red object in the cue and search array, if red was task relevant), and a different button with their right hand for target absent (eg, the shape of the red object in the search array was not the same as that in the cue array, if red was task relevant).

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 (length varied randomly). The shape of the target was randomly selected for each run, without repetition in adjacent runs. Each subject completed 720 trials in each condition (sham and anodal).

Results

Experiment 1

Patients exhibited marked impairments in visual search performance (see figure 2a, compare black lines from experiment 1). First, relative to controls, patients showed an overall increased RT for target detection as evidenced by a main effect of group ($F_{1,17}$ = 18.567, P < .01). This result is consistent with the classic behavioral impairment widely observed in schizophrenia.[35,36] Critically, patients did not improve in their ability to detect targets embedded in the array of objects as they looked for the same target across trials. 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 = .966), relative to the speeding of search RTs with target repetition in controls (significant main effect of target repetition, $F_{2,34}$ = 4.082, P = .039). A significant group × target repetition interaction was observed ($F_{2,34}$ = 5.391, P = .015). There was no evidence of a speed-accuracy tradeoff as accuracy was >90% in both groups (mean percent correct, patients: 91.5%; controls: 94.8%) and did not differ between groups or target repetitions (Ps > .42). These results show a clear impairment in the speed with which patients with schizophrenia

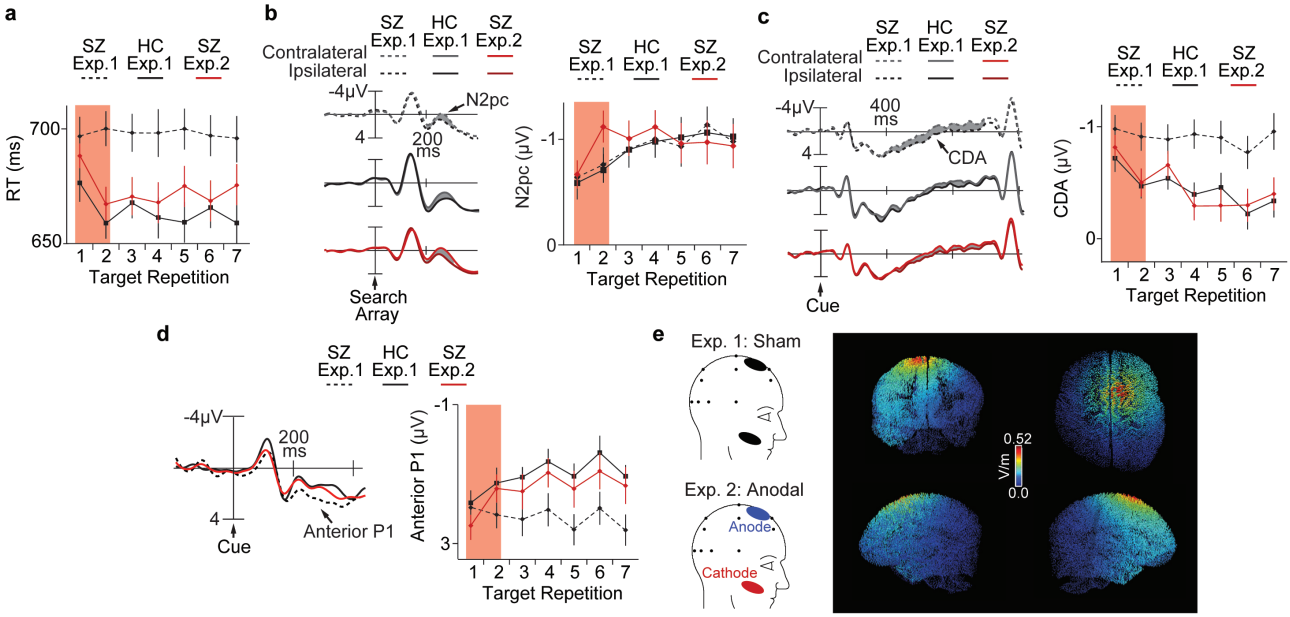

Fig. 2. Mean RTs (a), N2pc amplitudes (b), anterior P1 amplitudes (c), and CDA amplitudes (d) shown across target repetitions in patients with schizophrenia (SZ, dashed black lines) and healthy controls (HC, solid black lines) in the baseline conditions of experiment 1 and in patients with schizophrenia following active anodal stimulation in experiment 2 (solid red lines). Error bars are ±1 standard error of the mean. Red shading highlights dynamics across trials 1–2 where change in the speed of attentional selection was maximal. Grand average search array-locked event-related potentials (ERPs) at lateral occipital sites (OL/OR) contralateral and ipsilateral to the location of the target color averaged across target repetitions for each condition (b). Grand average cue-locked ERPs at lateral occipital sites (OL/OR) contralateral and ipsilateral to the location of the target cue averaged across target repetitions for each critical condition (c). Grand average cue-locked ERPs from the frontal midline electrode (Fz) averaged across target repetitions for each condition (d). The tDCS montage with frontocentral midline anode paired with a right cheek cathode for sham (used in experiment 1) and anodal stimulation (used in experiment 2 with SZ patients) (e, left). The modeled distribution of electrical current projected onto top, frontal, and lateral views of a 3D reconstruction of the cortical surface (e, right).

could attend to task-relevant objects in the visual scenes. However, the competing theoretical accounts explain these behavioral impairments in different ways. We compared these accounts by analyzing the electrophysiological data recorded simultaneously.

To determine whether an input-selection mechanism was responsible for the deficits in the patients,[6–8] we examined the neural signature of the focusing of covert visual attention (ie, the N2pc). Figure 2b (black lines, from experiment 1) shows the results, which indicate that 500 ms before the behavioral response, subjects allocated their attention to the target in the search array. The N2pc was fully intact in patients.[9] Specifically, patients and controls did not differ in the N2pc amplitude function, in terms its *y*-intercept (ie, amplitude at first target repetition) (no main effect of group, $F_{1,17} = 0.403$, $P = .534$), or its overall shape measured across the runs of same-target trials (no group × target repetition interaction, $F_{2,34} = 0.262$, $P = .769$). Both groups exhibited N2pc components that increased in amplitude as they searched for the same target across trials, evidenced by significant main effects of target repetition on N2pc amplitude (patients: $F_{2,34} = 4.091$, $P = .030$; controls, $F_{2,34} = 3.700$, $P = .041$). These results demonstrate that the patients can focus attention, as indexed by the N2pc, and thus their dysfunctional search performance cannot be explained by impaired attentional focus. These findings indicate that input selection is not the primary source of attentional dysfunction in schizophrenia.

To test whether the attentional deficit in schizophrenia is the result of impaired top-down control of attention by WM representations that maintain a template of the searched-for object, we analyzed the neural signature of visual WM (ie, the CDA) elicited by the target cues, appearing approximately 1 s before the search array. Patients' abnormal, unchanging RT for repeated target detection matched their abnormal, unchanging CDA amplitude (see figure 2c, black lines). First, we observed *y*-intercept differences in the CDA components between groups, which suggests that patients actually responded to the new search target by allocating more resources to maintain visual WM representations compared to control subjects. Specifically, patients had a larger CDA amplitude on the first target repetition for the storage of this single target item in memory (main effect of group, $F_{1,17} = 4.352$, $P = .050$). Critically, in contrast to the standard, decreasing CDA in controls ($F_{2,34} = 5.751$, $P = .012$), we observed an unchanging CDA amplitude function across same-target trials in the patients ($F_{2,34} = 0.233$, $P = .683$). Thus, we found electrophysiological evidence for greater WM engagement in schizophrenia patients than in healthy controls related to controlling attention, which challenges the conventional selection-guidance account of the attentional deficits in schizophrenia that attribute impaired attention to underactive WM processes.

Finally, we tested the hypothesis that abnormal attentional control is due to impaired LTM for the targets that should take over for WM in guiding attention across trials (ie, as indexed by the anterior P1). Although the anterior P1 of patients was no different from controls on the first trial of search with a given target object (no main effect of group on anterior P1 amplitude at the first target repetition, $F_{1,17} = 0.004$, $P = .949$), patients showed no evidence for the accumulation of memory traces (figure 2d), consistent with the hypothesis that attentional abnormalities in schizophrenia originate from an inability to rapidly transition from initially using WM representations to using LTM representations to control attention. Consistent with this, the anterior P1 became increasingly more negative in controls across same-target trials ($F_{2,34} = 9.072$, $P = .002$), but we found a severely blunted anterior P1 amplitude function across same-target trials in the patients ($F_{2,34} = 1.285$, $P = .288$), and the group × target repetition interaction on the anterior P1 amplitude was significant ($F_{2,34} = 7.427$, $P = .005$). In addition, when we assessed the amplitude changes between the N2pc, CDA, and anterior P1 across trials, we found significant relationships among these components for healthy controls (CDA–N2pc, $r = -.779$, $P = .039$; anterior P1–N2pc, $r = .871$, $P = .011$; anterior P1–CDA, $r = -.847$, $P = .016$), but not for patients (CDA–N2pc, $r = -0.603$, $P = .152$; anterior P1–N2pc, $r = -.121$, $P = .795$; anterior P1–CDA, $r = -.390$, $P = .387$). These results provide support for the hypothesis that attentional deficits in patients with schizophrenia arise from a disruption in the accumulation of target representations in LTM that typically guide attention to select the relevant objects in cluttered scenes. Interestingly, this is not because WM-related activity is absent, but instead patients appear to exclusively rely on WM representations of target objects without benefitting from LTM storage of these target representations. These results are consistent with work showing that patients with schizophrenia exhibit a reduced ability to initiate experience-based changes in the visual system and develop appropriate memory representations for certain repeated visual stimuli.[37,38] In contrast, healthy control subjects improve attentional selection with each trial of practice due to an increasing reliance on LTM (see supplementary discussion for extended discussion of these results).

Experiment 2

The goal of Experiment 2 was to provide converging evidence for the hypothesis that attentional deficits in schizophrenia originate from LTM by using a causal manipulation of brain activity that selectively improves LTM for the search targets. Recent work has shown that administering 20 min of tDCS over medial frontal cortex (figure 2e) can improve the efficiency of attentional selection in healthy young adults by increasing the quality

(or amount) of the LTM representations of targets, without changing the nature of WM storage.[39] If anodal tDCS of the medial-frontal region can cause rapid improvement of attentional performance in patients with schizophrenia, we can then ask whether this causal manipulation exerted its influence on attention by altering the functioning of the underlying memory mechanisms important for guiding selection. Theories that propose LTM plays an important role in selection guidance would predict that the anterior P1 measured a full second before performing visual search would have been augmented by the stimulation. Specifically, the prediction would be that after stimulation, the anterior P1 amplitudes would exhibit a function across learning trials that would gradually increase in negativity as subjects become more proficient at automating their attention to task-relevant objects, analogous to the function of anterior P1 amplitudes generated by healthy control subjects at baseline in experiment 1.

We found that 20 min of tDCS over medial frontal cortex effectively recovered the ability of patients to attend 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 2a (red line) shows that after anodal stimulation patients exhibited improved attentional selection of targets across trials, demonstrated by a significant main effect of target repetition on search RT ($F_{2,34}$ = 4.366, P = .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 2 trials of search for a particular Landolt C (stimulation × target repetition interaction, $F_{1,17}$ = 5.377, P = .033). Further, the normalization of patients' RT function following stimulation erased the discrepancy between patients' search efficiency and that of the controls at baseline (group × target repetition interaction, $F_{2,34}$ = 0.788, P = .462), with even greater overlap between groups across the first 2 trials in the same-target runs ($F_{1,17}$ = 0.282, P = .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 > .57). Thus, 20 min of electrical stimulation over medial frontal cortex was sufficient to temporarily eliminate the attentional deficits in schizophrenia, allowing patients to successfully automate their visual search performance, just like healthy control subjects.

The medial-frontal stimulation that normalized attentional selection in patients with schizophrenia changed how these patients used their memory mechanisms to direct selection. Figure 2b–d (solid red vs black lines) shows that anodal stimulation reshaped the amplitude functions of the electrophysiological responses related to the guidance of selection by LTM (ie, the anterior P1) representations, as well as WM (ie, the CDA) and input selection itself (ie, 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 = .002) and sharp increase (more negative) in anterior P1 amplitude ($F_{2,34}$ = 8.085, P = .008), effects that were significantly correlated (r = −.872, P = .010), as patients accumulated greater experience searching for the same target object. Mirroring the behavioral changes, the normalization of the memory-related electrophysiological markers across trials eliminated the 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: group × target repetition, $F_{2,34}$ = 0.151, P = .796; anterior P1: group × target repetition, $F_{1,17}$ = 0.181, P = .827), including across the first 2 trials of the same-target runs (CDA: $F_{1,17}$ = 0.073, P = .791; anterior P1: $F_{1,17}$ = 1.824, P = .195). In addition, the stimulation-induced changes in memory-related components led to a positive impact downstream on the focusing of attention, boosting N2pc amplitude between the first 2 target repetitions (stimulation × target repetition, $F_{1,17}$ = 4.848, P = .042) when the stimulation had its largest influence on behavior. Cross-trial amplitude correlations showed that only anterior P1 significantly predicted later N2pc dynamics (r = .777, P = .040), whereas the CDA did not predict changes in N2pc amplitude across trials (r = −.550, P = .200). Despite downstream effects on the N2pc, other electrophysiological components indexing lower-level perceptual processing (ie, the visual P1 and N1) or late-stage response selection (ie, the lateralized-readiness potential) during search remained unchanged by the tDCS (see supplementary results, supplementary figure S1, and supplementary table S1). Together, these results suggest that the processing efficiency following medial-frontal stimulation is due to these patients now being able to effectively transition between sources of top-down control; after stimulation patients were able to rely on LTM representations to drive attentional selection rather than WM representations, as we describe below.

Our results suggest that LTM plays a central role in attentional deficits of schizophrenia, based on previous functional interpretations of the anterior P1 and its modulation across short bursts of learning trials. However, if the anterior P1 is truly sensitive to the accumulation of information in LTM, we should be able to watch the anterior P1 of healthy controls increase in negativity not only across trial-by-trial repetitions but also over the entire recording period of the experiment, given that the set of 8 possible Landolt-C targets repeats multiple times throughout the task. Most important, if the electrical stimulation can normalize LTM-based attentional control in patients, as our data thus far indicates, then after stimulation we should see effects on attentional behavior and anterior P1 function across the full recording

session that mimic those of healthy controls: faster search RTs and greater anterior P1 negativity as patients accrue greater experience on the task.

To examine the cumulative effects of learning over a more protracted time course, we averaged together same-target runs for the first third, second third, and last third of all trials, allowing us to view how behavior, the anterior P1, and the CDA were changing from the beginning, middle, and end of the experiment. Figure 3 shows the learning across these long segments of the task. In healthy subjects, RTs were slowest at the beginning of the experiment, but became faster as experience with the 8 possible targets increased. In contrast, patients showed highly abnormal RT functions across the task, suggesting that they were unable to automate attention over the long term. The accumulation of experience across the entire session that sped RT in healthy subjects but not in the patients was matched by systematic changes in the amplitude of the anterior P1. The anterior P1 became progressively more negative across the experiment in healthy subjects but not for patients. These results were as predicted if the magnitude of the anterior P1 negativity indexed the quality (ie, strength or number) of the long-term memories for these targets that accumulated across the entire experiment, and if impaired attention in schizophrenia derives in part from an impairment in the quality of these long-term memories. Moreover, unlike the anterior P1, the CDA showed no change across the entire experiment in either subject group, suggesting that the role of WM in updating the target at the beginning of the same-target runs does not change with learning over a longer time course. It is possible that WM was re-instantiated to minimize proactive interference caused by a buildup of target representations during the previous run of trials, consistent with prominent theories of WM[40] and previous empirical findings in healthy adults.[11,39]

The largest effects were those induced by the medial-frontal tDCS. The stimulation preferentially normalized RT and anterior P1 amplitude functions in the patients with schizophrenia. After tDCS, patients' RT and anterior P1 data showed a general enhancement relative to sham, as well as normal cumulative learning effects in behavior and normal dynamics in anterior P1 evolution over time, analogous to data from controls. These results provide converging evidence for the proposal that contributions from LTM may play a key role in driving attentional dysfunction in schizophrenia, and suggest that tDCS can be used to rectify memory mechanisms directing selection and rescue attentional performance.

Discussion

The present study indicates that attentional deficits during visual search in patients with schizophrenia may arise from impaired access to top-down control governed by LTM systems that are important for the efficient analysis of complex visual scenes. By electrically stimulating regions of medial frontal cortex, it was possible to reconfigure selection-guidance mechanisms to automate search and rely on LTM, enabling patients to rapidly improve attentional selection of targets across the 2 s trials. Our results suggest that when tDCS remedies the LTM abnormality observed without stimulation (see supplementary discussion for additional discussion), this allows for the normal transition from WM to LTM of the control of visual selective attention during tasks in which the target identity is not changing every couple of seconds. Evidence from ERP amplitude correlations suggests that the tDCS-induced improvement in attention in the patients was more likely due to changes in how LTM was functioning after stimulation. However, we note that both the CDA, indexing WM, and the anterior P1, indexing LTM, were affected by stimulation. This raises the interesting

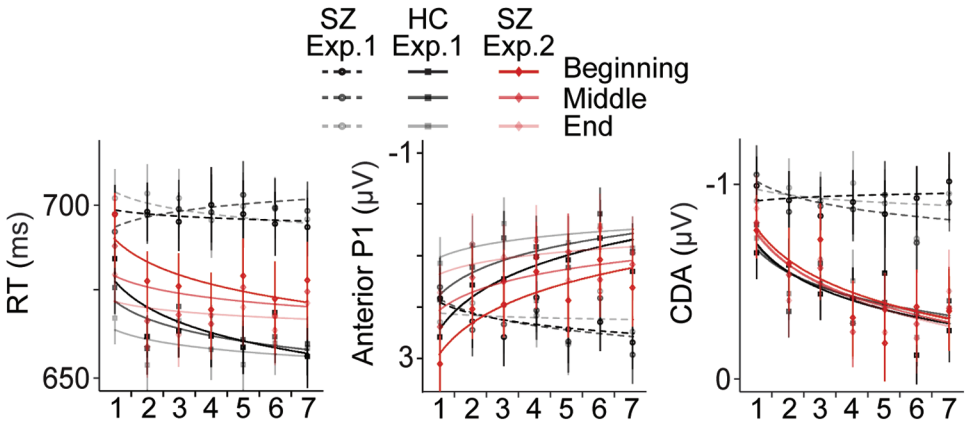

Fig. 3. Mean RT, anterior P1 amplitude, and CDA amplitude as a function of target repetitions binned according to the first third (dark), middle third (medium), and last third of runs (light) shown for patients with schizophrenia (SZ, experiment 1, dashed black) and healthy controls (HC, experiment 1, solid black) at baseline, and for patients with schizophrenia (SZ, experiment 1, solid red) after anodal stimulation. Trend lines show logarithmic model fits. Error bars are ±1 SEM.

possibility that the locus of the improvement could have been due to normalization of LTM, WM, or both of these memory subsystems. Future studies employing multiple tDCS protocols that can separately isolate and alter WM and LTM neural structures should be able to more definitively elucidate the causes of the attentional enhancement following stimulation in patients with schizophrenia.

The current study suggests that one locus of visual selective attentional deficits in schizophrenia is the abnormal operation of memory mechanisms. If LTM representations contribute to these visual attentional deficits, then effective treatments for attentional impairments must target LTM as well. The perspective emphasizing the mnemonic basis of impaired visual selective attention in schizophrenia is relevant to the growing neuroimaging literature examining the faulty memory systems in people with schizophrenia.[41] For example, the prefrontal cortex is the site of the most commonly reported fMRI activation abnormalities associated with impaired episodic LTM in schizophrenia,[42–46] especially in the frontal pole, consistent with the patients' anterior P1 abnormalities observed in the present study at baseline. Moreover, in the healthy brain, it is commonly found that WM and episodic LTM systems show overlapping fMRI activation patterns within areas, such as the prefrontal cortex, the dorsolateral cortex, and the dorsal anterior cingulate cortex,[47–51] suggesting that WM and LTM share some basic processing components. This is interesting because these are regions in the path of the direct electrical current used in the present study, and indeed, these are the very areas that are known to be compromised in schizophrenia.[52]

An alternative perspective is that the nature of impaired visual selective attention in schizophrenia is not based in memory representations per say, but rather in the recruitment of the memory representations via the 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,[53,54] and fMRI research demonstrates that the cognitive control network of medial frontal cortex (eg, the mid cingulate) plays an important role in the LTM guidance of visuo-spatial attention in the healthy brain.[55] 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.[56–58] The anatomy suggests that this region is well positioned to support the interactions between LTM 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 LTM and visual attention systems.

In summary, the present results challenge input-selection and selection-guidance models of cognitive dysfunction in schizophrenia, in which attentional problems are hypothesized to arise exclusively from the focusing of attention or abnormal WM, respectively. In contrast, we found patients over-represented task-relevant information in WM, instead of relying on the stable accumulation of representations in LTM. The proposal that our findings support is that impaired visual selective attention in schizophrenia may originate from over-reliance on WM and a dysfunction in LTM that prevent the accumulation of information from improving attentional selection during visual search. Further, we found that passing electrical current through the medial-frontal regions of the brain temporarily rectified the transmission of these control parameters that are passed between memory mechanisms, resulting in the normalization of how patients with schizophrenia could perform visual search. The latter results contribute to the development of nonpharmacological interventions targeting cognitive symptoms in neuropsychiatric disorders.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Funding

This work was supported by grants from the National Institutes of Health (R01-MH110378, R01-EY019882, R01-EY025275, P30-EY08126, F31-MH102042, and T32-EY007135) and a Vanderbilt University Discovery Grant.

Acknowledgment

The authors declare no competing financial interests.

References

1. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study. *The Lancet*. 2013;380:2129–2143.
2. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153:321–330.
3. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. 2000;26:119–136.
4. Kraepelin E. *Dementia Praecox and Paraphrenia*. 8th ed. Huntington, NY: Kreiger, R.E.; 1896.
5. Bleuler E. *Dementia Praecox: or the Group of Schizophrenias*. New York: International Universities Press; 1911.
6. Hemsley D. An experimental psychological model for schizophrenia. In: Hafner H, Gattaz W, Janzarik W, eds. *Search for the Causes of Schizophrenia*. Vol 1. New York: Springer; 1987:179–188.
7. Hemsley D. A simple (or simplistic?) cognitive model for schizophrenia. *Behav Res Ther.* 1993;31:633–646.
8. Hemsley DR. The development of a cognitive model of schizophrenia: placing it in context. *Neurosci Biobehav Rev*. 2005;29:977–988.

9. Luck SJ, Fuller RL, Braun EL, Robinson B, Summerfelt A, Gold JM. The speed of visual attention in schizophrenia: electrophysiological and behavioral evidence. *Schizophr Res*. 2006;85:174–195.
10. Gold JM, Fuller RL, Robinson BM, Braun EL, Luck SJ. Impaired top-down control of visual search in schizophrenia. *Schizophr Res*. 2007;94:148–155.
11. Woodman GF, Carlisle N, Reinhart RMG. Where do we store the memory representations that guide attention? *J Vis.* 2013;13:1–7.
12. Logan GD. An instance theory of attention and memory. *Psychol Rev*. 2002;109:376–400.
13. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature*. 2010;464:763–767.
14. Heckers S, Rauch S, Goff D, Savage C, Schacter D, Fischman A, Alpert N. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci.* 1998;1:318–323.
15. Woodman GF, Luck SJ. Electrophysiological measurement of rapid shifts of attention during visual search. *Nature*. 1999;400:867–869.
16. Verleger R, Talamo S, Simmer J, Śmigasiewicz K, Lencer R. Neurophysiological sensitivity to attentional overload in patients with psychotic disorders. *Clin Neurophysiol*. 2013;124:881–892.
17. Vogel EK, Machizawa MG. Neural activity predicts individual differences in visual working memory capacity. *Nature*. 2004;428:748–751.
18. Vogel EK, McCollough AW, Machizawa MG. Neural measures reveal individual differences in controlling access to working memory. *Nature*. 2005;438:500–503.
19. Woodman GF, Vogel EK. Selective storage and maintenance of an object's features in visual working memory. *Psychon Bull Rev*. 2008;15:223–229.
20. Ikkai A, McCollough AW, Vogel EK. Contralateral delay activity provides a neural measure of the number of representations in visual working memory. *J Neurophysiol*. 2010;103:1963–1968.
21. Luria R, Sessa P, Gotler A, Jolicoeur P, Dell'acqua R. Visual short-term memory capacity for simple and complex objects. *J Cogn Neurosci*. 2009;22:496–512.
22. Machizawa MG, Goh CC, Driver J. Human visual short-term memory precision can be varied at will when the number of retained items is low. *Psychol Sci*. 2012;23:554–559.
23. Leonard CJ, Kaiser ST, Robinson BM, et al. Toward the neural mechanisms of reduced working memory capacity in schizophrenia. *Cereb Cortex*. 2013;23:1582–1592.
24. Reinhart RM, Woodman GF. High stakes trigger the use of multiple memories to enhance the control of attention. *Cereb Cortex*. 2014;24:2022–2035.
25. Voss JL, Schendan HE, Paller KA. Finding meaning in novel geometric shapes influences electrophysiological correlates of repetition and dissociates perceptual and conceptual priming. *Neuroimage*. 2010;49:2879–2889.
26. Tsivilis D, Otten LJ, Rugg MD. Context effects on the neural correlates of recognition memory: an electrophysiological study. *Neuron*. 2001;31:497–505.
27. Duarte A, Ranganath C, Winward L, Hayward D, Knight RT. Dissociable neural correlates for familiarity and recollection during the encoding and retrieval of pictures. *Brain Res Cogn Brain Res*. 2004;18:255–272.
28. Friedman D. ERP studies of recogntion memory: differential effects of familiarity, recollection, and episodic priming. *Cogn Sci.* 2004;1:81–121.
29. Diana RA, Vilberg KL, Reder LM. Identifying the ERP correlate of a recognition memory search attempt. *Brain Res Cogn Brain Res*. 2005;24:674–684.
30. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders*: New York: Biometrics Research Department; 1995.
31. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep.* 1962;10:799–812.
32. Andreasen NC. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Iowa: University of Iowa; 1984.
33. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa: University of Iowa; 1983.
34. Woodman GF. A brief introduction to the use of event-related potentials (ERPs) in studies of perception and attention. *Atten Percept Psychophys*. 2010;72:2031–2046.
35. Cancro R, Sutton S, Kerr J, Sugerman AA. Reaction time and prognosis in acute schizophrenia. *J Nerv Ment Dis*. 1971;153:351–359.
36. Reinhart RM, Mathalon DH, Roach BJ, Ford JM. Relationships between pre-stimulus γ power and subsequent P300 and reaction time breakdown in schizophrenia. *Int J Psychophysiol*. 2011;79:16–24.
37. Silverstein SM, Bakshi S, Nuernberger S, Carpinello K, Wilkniss S. Effects of stimulus structure and target-distracter similarity on the development of visual memory representations in schizophrenia. *Cogn Neuropsychiatry*. 2005;10:215–229.
38. Silverstein SM, Bakshi S, Chapman RM, Nowlis G. Perceptual organisation of configural and visual patterns in schizophrenia: effects of repeated exposure. *Cogn Neuropsychiatry*. 1998;3:209–223.
39. Reinhart RMG, Woodman GF. Enhancing long-term memory with stimulation tunes visual attention in one trial. *Proc Natl Acad Sci USA*. 2015;112:625–630.
40. Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev*. 2002;9:637–671.
41. Kraguljac NV, Srivastava A, Lahti AC. Memory deficits in schizophrenia: a selective review of functional magnetic resonance imaging (FMRI) studies. *Behav Sci (Basel)*. 2013;3:330–347.
42. Barch DM, Csernansky JG, Conturo T, Snyder AZ. Working and long-term memory deficits in schizophrenia: is there a common prefrontal mechanism? *J Abnorm Psychol*. 2002;111:478–494.
43. Weiss AP, Schacter DL, Goff DC, et al. Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Biol Psychiatry*. 2003;53:48–55.
44. Ragland JD, Gur RC, Valdez J, et al. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. *Am J Psychiatry*. 2004;161:1004–1015.
45. Ragland JD, Gur RC, Raz J, et al. Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. *Am J Psychiatry*. 2001;158:1114–1125.
46. Ragland JD, Gur RC, Valdez JN, et al. Levels-of-processing effect on frontotemporal function in schizophrenia during word encoding and recognition. *Am J Psychiatry*. 2005;162:1840–1848.

47. Nyberg L, Marklund P, Persson J, et al. Common prefrontal activations during working memory, episodic memory, and semantic memory. *Neuropsychologia*. 2003;41:371–377.
48. Schacter DL, Wagner RL, Buckner RL. *Memory Systems of 1999*. New York, NY: Oxford University Press; 2000.
49. Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000;12:1–47.
50. Nyberg L, Forkstam C, Petersson KM, Cabeza R, Ingvar M. Brain imaging of human memory systems: between-systems similarities and within-system differences. *Brain Res Cogn Brain Res*. 2002;13:281–292.
51. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci*. 2000;23:475–483.
52. Ranganath C, Minzenberg MJ, Ragland JD. The cognitive neuroscience of memory function and dysfunction in schizophrenia. *Biol Psychiatry*. 2008;64:18–25.
53. Tamminga CA, Vogel M, Gao X, Lahti AC, Holcomb HH. The limbic cortex in schizophrenia: focus on the anterior cingulate. *Brain Res Brain Res Rev*. 2000;31:364–370.
54. Sanders GS, Gallup GG, Heinsen H, Hof PR, Schmitz C. Cognitive deficits, schizophrenia, and the anterior cingulate cortex. *Trends Cogn Sci*. 2002;6:190–192.
55. Rosen ML, Stern CE, Michalka SW, Devaney KD, Somers DC. Cognitive control network contributions to memory-guided visual attention. *Cereb Cortex*. 2016;26:2059–2073.
56. Baleydier C, Mauguière F. Network organization of the connectivity between parietal area 7, posterior cingulate cortex and medial pulvinar nucleus: a double fluorescent tracer study in monkey. *Exp Brain Res*. 1987;66:385–393.
57. Vogt BA, Vogt L, Laureys S. Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage*. 2006;29:452–466.
58. Beckmann M, Johansen-Berg H, Rushworth MF. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J Neurosci*. 2009;29:1175–1190.