# Neural Correlates of Impaired Cognitive Control over Working Memory in Schizophrenia

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**Background:** One of the most common deficits in patients with schizophrenia (SZ) is in working memory (WM), which has wide-reaching impacts across cognition. However, previous approaches to studying WM in SZ have used tasks that require multiple cognitive-control processes, making it difficult to determine which specific cognitive and neural processes underlie the WM impairment.

**Methods:** We used functional magnetic resonance imaging to investigate component processes of WM in SZ. Eighteen healthy controls (HCs) and 18 patients with SZ performed an item-recognition task that permitted separate neural assessments of 1) WM maintenance, 2) inhibition, and 3) interference control in response to recognition probes.

**Results:** Before inhibitory demands, posterior ventrolateral prefrontal cortex (VLPFC), an area involved in WM maintenance, was activated to a similar degree in both HCs and patients, indicating preserved maintenance operations in SZ. When cued to inhibit items from WM, HCs showed reduced activation in posterior VLPFC, commensurate with appropriately inhibiting items from WM. However, these inhibition-related reductions were absent in patients. When later probed with items that should have been inhibited, patients showed reduced behavioral performance and increased activation in mid-VLPFC, an area implicated in interference control. A mediation analysis indicated that impaired inhibition led to increased reliance on interference control and reduced behavioral performance.

**Conclusions:** In SZ, impaired control over memory, manifested through proactive inhibitory deficits, leads to increased reliance on reactive interference-control processes. The strain on interference-control processes results in reduced behavioral performance. Thus, inhibitory deficits in SZ may underlie widespread impairments in WM and cognition.

Schizophrenia (SZ) is a psychiatric illness characterized by a diverse range of clinical symptoms and disturbances in behavior. Although diagnosis is made based on the occurrence of positive and negative symptoms (1), it is the cognitive symptoms that are most strongly associated with patients' functional outcome (2). Among the most frequently noted of the cognitive symptoms in SZ are deficits in working memory (WM) (3–6). WM is a complex construct comprising component processes that enable the short-term retention of information to guide goal-directed behavior (7,8). WM supports a variety of cognitive abilities, including learning, reasoning, verbal comprehension, and academic success (9) and might be an even better predictor of academic success than IQ (10). Because of its centrality in cognition, it is not surprising that WM deficits in SZ are associated with impairments in social and occupational functioning (11,12). Hence, understanding breakdowns in the component processes in WM in SZ is fundamental to understanding not only cognitive function in the disorder but also the disorder itself.

Previous studies have provided the groundwork for addressing behavioral WM deficits in SZ. Deficits have been attributed to a failure in cognitive-control over the inhibition of irrelevant information in WM or the selection of responses at retrieval (e.g., 13–18). However, previous approaches to studying WM in SZ have used tasks requiring multiple cognitive-control processes that are challenging to disentangle, making it difficult to determine which specific component processes are impaired (16,19–25).

To help address this issue, we previously examined patients with SZ and healthy controls (HCs) in a task that dissociated two forms of cognitive control over WM (26). We compared the filtering of irrelevant distractors before items entered WM and the inhibition of irrelevant distractors after information had entered WM (27,28). We found that patients with SZ were unimpaired when they had to filter items before they entered WM, indicating intact encoding processes and ruling out a general WM deficit. Yet the same patients were impaired when they had to inhibit irrelevant distractors after information had entered WM. These data support the idea that WM deficits are not global in SZ. However, because the behavioral data could not examine ongoing processing and only reflected the response to the probe, we could not determine whether the deficit was due to a failure to inhibit irrelevant information in WM or to interference at retrieval.

In the current study, we used functional magnetic resonance imaging (fMRI) to examine patients with SZ and HCs during a single cognitive task that allowed us to separate the neural mechanisms contributing to 1) the maintenance of information in WM before inhibitory demands, 2) the inhibition of irrelevant items from WM, and 3) the resolution of interference of irrelevant information at the time of retrieval. Thus, the design separated various phases of WM to investigate the precise subcomponents of WM that are impaired in patients with SZ, which ultimately lead to difficulties during retrieval.

Participants were first presented with a memory-set consisting of two red and two blue words (Figure S1 in Supplement 1). Thereafter, the four words were removed from view. This constituted the PreCue, maintenance-only phase. Participants

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were then instructed, via an instruction cue, to retain only two of the words, corresponding to the instruction cue's color (e.g., blue) and to consider only these words when responding to the test probe. The PostCue phase measured inhibitory control of items in WM. Here, participants should reduce their WM load by inhibiting memory representations of the two irrelevant (e.g., red) words, retaining representation of only the two relevant (e.g., blue) words. Finally, in the third and final phase of the task, participants retrieved information from WM. A test probe required a positive response if it matched one of the two target words (Valid; e.g., either of the blue words) and a negative response if it either matched a word that should have been inhibited (Lure; e.g. either of the red words), or if it had not been presented in the trial (Control).

We hypothesized that patients with SZ would be specifically impaired at inhibiting information in WM, reflected in the second phase of the task. The hypothesis makes the following predictions: in the maintenance-only portion of the task before the cue (PreCue), patients and HCs should show equivalent neural activations in areas involved in WM maintenance, particularly the posterior areas of the left ventrolateral prefrontal cortex (VLPFC, Brodmann's area 44), thought to reflect phonologic rehearsal (29,30). After the instruction cue (PostCue), HCs were predicted to show a reduction in maintenance-related activation in posterior VLPFC, which has been shown to vary linearly on the basis of the verbal WM load (29), because of the inhibition of irrelevant items. By contrast, activation in this area was predicted to remain elevated in patients commensurate with their inability to inhibit items from WM. These inhibitory failures in patients were expected to lead to increased interference during the third, retrieval-phase of the task. Here, we predicted that patients would have more difficulty distinguishing Lures from Valid items. If Lure word representations were successfully inhibited from WM, performance on Lure probes should be equivalent to performance on Control probes. However, if items were not appropriately inhibited, then Lure probes would require additional interference-control processes to be distinguished from Valid probes. This difficulty was expected to be reflected in increased activation in the left mid-VLPFC (Brodmann's area 45), an area associated with the resolution of WM-based conflict (31). Hence, a deficit in inhibiting information in WM was predicted to lead a dynamic pattern of neural differences between patients with SZ and HCs.

## Methods and Materials

### Participants

Data from 18 HCs and 18 patients with SZ are reported. Demographics are shown in Table 1, along with clinical ratings for the patients. Another 4 patients and 4 HCs were tested but not included in the analysis because they did not respond on more than 20% of trials or had an error rate 2 SD above the respective group average in one of the probe-type conditions. See Supplemental Methods in Supplement 1 for a complete description of the participants.

### Materials

The stimuli consisted of 80 four-letter nouns that have been used in previous studies with this paradigm (26–28).

### Procedure

Participants were presented with a four-word memory set for 4000 milliseconds and were instructed to retain the items in

**Table 1.** Demographic, Clinical, and Neuropsychological Characteristics

| Variable | SZ Patients | HC Subjects |
|---|---|---|
| *N* | 18 | 18 |
| Age (yr) | 37.9 (9.3) | 36.3 (8.2) |
| Sex (Female/Male) | 7/11 | 5/13 |
| Handedness | | |
|   Right | 17 | 17 |
|   Left | 1 | 1 |
|   Ambidextrous | 0 | 0 |
| Education | 14.3 (2.4) | 15.6 (2.0) |
| Negative Symptoms (SANS) | | |
|   Affective flattening | 2.00 (1.14)/5 | |
|   Alogia | .83 (1.42)/5 | |
|   Avolition/apathy | 1.71 (1.40)/5 | |
|   Asociality/anhedonia | 2.39 (1.42)/5 | |
|   Attention | 1.41 (1.33)/5 | |
| Positive Symptoms (SAPS) | | |
|   Hallucinations | 1.17 (1.76)/5 | |
|   Delusions | 1.22 (1.40)/5 | |
|   Bizarre behavior | 1.06 (1.30)/5 | |
|   Thought disorder | .72 (1.23)/5 | |
| Depression (Calgary) | 2.61 (2.28)/9 | |

HC, healthy control; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SZ, schizophrenia.

memory (Figure S1 in Supplement 1). Two of the words were presented in red and the other two were in blue. The PreCue phase consisted of a 6000- to 8000-millisecond retention interval following the memory-set presentation. Thereafter, a cue, presented for 2000 milliseconds, instructed participants to retain in memory only the words of one color (red on half the trials, blue on the other half). The PostCue WM retention-interval was 6000 to 8000 millisecond. Participants were then presented with a probe word requiring an affirmative response if the probe matched either of the words that should have been retained in WM (e.g., POOL and TILL) and a negative response otherwise. All responses were made using the nondominant hand with a middle finger press indicating a negative response and an index finger press indicating a positive response. On 50% of the trials, the probe matched one of the words that should be in WM (Valid probes); on 25% of the trials, the probe matched one of the words that should have been inhibited from WM (Lure probes), and on the remaining 25% of the trials, the probe did not match any word presented on that trial (Control probes). Control probes were restricted to stimuli that had not appeared for at least 3 subsequent trials to minimize effects of proactive interference. Participants completed 8 blocks of 12 trials each. Feedback was given on practice trials, completed outside of the scanner, but not on experimental trials.

See Supplemental Methods in Supplement 1 for additional details regarding the procedure and fMRI methods.

### fMRI Analysis

Univariate analyses were conducted using the general linear model implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Regressors of interest included the WM maintenance period before the cue (PreCue), the WM maintenance period following the cue (PostCue), and the retrieval probe. Maintenance-related regressors spanned the length of the maintenance interval, and probe-related regressors were modeled as an impulse. Separate probe-related regressors were included for each probe type

(Valid, Lure, Control). Events from trials in which an error occurred were modeled separately and were excluded from subsequent analyses. Two 16-second fixation periods were included in each run that were modeled with a separate regressor that served as a measure of baseline activation. Additional nuisance regressors were included to capture activation related to encoding and the cue. All of the regressors described earlier were convolved with a canonical hemodynamic response function.

Two contrasts of interest were estimated for each participant. The first examined WM maintenance-related activation by contrasting PreCue and PostCue. The second examined interference-control processes at retrieval by contrasting Lure and Control trials. Contrast images for each participant were submitted to second-level two-sample *t* tests. Additional analyses separately examining Encoding and PreCue are reported in Supplemental Results in Supplement 1.

To identify regions involved in WM-maintenance and interference-control, we performed whole-brain analyses collapsing across group. These analyses were thresholded at $p < .001$ at the voxel-level with a 74-voxel cluster extent providing correction for multiple comparisons ($p < .05$ family-wise error corrected) according to simulations using the AlphaSim tool included in AFNI (http://afni.nimh.nih.gov/af). Areas demonstrating significant activation were subsequently tested for group differences. Because these regions were identified through analyses that collapsed across group, these areas provide unbiased estimates for examining group differences. Given previous demonstrations of the role of the left posterior VLPFC in WM maintenance (29) and left mid-VLPFC in interference control (27,28–33), we focused on voxels showing significant activation within these regions (see Supplemental Methods in Supplement 1 for region of interest definitions). For completeness, we also report whole-brain analyses separately for each group, as well as whole-brain group differences (Tables S1–S3 in Supplement 1).

Brain–brain and brain–behavior relationships were estimated in the left posterior VLPFC and mid-VLPFC (see Supplemental Methods in Supplement 1). We used the Lure–Control difference in error rate as a behavioral metric of interference control. Neural effects assessed the PreCue–PostCue and Lure–Control contrast. Relationships were tested using robust regression, which is more robust to outliers than other correlation methods (34). Spearman correlations are also reported for completeness. To examine the relationship between mid-VLPFC, posterior-VLPFC, and behavioral performance, we performed mediation analysis using the mediation toolbox implemented in SPM (http://www.fil.ion.ucl.ac.uk/spm/) (35,36). Paths were estimated with robust regression, and significance was assessed using a permutation test with 10,000 samples.

## Results

### Behavioral Performance

The data of interest were the mean error rates and the reaction times for correct trials (Valid, Lure, and Control). For each participant, trials on which reaction times were $\pm 2.5$ SD of their individual mean in each probe-type condition were excluded from the analysis (mean 2.25 trials for HCs; 2.43 for patients).

Separate repeated-measures analysis of variance with Probe Type as a within-subjects variable and Group (HC or SZ) as a between-subjects variable were computed for error rates and reaction times. For error rate, there was a significant main effect of Probe Type ($F_{2,68} = 27.1$, $p < .001$) and a significant main effect of Group ($F_{1,34} = 15.3$, $p < .001$), such that the patients made

more errors than the HCs. Critically, there was a significant interaction between Probe Type and Group ($F_{2,68} = 5.7$, $p = .005$). Although patients made more errors than HCs in all three Probe Types (Valid: $t_{34} = 3.46$, $p = .001$; 18.1 [13.5] vs. 5.9 [6.6]; Lure: $t_{34} = 3.76$, $p = .001$; 18.15 [13.54] vs. 5.88 [6.58]; and Control: $t_{34} = 2.27$, $p = .03$; 5.19 [8.2] vs. .72 [1.64]), patients made significantly more errors to Lure probes compared with Control probes relative to HCs ($t_{34} = -2.9$, $p = .007$; Figure 1). This replicates our previous finding that patients with SZ demonstrate a deficit in the Lure condition (26). Patients also made more errors on Valid probes compared with Control probes relative to HCs ($t_{34} = -2.6$, $p = .02$), suggesting that patients had difficulty distinguishing Valid from Lure probes.

For reaction time, there was a significant main effect of Probe Type ($F_{2,68} = 62.2$, $p < .001$) and a significant main effect of Group ($F_{1,34} = 20.82$, $p < .001$). Patients were significantly slower than HCs for all three probes types (Valid: 1067.15 [273.8] vs. 709.4 [183.67]; Lure: 1270.41 [295.79] vs. 886.71 [250.74]; Control: 1043.3 [272.1] vs. 717.19 [156.67]). However, the Probe Type $\times$ Group interaction was not significant ($F_{2,68} = .96$, nonsignificant). Planned between-group comparison of the Lure versus Control reaction times difference was not significant ($t_{34} = -1.28$, nonsignificant), although a trend toward patient's exhibiting a greater difference score was evident.

### fMRI Results

**Maintenance and Inhibitory Control of WM.** To isolate specific patient deficits, we began by identifying areas involved in maintaining information in WM by contrasting PreCue and PostCue activations (Figure 2). This contrast measured a load effect (i.e., four items PreCue, two items PostCue) predicated on appropriate use of the cue to inhibit items from WM. Previous research has indicated that this assumption is valid in healthy young and older participants (37). As anticipated, the contrast revealed significant differences in the left posterior VLPFC consistent with known WM load-related effects in this region (29) (see Table S1 in Supplement 1 for additional areas).

To examine whether patients demonstrated impaired control over WM, we compared left posterior VLPFC activation between HCs and patients. Failure to inhibit irrelevant content from WM would be expected to reduce the difference between PreCue and PostCue activation in patients due to elevated PostCue activation. Averaging across activation in the entire left posterior VLPFC cluster revealed by the whole-brain analysis, HCs demonstrated a
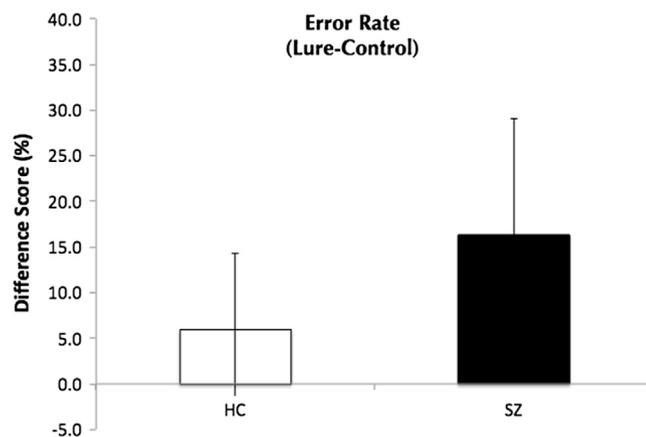


**Figure 1.** Error rate difference-scores (Lure–Control) for healthy controls (HC) and patients with schizophrenia (SZ). Error bars represent SEM.
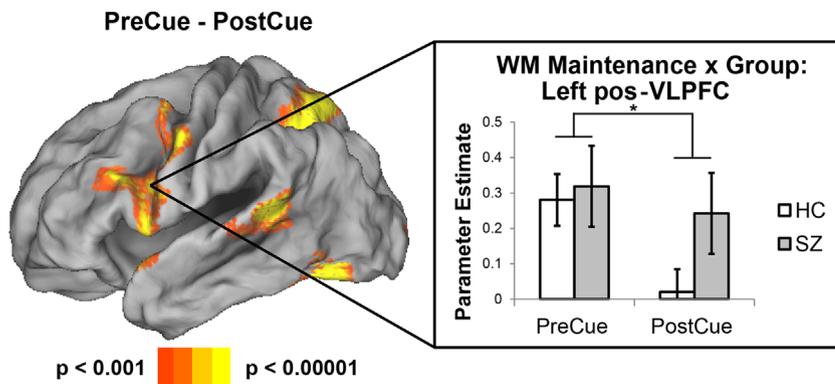
**PreCue - PostCue**



Figure 2. Maintenance and inhibition-related activations. Left: contrast of PreCue–PostCue maintenance activations collapsing across groups. Right: parameter estimates extracted from the left posterior ventrolateral prefrontal cortex (pos-VLPFC) averaged across a 5-mm sphere centered around –50 8 22. In this region, healthy controls (HC) and patients with schizophrenia (SZ) demonstrated equivalent PreCue activation. Whereas HCs demonstrated reduced activation PostCue, patients with SZ did not. These results indicate inhibition-related reductions in pos-VLPFC activation in HCs but not patients with SZ. *$p < .05$. WM, working memory.

robust PreCue > PostCue difference ($t_{17} = 6.90$, $p < .00001$). Patients showed a similar, albeit muted effect ($t_{17} = 3.05$, $p < .01$). Direct comparison between the groups revealed a significant interaction with a greater PreCue > PostCue difference in HCs compared with patients ($t_{34} = 2.39$, $p < .05$). To interrogate this difference further, we separately examined ROIs centered around each left posterior VLPFC peak revealed by the whole-brain analysis (see Methods in Supplement 1). Although all portions of the left posterior VLPFC demonstrated a numerical trend for a reduced PreCue > PostCue difference in patients relative to HCs, a significant group difference ($t_{34} = 2.48$, $p < .05$) was found in only a single region (center: $-50\ 8\ 22$; Table 2). In this region, HCs showed a significant PreCue > PostCue difference ($t_{17} = 5.90$, $p < .0001$), whereas patients did not ($t_{17} = 1.29$, $p > .2$), resulting in a group difference ($t_{34} = 2.48$, $p < .05$). HCs and patients showed similar PreCue activation ($t_{34} = .28$, $p > .75$), whereas patients showed significantly increased activation PostCue relative to HCs ($t_{34} = 1.72$, $p < .05$ one-tailed). This is consistent with the behavioral findings that patients with SZ demonstrate a failure to inhibit irrelevant items from WM (Figure 2).

**Interference Control at Retrieval.** Next, we examined regions involved in interference control, comparing probe-related activations for Lure probes to Control probes. Here, when collapsing across group, significantly greater activations were observed in the left mid-VLPFC for Lure probes relative to Control probes (Figure 3), consistent with the hypothesized role of this region in interference control (27,31,33,38) (see Table S2 in Supplement 1 for additional areas).

In the analyses of maintenance epochs, we observed that patients showed impairments in inhibiting irrelevant content from WM. Such impairments should lead to increased demands on interference control when responding to Lure probes. Thus, we predicted that patients would show increased Lure > Control activation than HCs. Averaging across the left mid-VLPFC cluster revealed by the whole-brain analysis described earlier, patients indeed demonstrated strongly increased activation for Lure probes relative to Control probes ($t_{17} = 4.86$, $p < .0005$). By contrast, HCs showed a weaker effect ($t_{17} = 1.87$, $p < .05$ one-tailed). Direct comparisons between groups revealed a significant difference as patients showed a stronger Lure > Control effect than HCs ($t_{34} = 2.38$, $p < .05$). To further explore this difference, we separately examined regions of interest centered around each left mid-VLPFC peak revealed by the whole-brain analysis. Although no group difference was found in the posterior-most peak ($-38\ 16\ 22$: $t_{34} = 1.18$, $p > .2$), group differences were progressively stronger as activations proceeded anteriorly ($-48\ 24\ 22$: $t_{34} = 2.28$, $p < .05$; $-40\ 32\ 22$: $t_{24} = 3.12$, $p < .005$). As depicted in Figure 3, in the anterior-most mid-VLPFC peak, HCs and patients showed nearly identical activation to Control probes ($t_{34} = .01$, $p > .99$), whereas patients showed significantly increased activation to Lure probes ($t_{34} = 2.18$, $p < .05$). These results suggest that patients require increased interference control to Lure probes relative to HCs but are identical to HCs when no interference control is required.

**Relation Among Inhibition, Interference Control, and Behavior**

The data demonstrate differences between HCs and patients with SZ in neural measures of inhibition and interference control, and behavioral measures of performance. These measures are likely to be interrelated: impaired control over memory (manifested through inhibitory deficits PostCue) leads to the increased reliance on interference-control processes at the time of the probe. The strain on interference-control processes results in increased behavioral errors at retrieval. To explore this hypothesis, we examined the relation among maintenance-related activations in the posterior VLPFC, interference-control-related activations in the mid-VLPFC, and behavioral performance. To maximize power, the groups were pooled. Neural measures of the posterior VLPFC were drawn from the ROI demonstrating a significant group effect ($-50\ 8\ 22$), and neural measures of the mid-VLPFC were drawn from the anterior-most ROI ($-40\ 32\ 22$) that was maximally distant from the posterior VLPFC. The latter choice minimized overlap in the activation clusters that might occur due to spatial smoothing.

Starting with the posterior VLPFC, we tested the relationship between inhibition-related reductions in maintenance
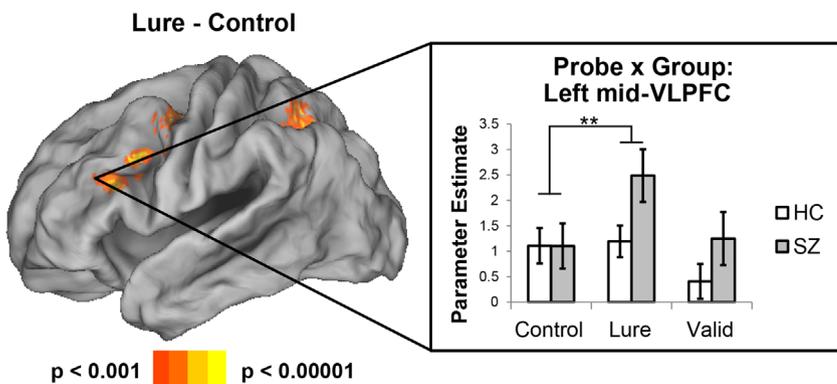
**Table 2.** Results in Ventrolateral Prefrontal Cortex

| Peak | HC | SZ | HC vs. SZ |
|---|---|---|---|
| PreCue–PostCue | | | |
| $-52\ 10\ 6$ | $6.49^d$ | $2.03^a$ | 1.23 |
| $-54\ 8\ 16$ | $4.75^d$ | $1.91^a$ | 1.25 |
| $-50\ 8\ 22$ | $5.90^d$ | 1.29 | $2.48^a$ |
| $-52\ 16\ 22$ | $4.71^d$ | $2.09^a$ | $1.71^a$ |
| $-50\ 12\ 28$ | $4.49^d$ | $2.40^b$ | 1.69 |
| Lure–Control | | | |
| $-48\ 24\ 22$ | 1.71 | $4.42^d$ | $-2.28^b$ |
| $-40\ 32\ 22$ | .31 | $4.45^d$ | $-3.12^c$ |
| $-38\ 16\ 22$ | $2.22^b$ | $3.04^b$ | $-1.18$ |

Numbers represent *t* statistics for each respective contrast.
HC, healthy control; SZ, schizophrenia.
[a] $p < .1$.
[b] $p < .05$.
[c] $p < .005$.
[d] $p < .0005$.

## Lure - Control



**Figure 3.** Interference-control-related activations. Left: contrast of Lure–Control probe activations collapsing across groups. Right: parameter estimates extracted from the left mid ventrolateral prefrontal cortex (mid-VLPFC) averaged across a 5-mm sphere centered around –40 32 22. In this region, healthy controls (HC) and patients with schizophrenia (SZ) demonstrated equivalent activation to Control probes. However, activation was significantly elevated for Lure probes in patients with SZ but not HCs. These results indicate increased demands on interference control to Lure probes in patients with SZ. **$p < .005$.

(PreCue–PostCue activation) and behavioral performance (Lure–Control error rate). Robust regression indicated a significant negative relationship ($t_{34} = -3.22$, $p < .005$; Spearman's $\rho = -.5753$, $p < .0005$), such that participants who appropriately inhibited irrelevant items from WM showed reduced behavioral errors. Next, we examined the relationship between interference-control-related activations in the mid-VLPFC (Lure–Control activation) and behavioral performance. Robust regression indicated a significant positive relationship ($t_{34} = 2.88$, $p < .01$; Spearman's $\rho = .4135$, $p < .05$): participants who demonstrated the greatest

difficulty with the Lure probes behaviorally also demonstrated the greatest interference-control-related activations in the mid-VLPFC. Finally, we examined the relationship between inhibition, as indexed by PostCue reductions in maintenance-related activation in the posterior VLPFC, and interference control, as indexed by Lure > Control activations in the mid-VLPFC. Robust regression indicated a significant negative relationship ($t_{34} = -3.04$, $p < .005$; Spearman's $\rho = -.4829$, $p < .005$). Repeating the analyses with a covariate for group led to similar results (posterior VLPFC and behavior: $t_{33} = -2.34$, $p < .05$; mid-VLPFC and behavior:
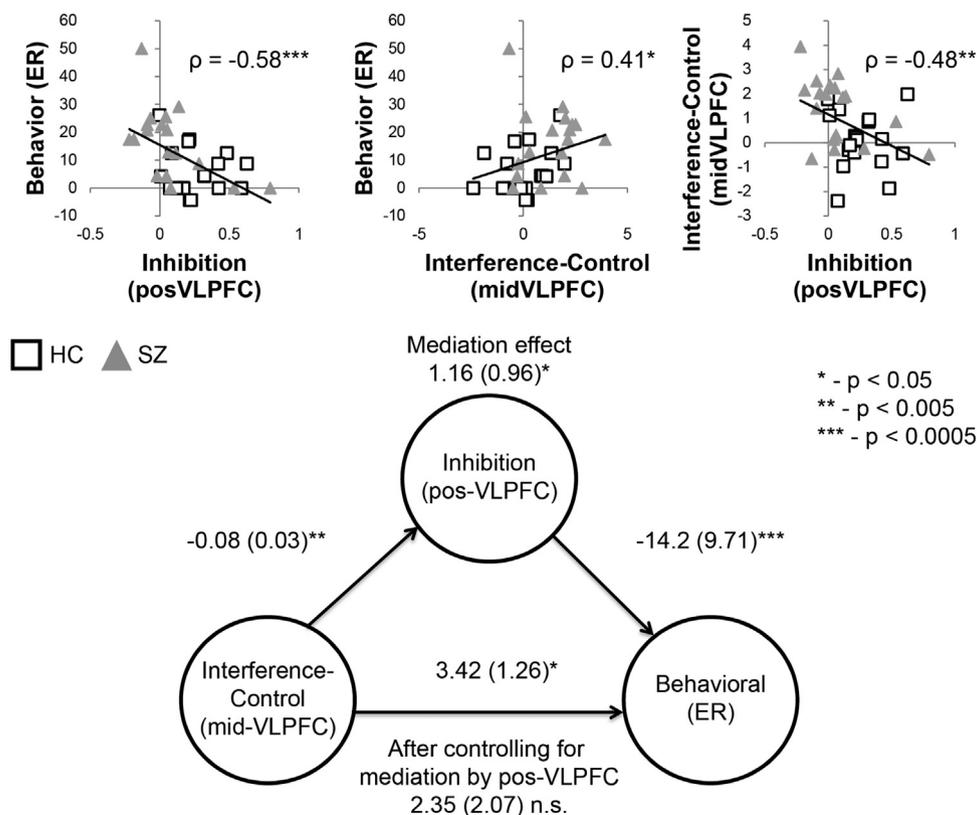


**Figure 4.** Correlations and mediation analysis. Top: correlations between measures of interest. Behavioral performance reflects the behavioral difference in error rate (ER) between Lure and Control probes. Inhibition reflects the neural difference in activation in the posterior ventrolateral prefrontal cortex (pos-VLPFC) between PreCue and PostCue. Interference control reflects the neural difference in activation in the mid-VLPFC between Lure and Control probes. Bottom: mediation analysis results depicting the mediating effect of inhibition on the relationship between neural measures of interference control and behavioral performance. After controlling for the mediating effect of inhibition, the relationship between interference control and behavior was no longer significant. HC, healthy controls; SZ, patients with schizophrenia.

**Table 3.** Mediation Results

| X-M-Y | a | b | c' | c | ab |
|---|---|---|---|---|---|
| midVLPFC–posVLPFC-ER | | | | | |
|   Paths (SE) | −.08 (.03) | −14.2 (9.71) | 2.35 (2.07) | 3.42 (1.26) | 1.16 (.96) |
|   z | −3.03[c] | −3.81[d] | 1.22 | 2.40[b] | 2.08[b] |
| ER-posVLPFC–midVLPFC | | | | | |
|   Paths (SE) | −.01 (.00) | −2.42 (1.54) | .02 (.04) | .06 (.03) | .03 (.02) |
|   z | −3.57[d] | −1.64 | .33 | 1.51 | 1.74[a] |
| ER-midVLPFC–posVLPFC | | | | | |
|   Paths (SE) | .06 (.03) | −.06 (.03) | −.01 (.00) | −.01 (.00) | −.00 (.00) |
|   z | 1.54 | −2.19[b] | −1.95[a] | −3.57[d] | −1.23 |
| midVLPFC-ER–posVLPFC | | | | | |
|   Paths (SE) | 3.53 (1.25) | −.01 (.00) | −.06 (.03) | −.08 (.03) | −.03 (.01) |
|   z | 2.38[b] | −1.94[a] | −2.17[b] | −2.89[c] | −1.73[a] |
| posVLPFC-ER–midVLPFC | | | | | |
|   Paths (SE) | −23.3 (6.20) | .02 (.04) | −2.42 (1.55) | −2.81 (1.15) | −.41 (.90) |
|   z | −3.21[c] | .30 | −1.67[a] | −2.80[b] | −.61 |
| posVLPFC–midVLPFC-ER | | | | | |
|   Paths (SE) | −2.81 (1.15) | 2.35 (2.09) | −14.2 (9.80) | −23.33 (6.22) | −6.59 (6.53) |
|   z | −2.78[b] | 1.20 | −3.89[d] | −3.13[c] | −.45 |

Results from mediation analysis from all six possible models of mid-ventrolateral prefrontal cortex (midVLPFC), posterior VLPFC (posVLPFC), and error rate (ER) interactions. X-M-Y denotes the relation among the predictor (X), mediator (M), and outcome (Y).

[a]$p < .1$.
[b]$p < .05$.
[c]$p < .005$.
[d]$p < .0005$.

$t_{33} = 1.87$, $p = .07$; posterior VLPFC and mid-VLPFC: $t_{33} = -2.48$, $p < .05$). Together, these results indicate a strong interrelationship among the posterior VLPFC, mid-VLPFC, and behavioral performance.

Thus far we have speculated that impaired inhibitory control over WM in patients leads to increased reliance on interference control at the probe and subsequent behavioral impairments. Such an account predicts that inhibitory control over WM mediates the relationship between activations in the mid-VLPFC related to interference control and behavioral interference. To examine this possibility, we performed mediation analysis including the PreCue–PostCue contrast in posterior VLPFC (inhibition), the Lure–Control contrast in mid-VLPFC (interference control), and the Lure–Control difference in error rate (behavioral performance). Confirming the centrality of inhibitory control over WM, a significant mediation effect was found ($z = 2.08$, $p < .05$; Figure 4). When accounting for the mediating effect of inhibitory control over WM, the relationship between interference control in the mid-VLPFC and behavioral performance was no longer significant ($z = 1.30$, $p > .15$). All other paths were significant (all $z$s $> 2.40$, $p < .05$). To determine the selectivity of this effect, we calculated an alternative model using the interference-control-related activations in the mid-VLPFC as a mediator between the posterior VLPFC (inhibitory control) and behavioral performance. In this model, the mediation effect was not significant ($z = .61$, $p > .5$).

For completeness, we calculated all other possible models by fully rotating all measures. No other significant mediation effects were found (Table 3). Hence, the hypothesized model—inhibition mediates the relationship between interference control and behavior—was the only model that yielded significant results. Taken together, these results provide strong evidence that control over WM is the crux that links interference control and behavioral WM impairments in SZ.

Additional analyses are reported in Supplement 1.

## Discussion

This study investigated the component processes that underlie WM deficits in SZ. Our results indicate WM impairments in SZ in three specific ways. First, patients demonstrated impaired inhibition of irrelevant content in WM evidenced by reduced PreCue to PostCue activation difference in the posterior VLPFC. Second, patients exhibited a failure to overcome familiarity-induced interference of Lure probes demonstrated by increased behavioral error rates to Lure probes relative to Control probes. Finally, patients exhibited increased reliance on interference control at the time of retrieval, evidenced by selectively increased activation to Lure probes relative to Control probes in the mid-VLPFC. These data indicate that impaired inhibitory control in WM has downstream consequences that adversely impact behavior.

Our data also indicated that patients made more errors on Valid probes than HCs, even after controlling for performance on Control probes. This result may also stem from inappropriate inhibitory control. When irrelevant items are appropriately removed from WM, Valid probes are distinguished from Lure probes as a function of memory strength. However, if irrelevant items are not inhibited, Valid and Lure items are more difficult to distinguish. Hence, impaired inhibitory control can simultaneously lead to erroneous endorsements of Lure probes and rejections of Valid probes.

A recent review (39) suggested that SZ-related deficits in a variety of cognitive domains including WM could be explained by impairments in proactive control, which allows for goal-relevant information to be activated and irrelevant information to be inhibited in anticipation of cognitive demands that require use of the information (40,41). The present results fit well within such a framework. Although HCs appropriately inhibited irrelevant items from WM in anticipation of the probe, SZs failed to do so, consistent with impaired proactive control. The engagement of proactive control is flexible and may be useful during different

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phases of tasks depending on demands (40). Previous research has demonstrated impairments during WM encoding and maintenance in patients with SZ (42–45), a pattern that contrasts with the present results. In those studies, encoding and maintenance demands were likely increased due to the use of abstract stimuli (42,43) or increased loads (44,45). In such cases, HCs may enlist proactive control processes to facilitate encoding and maintenance, whereas SZs do not. This may take the form of chunking or recoding strategies to ease demands on maintenance processes. Our data indicate that with verbal material and manageable load, patients with SZ exhibit largely intact encoding and maintenance but are impaired in proactively inhibiting items from WM in preparation for future responding. These data suggest that patients with SZ have preserved basic maintenance processes but impaired cognitive control over maintained information.

Our results corroborate a growing body of research in HCs that links the mid-VLPFC to resisting interference and appropriate selection of information at the time of retrieval (8,46). The mid-VLPFC (Brodmann's area 45) is thought to select goal-relevant information when multiple competing representations are active in memory (47). The left mid-VLPFC has also been implicated in the resolution of proactive interference in which memory of a past experience interferes with processing of a subsequent experience (31–33,38,47). A common selection mechanism may account for both forms of control (48).

Similar impairments in inhibitory control may underlie cognitive deficits in other psychiatric disorders such as depression, obsessive-compulsive disorder, or attention-deficit/hyperactivity disorder (49–53). In a similar task to that used here, patients with depression demonstrated a specific deficit in inhibiting negatively but not positively valenced content from WM (51,54). This deficit was hypothesized to underlie the rumination of negative information in depression. Thus, examining inhibition and its correlates is an important endeavor to pinpoint cognitive impairments in psychiatric populations in general.

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