

Negative and Nonemotional Interference with Visual Working Memory in Schizophrenia

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Background: Schizophrenia (SCZ) results in abnormalities affecting both working memory (WM) and emotional processing. Prior work suggests that individuals with SCZ exhibit increased effects of distraction on WM—a deficit that might be exacerbated via emotional interference. However, no study characterized effects of negative and nonemotional interference on visual WM in SCZ with functional magnetic resonance imaging. We tested the hypothesis that SCZ is associated with a general inability to filter distraction versus a specific deficit in the ability to filter aversive emotional distraction.

Methods: Twenty-eight patients with DSM-IV–diagnosed SCZ and 24 matched control subjects underwent blood-oxygen-level-dependent imaging with functional magnetic resonance imaging at 3-T. Subjects performed a modified delayed-response visual WM task faced with affectively negative, neutral, or task-related interference.

Results: Control subjects showed maximal interference after aversive distraction, whereas patients were more distracted irrespective of interference type. Importantly, aversive distraction resulted in similar across-group activation in regions previously showing robust effects of negative interference. Conversely, after any distraction, patients showed reduced blood-oxygen-level-dependent activity in prefrontal regions previously implicated in filtering interference. Particularly when distracted, SCZ subjects exhibited aberrant responses to nonemotional distraction across posterior cortical regions.

Conclusions: Results suggest that patients fail to deploy activity associated with distracter filtering exhibited by control subjects. Although SCZ subjects show similar responses to aversive interference across certain regions, there is also evidence of enhanced responses to nonemotional inputs. These results are consistent with a general deficit in the ability of patients to filter distraction, which might be in line with aberrant salience processing as a pathophysiological mechanism in SCZ.

Key Words: Amygdala, distraction, emotion, fMRI, schizophrenia, working memory

Schizophrenia (SCZ) is a severe neuropsychiatric illness impacting cognitive and emotional functioning (1–3). Working memory (WM) specifically has been postulated as a core deficit (4). Functional magnetic resonance imaging (fMRI) WM meta-analyses have consistently documented lateral prefrontal cortex (PFC) abnormalities in SCZ (5,6) evident during the delay period of WM maintenance (7). The overall goal of this study was to examine the impact of negative and nonemotional interference on maintenance of visual WM in SCZ—postulated by some as a core WM deficit (8)—to understand how cognitive and emotional deficits interact in this illness.

Optimal WM function critically depends on interference filtering (9). Since the classic study by Oltmanns and Neale (10) demonstrating reduced digit-span performance with distraction, SCZ has been associated with interference deficits (11). Furthermore, a vast literature on sensory gating (e.g., prepulse inhibition) indicates that SCZ is associated with a deficit in filtering information (12,13). However, no study has tested such “filtering” deficits during maintenance of visual WM with behavior and fMRI. Furthermore, such deficits might be exacerbated in contexts where interfering information communicates survival-relevance. Thus, affective information, as an important source of distraction, might have privileged access to neural

resources (14–17) and might be a particularly potent source of interference for SCZ patients.

Work with healthy adults has shown greater WM costs for aversive versus neutral distraction (18,19) and demonstrated an activation dichotomy in dorsal fronto-parietal as compared with ventral frontal-occipital areas (18,19). Dorsal fronto-parietal regions exhibited activity reductions in response to negative versus neutral distracters, possibly reflecting dorsal regions temporarily being driven “off-line” by circuitry responsible for detecting emotional salience such as the amygdala. Emotional interference, particularly in the context of WM, might exert a more potent effect, given well-demonstrated WM impairments in SCZ and deficits in the neural systems involved in “top-down” control and interference resolution (20).

Although evidence with regard to deficits in distracter resistance in SCZ would predict potentially greater effects of emotional interference on WM (21–23), such a prediction depends on the integrity of emotion processing in SCZ. Presently, evidence suggests certain emotional processing deficits in SCZ: 1) expression of emotion (24–26), 2) recognition of emotional facial expressions and emotional classification (27,28), and 3) anticipation of hedonic experience (29,30). Furthermore, some studies examining fMRI responses to emotional information in SCZ have suggested activation reductions in regions associated with emotional function in healthy adults (1): two meta-analyses have suggested possible reduced amygdala responsiveness (31,32) (although meta-analytic findings are not entirely clear-cut). If such neural deficits in response to emotion indicate that patients detect emotionally evocative stimuli less potently, then SCZ might actually be associated with less emotional interference on WM (i.e., patients might experience less distraction than control subjects [CON] from emotional information). However, somewhat paradoxically, other SCZ studies have reported largely intact ability to experience affect “in-the-moment” (33,34). This suggests that patients might indeed show intact ef-

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Table 1. Clinical and Demographic Characteristics

Characteristic	Control Subjects		Patients		Significance	
	Mean	SD	Mean	SD	<i>t</i> / χ^2	<i>p</i> (two-tailed)
Age (in yrs)	37.18	7.59	36.39	9.54	.31	.759
Gender (% male)	74		78		.34	.737
Paternal Education (in yrs)	12.70	1.46	13.26	2.61	.90	.370
Maternal Education	12.48	1.53	13.50	3.07	1.42	.162
Paternal SES	21.59	8.92	26.59	10.73	1.67	.100
Maternal SES	17.27	8.55	25.24	11.88	2.51	.015
Participant Education (in yrs)	15.26	2.12	13.04	2.14	3.50	.001
Handedness (% right)	100.00		86.96		1.45	.152
IQ Verbal	110.23	10.85	95.23	14.18	3.88	.000
IQ Performance	115.45	11.64	101.82	15.24	3.30	.002
Medication (CPZ equivalents)	—	—	584.63	563.63		
Mean SAPS Global Item Score	—	—	1.91	1.21		
Mean SANS Global Item Score	—	—	2.50	.78		
Disorganization	—	—	5.48	2.71		
Poverty	—	—	10.43	3.53		
Reality Distortion	—	—	4.26	3.53		

Mean Scale for Assessment of Positive Symptoms (SAPS) global item score for each subject was the average of SAPS global item scores for hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Mean Scale for the Assessment of Negative Symptoms (SANS) global item score for each subject was the average of affective flattening or blunting, alogia, avolition/apathy, anhedonia-asociality, and attention. Disorganization symptoms were the sum of global scores for bizarre behavior, positive formal thought disorder, and attention. Poverty symptoms were the sum of affective flattening, alogia, avolition/apathy, and anhedonia-asociality. Reality distortion symptoms were the sum of hallucinations and delusions.

CPZ, chlorpromazine; SES, socioeconomic status.

fects of emotional interference in the context of WM or might exhibit even stronger effects of affective distraction, given deficits in WM filtering. Such a prediction is also consistent with studies examining emotion–cognition interactions in SCZ, such as emotional reactivity of language (21–23,35), which have suggested increased effects of affective interference in SCZ.

Only one study (36) to date examined effects of emotional interference on verbal WM in SCZ, suggesting that patients fail to respond differentially to emotional distraction. However, there were numerous limitations to that study that make clear interpretation challenging, including significant group differences in age, gender, and behavioral performance and no group matching on developmental socioeconomic status (SES), movement, or signal-to-noise ratios. In this investigation, we address these concerns prospectively.

We hypothesized that SCZ patients would show a deficit in filtering interference during WM maintenance, which might be associated with lower signals in regions implicated in distracter filtering, such as the dorsolateral prefrontal cortex (DLPFC). Furthermore, we investigated the influence of aversive content on WM in SCZ, to arbitrate among several competing hypotheses. As articulated in the preceding text, these alternative hypotheses (each supported by a different literature) are: 1) SCZ might be associated with a general interference filtering deficit during WM but no specific effect of negative interference; 2) SCZ might be associated with a specifically greater effect of negative interference relative to other types of distraction; or 3) patients might show a reduction in emotional processing, which might result in dampened effects of aversive interference on WM.

Methods and Materials

Subject Recruitment

Twenty-eight subjects meeting DSM-IV criteria for SCZ and 24 demographically matched CON provided informed consent ap-

proved by Washington University. Subjects underwent the Structured Clinical Interview for DSM-IV-TR (37), symptom ratings with the Scale for Assessment of Positive and Negative Symptoms (38,39), and were administered selected sections of the Wechsler Adult Intelligence Scale—Third Edition (40). Control subjects were recruited from the same community as patients but were excluded for lifetime history of Axis I psychiatric disorder or a first-degree relative with a psychotic disorder. Subjects were excluded if they: 1) met DSM-IV criteria for substance

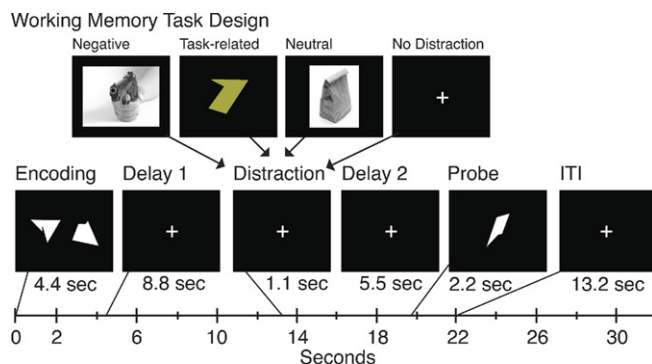


Figure 1. The task design is displayed along with different trial components and their onsets marked along the timeline. Each box represents a trial component with the duration marked below. Memory sets were presented centrally, subtending a visual angle of 15.75 for 4.4 sec, followed by an 8.8-sec delay. The delay was followed by a 1.1-sec presentation of the distracter (if present) and then by a 5.5-sec post-distracter delay and a probe presented for 2.2 sec. Each trial was followed by a 13.2-sec fixation period (intertrial interval [ITI]) to allow the hemodynamic response to return to baseline, as employed in our prior work (18,42). Distracters were: 1) affectively negative complex image, 2) a task-related geometric shape distracter of a different color distinguishing it from the probe, 3) neutral complex image, or 4) no distraction. As noted, neutral and negative images were matched on relevant visual characteristics.

abuse/dependence within the past 6 months, anxiety, or depression; 2) had any severe medical conditions; 3) suffered head injury (past or present) with neurological symptoms or loss of consciousness; or 4) met DSM-IV criteria for mental retardation. All patients received stable medication for 2 weeks or more (although virtually all exceeded 6 weeks). The groups did not differ for handedness, gender, age, education of father, education of mother, and SES of father, but maternal SES was higher for patients (Table 1). Patients were impaired on standard measures of verbal and nonverbal IQ (40).

Performance Matching

First, subjects completed a delayed match-to-sample visual WM task to pinpoint subject-specific difficulty level for the in-scanner portion by manipulating the nontarget probe similarity but holding the encoding load constant (Figures S1 and S2 in Supplement 1). Specifically, the fMRI task was difficulty-matched across subjects at approximately 80% correct in the absence of distraction, given our pilot work indicating that maximal distraction occurs at approximately 80% accuracy (i.e., neither ceiling nor chance performance). To assess across-group distracter ef-

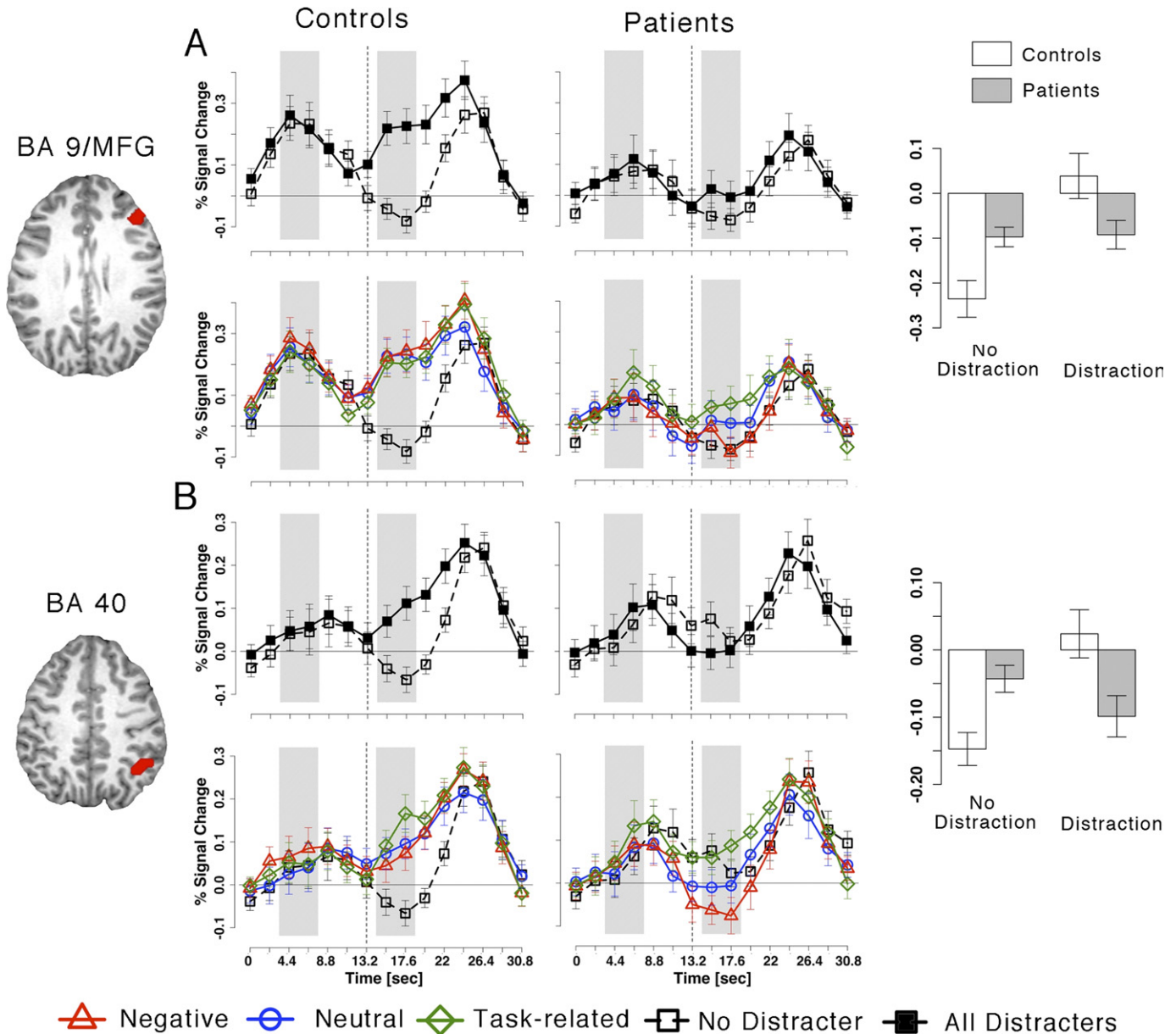


Figure 2. Results showing a Distracter (all distracters vs. none) × Diagnosis interaction are displayed with corresponding time courses (left) and magnitudes reflecting distracter component specifically (right) for (A) right Brodmann area (BA) 9/46 ($x = 42, y = 27, z = 29$) and (B) right BA 40 region ($x = 39, y = -51, z = 39$). Top time courses in each panel show activation averaged across all distracters (filled black squares) versus no distraction (empty black squares). For completeness, bottom time courses show activation across all conditions to illustrate that a single distracter condition is not driving the effect in control subjects; rather, there is a signal increase for all distracters (negative distracters: red triangles, neutral distracters: blue circles and task-related distracters: green diamonds). Approximate encoding and maintenance periods are marked with gray vertical bars. Distracter onset is marked with a dotted vertical line. MFG, middle frontal gyrus.

fects, it was critical to ensure the same baseline starting point from which performance deviates. Furthermore, given well-documented encoding deficits in SCZ (41), it was imperative to optimize performance in the absence of distraction to rule out encoding difficulties.

fMRI Acquisition and Stimuli

Structural and blood-oxygen-level-dependent (BOLD) data were acquired with a 3-T Tim-TRIO scanner (Siemens, Malvern, Pennsylvania) at Washington University (acquisition and preprocessing details presented in Supplement 1). Stimuli were projected behind the scanner, visible through a mirror above the eyes. Subjects completed 96 task trials (18,42) (Figure 1). Twenty-four interference-free trials (three 5.09-min runs) to estimate distracter-free maintenance activity were followed by 72 trials (six 7.44-min runs) with distracters presented during the delay period: 1) negative images; 2) neutral images; and 3) task-related geometric shapes (i.e., these distracters resembled the memoranda). Task-related distracters allowed examination of negative distracter effect specificity. Although neutral distracters help in this regard, it was critical to incorporate distracting and performance-impairing nonemotional stimuli that are salient (42) (given their relevance to the task) to contrast against affectively salient negative distracters (see Supplement 1 for stimuli details). Negative and neutral distracters were selected from the International Affective Picture System (43) and were equated on luminance, contrast, figure-ground relationships, spatial frequency, and color (44–46). After scanning, subjects rated pictures for experienced arousal and valence (47), with a computer version of the self-assessment manikin.

To ensure comparable signal-to-noise ratios (SNR) (48,49), subjects were excluded if a BOLD run had $SNR < 150$ (5 SCZ and 1 CON were excluded on the basis of this criterion; see Supplement for SNR computation details). After removal, there were no between-group differences across BOLD runs [$SNR-SCZ = 286.2$, $SNR-CON = 288.3$, $t(44) = .08$, $p = .93$, NS].

fMRI Analyses

First, a general linear model (GLM) approach was used to estimate voxel-wise magnitudes of task-related activity (50). An assumed-response GLM approach validated in our prior work (18,42) was used to estimate five trial components: encoding, pre-dis-

tracter delay, distracter response, post-distracter delay, and probe (Figure S3 in Supplement 1) (51). An additional GLM was computed with an accuracy covariate, enabling examination of within-subject trial-by-trial relationship between behavioral performance and brain activity. To visualize activation time courses, we employed an assumption-free GLM approach to estimate activity across the first 15 frames of each trial (52). For completeness, we present distracter-related assumed-response magnitudes and reconstructed time courses.

At the second level, with the assumed-response estimates described in the preceding text, we computed all analyses of variance (ANOVAs) with a tiered approach involving three levels of analysis that balanced power concerns for specific regions known to be involved in the current task while searching for effects at the whole-brain level:

1. Analyses using a priori regions of interest (ROIs) from our prior work showing robust effects of negative versus neutral distraction on maintenance activity in healthy individuals (18,42): fronto-polar PFC, DLPFC, ventrolateral PFC (VLPFC), and the amygdala.
2. Analyses constrained to regions showing meta-analytic evidence of involvement in WM by computing ANOVAs within a mask comprising specific working memory-related areas (WMRA) (53,54) (with appropriate multiple comparison correction, see Figure S4 in Supplement 1).
3. Whole-brain voxel-wise analyses with appropriate type I error correction following our prior work (55), implemented via the Analysis of Functional NeuroImages AlphaSim ($Z > 3$, $k = 13$ voxels) (56). Details regarding task conditions used when testing specific hypotheses are presented in Results.

Results

Behavioral Results—Effects of Distraction

We examined accuracy effects with repeated-measures ANOVA, with Diagnosis (2 levels, SCZ vs. CON) and Distraction (4 levels: no distraction, neutral, negative, task-relevant) as factors. Hedge's g (H_g) was calculated for all statistics where there was a difference between means (57). Classical η^2 (not partial) was calculated for all ANOVAs (58). Results revealed no differences for no distraction condition, confirming close performance matching [$t(50) = 1.2$,

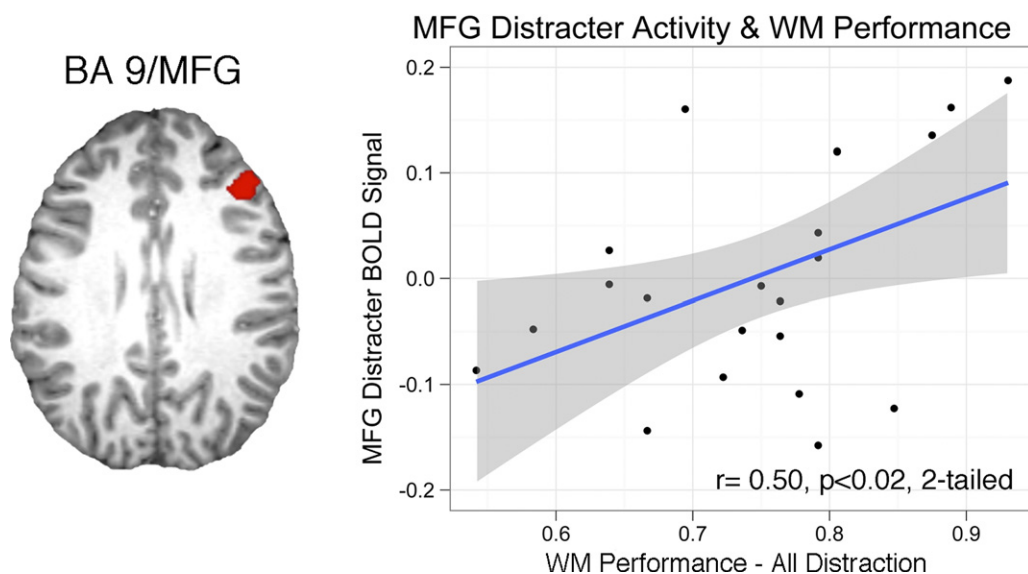


Figure 3. Cross-subject correlation for control subjects showing the significant association between working memory (WM) performance and right BA 9/46 MFG signal in response to all distraction [$r = .5$, $p < .02$, two-tailed]. Such a relationship was absent for patients [$r = .04$, NS] and when examining responses in the absence of distraction for control subjects [$r = -.06$, NS]. This confirms the specificity of this effect for control subjects when distraction is presented and implicates the BA 9/46 region in distracter filtering as well as suggesting a breakdown in its recruitment for patients. BOLD, blood-oxygen-level-dependent, other abbreviations as in Figure 2.

$p = .23$, two-tailed, NS, $H_g = .33$). Results revealed a trend-level main effect of Diagnosis [$F(1,150) = 3.85, p < .055, \eta^2 = .45$], with lower accuracy for patients; significant main effect of Distraction [$F(3,150) = 9.43, p < .0001, \eta^2 = .42$]; and a significant Diagnosis \times Distraction interaction [$F(3,150) = 2.93, p < .04, \eta^2 = .13$], indicating different across-group Distraction effects (Figure S5A in Supplement 1). Control subjects exhibited a stronger effect for negative versus other distraction, whereas patients were distracted across all conditions (Figure S5B in Supplement 1). Follow-up t tests confirmed a stronger effect of negative versus neutral distraction for

CON [$t(23) = 2.86, p < .01$, two-tailed, $H_g = .57$] but not patients [$t(27) = .92, p = .36$, NS, $H_g = .17$]. Also, there was a stronger effect of negative versus task-related distraction for CON [$t(23) = 3.61, p < .001$, two-tailed, $H_g = .72$] but not patients [$t(27) = .63, p = .53$, NS, $H_g = .13$]. In summary, patients performed worse across distracter categories but did not exhibit a specifically greater effect of negative distraction relative to CON. Analyses of valence (no group differences) and arousal ratings (slightly higher in SCZ) on post-scan picture ratings are presented in Figure S6 in Supplement 1 along with response time results (no significant differences).

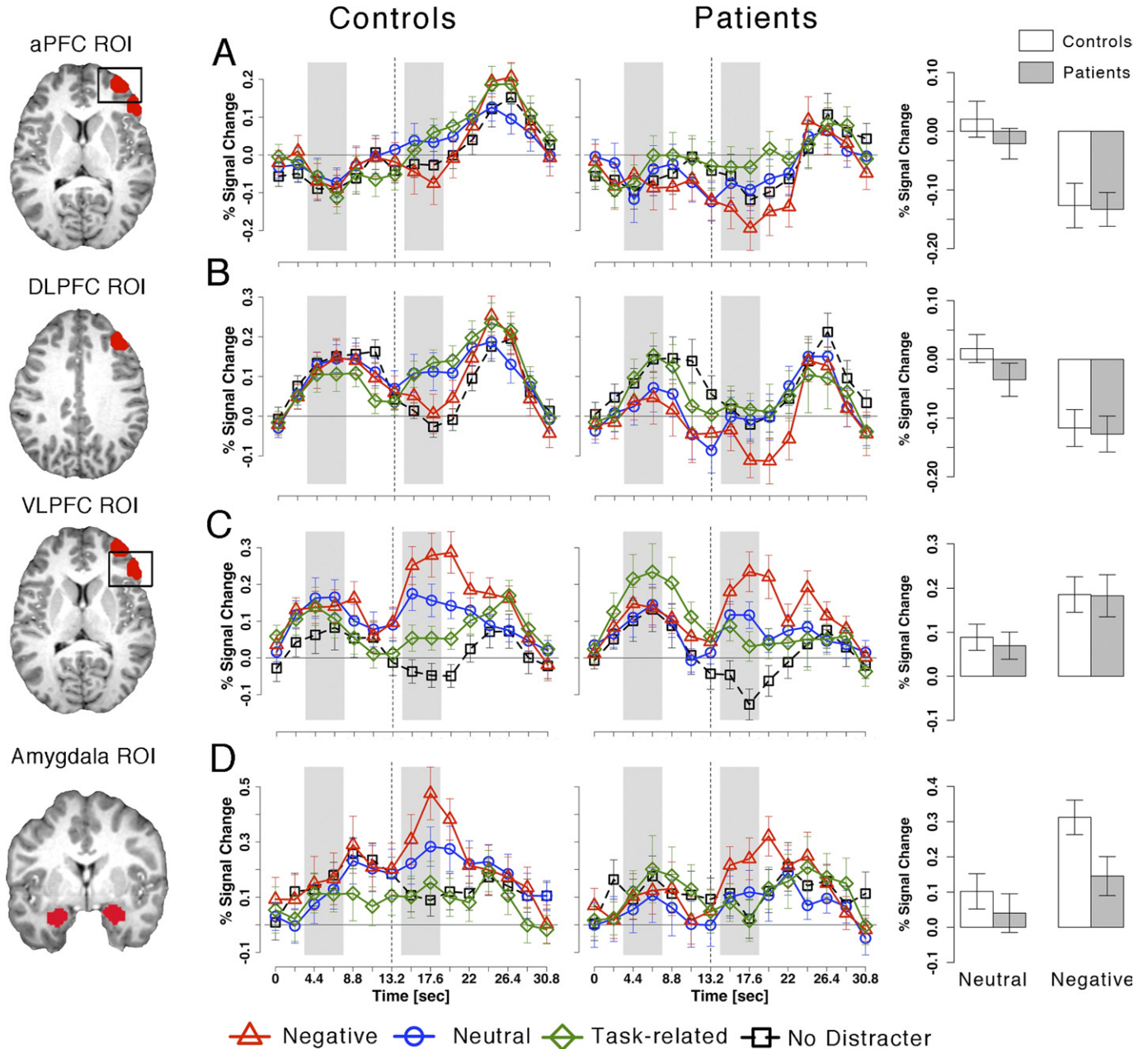
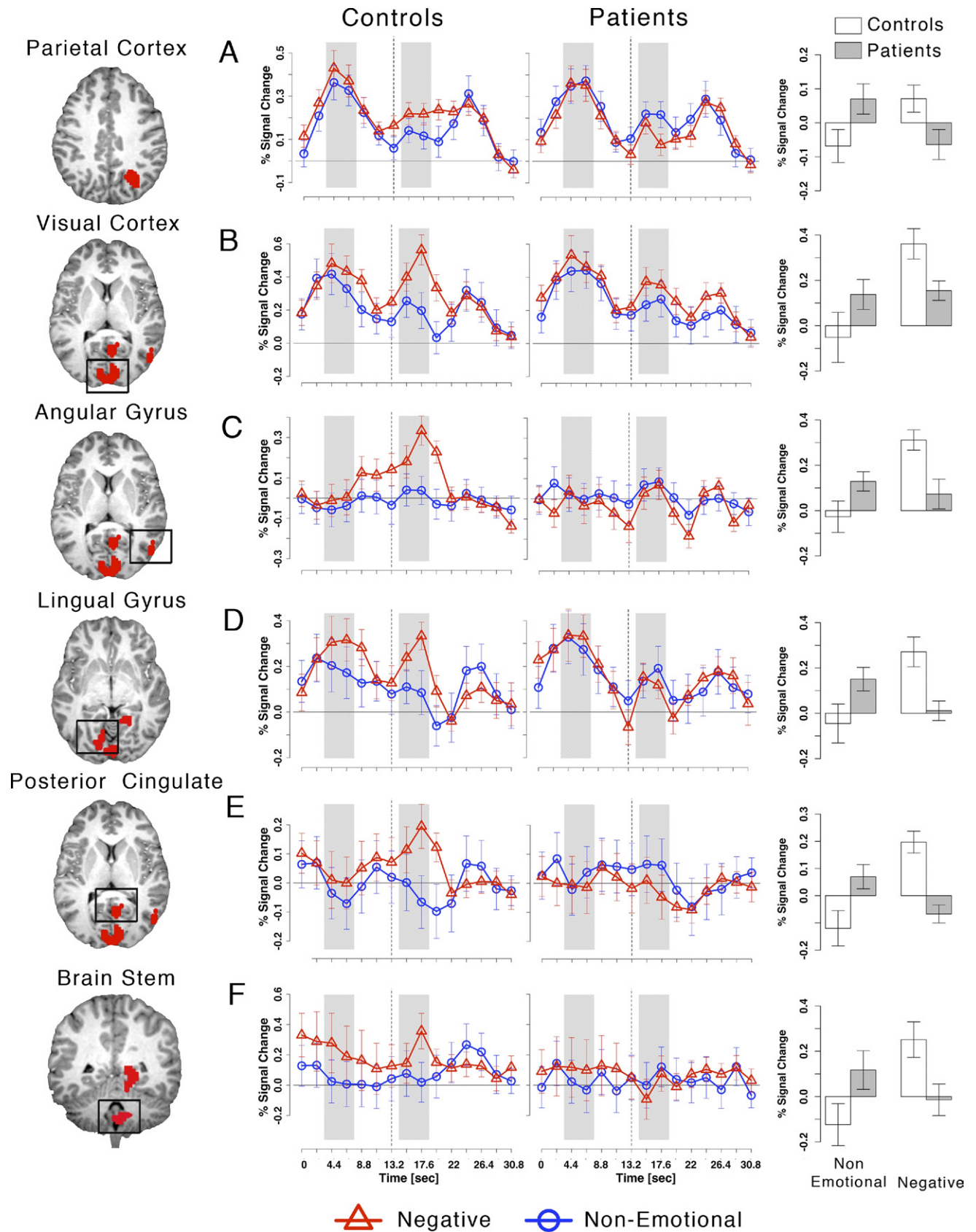


Figure 4. Results showing Emotion (negative vs. neutral distraction) \times Diagnosis interaction are displayed with corresponding time courses (left) and magnitudes reflecting distracter component specifically (right) for a priori regions identified in our prior work (18): **(A)** right fronto-polar prefrontal cortex (aPFC) ($x = 37, y = 52, z = 15$), **(B)** right dorsolateral prefrontal cortex (DLPFC) ($x = 40, y = 34, z = 33$), **(C)** right ventrolateral prefrontal cortex (VLPFC) ($x = 51, y = 33, z = 14$), and **(D)** bilateral amygdala. Time courses in each panel show activations for negative distracters (red triangles), neutral distracters (blue circles), task-related distracters (green diamonds), and no distraction condition (black squares). Approximate encoding and maintenance periods are marked with gray vertical bars. Distracter onset is marked with a dotted vertical line. Left hemisphere cortical effects were consistent. ROI, region of interest.



fMRI Results—Evidence for General Deficits in Distracter Filtering

Given behavioral findings indicating general distractibility in SCZ, we investigated whether activity patterns in any regions were consistent with general filtering deficits (i.e., irrespective of distracter type). With the tiered approach described in the preceding text, we computed two-way repeated-measures ANOVA with Distraction (two levels—all distracters combined vs. no distraction) as a within-subject factor and Diagnosis (SCZ vs. CON) as a between-subject factor. The logic was that, if SCZ subjects exhibit a general filtering deficit, then there should be regions showing generally less recruitment irrespective of distraction relative to CON. No significant Distraction \times Diagnosis effects emerged within a priori ROIs or at the whole-brain level. However, analyses constrained to WMRA revealed two regions showing a significant Distraction \times Diagnosis interaction: right Brodmann area (BA) 9/46 and BA 40 (Figures 2A and 2B). Both regions exhibited more distracter-related activity for CON versus SCZ. This was true, irrespective of modeling approach (Figure 2: left panel shows time courses; right panel shows magnitudes). Critically, the DLPFC region has been implicated in distracter filtering in prior work (59).

To investigate the functional relevance of activation in identified ROIs for filtering, we examined whether the magnitude of overall distracter-related activity (across all distraction) in these ROIs predicted accuracy. Results for BA 40 did not reach significance. Higher levels of distracter-related DLPFC signal predicted better performance for CON ($r = .5, p < .02$, two-tailed) (Figure 3) but not SCZ ($r = .04$, NS). There was no such relationship for CON when no distraction was present ($r = -.06$, NS). Thus, patients demonstrated reduced distracter-related activity in DLPFC, whose activity predicted better performance in CON.

fMRI Results—Effects of Emotional Distraction

A critical aim was to search for areas where patients exhibited altered responses to negative versus neutral distracters. Thus, with the tiered approach, we computed a mixed-model two-way ANOVA with one between-subject (Diagnosis, SCZ vs. CON) and one within-subject (Emotion, negative vs. neutral) factor. We omitted task-relevant and no-distracter conditions to specifically isolate group differences in the aversive versus neutral condition.

First, we investigated group differences in response to negative versus neutral distraction in a set of a priori prefrontal ROIs, consistently showing such effects in prior work (18,19). No significant Emotion \times Diagnosis interaction results emerged (all $p > .16$) (Figure 4), because both groups showed similar responses for negative versus neutral distraction. Focused within-group t test groups confirmed a significant effect of neutral versus negative distracters across all ROIs (all $p < .015$, one-tailed), except a trend effect for bilateral amygdala in patients [$t(23) = 1.3, p = .1, H_g = .24$]. Thus, consistent with past work suggesting intact “in-the-moment” responsiveness to emotional stimuli (34), present results revealed little evidence for altered responsiveness to negative versus neutral distraction in patients across the amygdala, VLPFC, and DLPFC.

Analyses constrained to WMRA revealed a ventro-lateral tha-

lamic region (Figure S7A in Supplement 1) showing an Emotion \times Diagnosis interaction. Whole-brain results revealed an additional dorsal posterior cingulate area (BA 31) (Figure S7B in Supplement 1). For both regions, CON showed a prominent response to negative versus neutral distraction, but this pattern was reversed or attenuated for patients (i.e., patients failed to show an activation increase in response to negative but showed an increase after neutral distraction).

Overall, results suggest similar group effects of negative interference in regions showing such effects in prior work (18,19). However, we also found evidence consistent with elevated responsiveness to neutral interference in SCZ. Patients exhibited increased activation after neutral distraction possibly consistent with the hypothesis of aberrant salience detection (60).

fMRI Results—Examining Group Differences When Filtering Fails

One possibility is that patients show activation abnormalities specifically when they are distracted (i.e., on incorrect trials) due to a failure to regulate responses to otherwise nonemotional stimuli. That is, SCZ might fail to filter nonsalient events, leading to increased distractibility on such trials and aberrant responses to nonemotional (both neutral and task-relevant) stimuli. Such a response pattern might help explain general distractibility in SCZ and would be consistent with the hypothesis that SCZ fail to deploy appropriate interference resolution mechanisms when faced with any distraction. In other words, we examined whether the “aberrant” pattern of responses to nonemotional distraction was even more pronounced when patients were distracted.

To test this hypothesis, we computed a Diagnosis (SCZ vs. CON) \times Emotion (negative vs. nonemotional; neutral and task-related combined) interaction specifically for incorrect trials. Reported significant effects focus on this interaction. We combined neutral and task-related conditions, because SCZ subjects were more distracted across both nonemotional conditions (similar results emerged for neutral condition only). We employed the aforementioned tiered approach to remain maximally sensitive to group differences. No significant effects were found within a priori ROIs (18). However, ANOVA results for WMRA and whole-brain analysis revealed a set of posterior cortical regions and one subcortical region localized around the brainstem (Figure 5).

The pattern of responses across detected regions was consistent: patients showed increased responses to nonemotional distraction. That is, when examining trials on which both groups exhibited compromised WM performance (incorrect trials), responses of patients to nonemotional distraction resembled responses to emotional distraction in CON. Control subjects showed a clear increase in responses to negative compared with nonemotional stimuli on incorrect trials, whereas patients either showed no difference between negative and nonemotional stimuli or showed higher responses to nonemotional distraction. We examined whether symptom severity correlated with signals to nonemotional distraction in these ROIs, but no significant correlations emerged.

Figure 5. Results showing Emotion (negative vs. nonemotional distraction) \times Diagnosis interaction are displayed with corresponding time courses (left) and magnitudes reflecting distracter component (right) for incorrect trials specifically. The following regions were identified: (A) parietal cortex (Brodmann area [BA] 7) ($x = 23; y = -63; z = 42$), (B) visual cortex (BA 17/18) ($x = 3; y = -85; z = 5$), (C) angular gyrus (BA 19/39) ($x = 50; y = -64; z = 13$), (D) lingual gyrus (BA 18) ($x = -11; y = -74; z = -1$), (E) posterior cingulate (BA 23/29) ($x = 3; y = -55; z = 13$), and (F) brain stem ($x = 4, y = -50; z = -41$). Parietal ($x = 23; y = -63; z = 42$) and visual cortex ($x = 3; y = -85; z = 5$) areas were identified when constraining analyses to working memory-related areas, whereas the other regions were identified at the whole-brain level. Time courses in each panel show activations for negative distracters (red triangles) and nonemotional distracters combining across neutral and task-related conditions (blue circles). As noted, we averaged across the two nonemotional conditions, because patients showed similar levels of overall distraction for both conditions, but similar results emerged when focusing on the neutral or task-relevant conditions only. Approximate encoding and maintenance periods are marked with gray vertical bars. Distracter onset is marked with a dotted vertical line.

Discussion

Although filtering deficits have long been established in SCZ, this is the first study examining effects of negative and nonemotional distraction on visual WM in SCZ with fMRI. We replicated negative interference effects for CON; however, SCZ showed increased distractibility across distracters. This was consistent with a priori hypotheses that SCZ might be associated with a general interference-filtering deficit. Consistently, SCZ failed to recruit regions previously implicated in distracter filtering. However, groups exhibited similar neural responses to negative versus neutral distraction, arguing against substantial impairments in responsiveness to negative interference per se in SCZ. Nevertheless, after primary and post hoc analyses, we found posterior foci for which patients showed aberrant responses to nonemotional distraction. Overall, these findings suggest an interference-filtering deficit in SCZ and are potentially consistent with an aberrant salience hypothesis in psychosis but argue against abnormally strong effects of aversive interference.

Behavioral Effects of Distraction

Patients were distracted irrespective of distraction type. This result was somewhat surprising, given evidence for intact in-the-moment processing of affective material (34) coupled with WM abnormalities (7) in SCZ. That is, given well-documented behavioral and neural deficits in stability of WM representations (20), if anything, we would have expected that patients would exhibit equal or higher levels of negative interference, because survival-relevant information plays a privileged role in capturing attention (14–17). This pattern of results suggests two alternative interpretations. First, it is possible that negative interference did not exert equal effects in SCZ when demands of performing a WM task increased cognitive load. This interpretation is consistent with research showing an attentional “bottleneck” such that aversive interference is not detected when cognitive resources are reduced (61). Alternatively, negative interference might exert similar across-group effect, but for patients there might be an additional failure to deploy adequate interference resolution for less salient material—a general filtering deficit. We discuss present fMRI findings that help arbitrate between these alternatives.

General Filtering Deficits in SCZ

We found two regions (DLPFC and BA 40) that SCZ failed to recruit in response to any distraction. Furthermore, DLPFC activation predicted performance across all distraction for CON but not SCZ. These findings are consistent with the hypothesis that patients fail to deploy interference resolution mechanisms possibly critical for overall suppression of distraction and protection of WM from interference. Furthermore, results suggest that such deficits are present across distraction categories and are not specifically exacerbated for aversive interference. One possibility is that, given prominent deficits in this illness in regions implicated in top-down control (20), SCZ might fail to regulate interference in situations where CON might successfully filter distraction (i.e., when stimuli contain no survival relevance). Consistent with this possibility, a recent elegant behavioral study by Hahn *et al.* (11) manipulated spatial WM encoding by rendering specific encoding items more salient (by surrounding them with a flicker). Their results demonstrated that patients and CON benefit from bottom-up effects on attention during WM encoding. However, when the bottom-up manipulation was distracting (by flickering around items not required to be encoded), SCZ subjects were unable to override prepotent bottom-up visual distraction during WM encoding and bias their attention away from such distraction. In fact, SCZ subjects

more robustly encoded items that co-occur with salient distracters, whereas such distraction was successfully filtered by CON subjects.

Evidence for Similar Group Responses to Negative Distraction

To examine whether negative interference exerted similar across-group activation patterns, which would argue against deficits in detection of negative distraction, we assayed activation for a priori regions showing modulation as a function of negative distraction during WM (18,19,62,63). Prior work showed a marked BOLD signal reduction in response to negative distraction in bilateral DLPFC and fronto-polar PFC. Conversely, amygdala and VLPFC showed signal increases after negative interference. This pattern was closely replicated across groups, suggesting that SCZ might have an intact capacity to detect aversive information; even when cognitive resources are engaged. Therefore, the possibility that patients simply failed to process negative stimuli during WM maintenance in our study seems unlikely. However, there was a dissociation between behavior and neural responses in patients. That is, behavioral data showed increased interference across distracters but no enhanced effects of negative interference in patients, whereas differential neural responses to negative interference were evident in a priori ROIs. The possibility articulated in the preceding text is that patients fail to deploy interference resolution, irrespective of distracter category (64). Furthermore, incorrect trial analyses (discussed in the following text) seem to explain this pattern of behavioral results.

Of note, a recent patient study (36) presented some intriguing results supporting lack of responsiveness to emotional distraction during WM. However, Diaz *et al.* failed to address a number of critical controls, rendering their findings difficult to interpret (e.g. small sample sizes, group differences in age, gender, and behavioral performance, no group signal-to-noise matching, and emotional vs. neutral distracters not matched on relevant behavioral characteristics). Therefore, this discrepancy needs to be addressed in prospective replications that control for aforementioned critical variables across verbal and nonverbal WM.

Evidence for Aberrant Salience

Imaging findings suggested similar group responsiveness to aversive distraction across regions previously shown to be responsive to such interference (18). However, there were prominent group differences in WM performance for nonemotional distraction. One possibility is that, specifically when distracted, patients show activation differences in response to nonemotional distraction. Consistent with this hypothesis, in a post hoc analysis we identified a number of posterior cortical and subcortical regions exhibiting group differences in their responses to negative versus nonemotional distraction—all of which have been implicated in aspects of emotional processing (65–68). For all foci, CON showed an increase for negative versus nonemotional distraction specifically when distracted (i.e., on error trials). Conversely, responses of patients after negative versus nonemotional distraction either did not differ or showed an activity increase in response to nonemotional information—highly consistent with recent findings by Holt *et al.* (69) during emotional appraisal.

This pattern of group differences is consistent with the hypothesis that SCZ might exhibit abnormalities in filtering and/or detecting nonemotional information during WM maintenance. These findings might also reflect an increased salience of nonemotional stimuli, in line with a theoretical model of the pathophysiology of SCZ that emphasizes the role of aberrant salience (60,70). This hypothesis suggests that, to SCZ patients, different things seem important and important things seem different, manifest as a blurring

of the distinction in brain responses to salient and nonsalient events (71,72).

Study Limitations

Best efforts were made, on the basis of a pretesting session, to performance-match groups when no distraction was presented. Although SCZ were slightly less accurate than CON, worse performance in the absence of distraction was not associated with a bigger performance reduction in any distraction condition, arguing against a performance-related confound explanation for distraction results. However, prospective work should accomplish even tighter performance matching.

The present study cannot fully rule out the contribution of encoding deficits, because we did not include a control task to assess the ability of a subject to discriminate polygons with no WM demands. Nevertheless, matched group performance during no distraction argues that SCZ distraction effects are not driven solely by encoding/perceptual deficits. Nonetheless, an important question for future work is whether distraction interacts with both maintenance and encoding abnormalities present in SCZ.

Although similar neural responses to aversive distraction suggest that medication status did not impact group differences, it cannot be ruled out that medication influenced distracter responses. To further rule out medication effects, results should be replicated in unmedicated patients, at-risk populations, or subjects in prodromal stages of psychosis. Lastly, we employed negative stimuli only. It is important, given well-established hedonic deficits in SCZ (29), to investigate whether results generalize for positive distracters.

Conclusions

This is the first direct investigation of aversive and nonemotional distraction on visual WM using behavior and fMRI in a well-powered and behaviorally matched sample. Present results replicate negative interference during WM in CON and advance our understanding of WM filtering deficit in SCZ by demonstrating interference across distracter categories. Importantly, results illustrate the power of fMRI in probing neural correlates of affective dysfunction in SCZ. One plausible conclusion, solely on the basis of behavioral effects, is that patients are distracted in general but do not show specific added effects of negative interference, suggested by reduced responses to negative stimuli in some studies (1). However, when examining fMRI findings, it is hard to argue that patients exhibit no responsiveness to aversive distraction, at least for some regions. Instead, present results are more consistent with a general interference resolution deficit and aberrant responsiveness to salience in SCZ.

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Supplementary material cited in this article is available online.

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