Influence of Emotional Processing on Working Memory in Schizophrenia

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Research on emotional processing in schizophrenia suggests relatively intact subjective responses to affective stimuli "in the moment." However, neuroimaging evidence suggests diminished activation in brain regions associated with emotional processing in schizophrenia. We asked whether given a more vulnerable cognitive system in schizophrenia, individuals with this disorder would show increased or decreased modulation of working memory (WM) as a function of the emotional content of stimuli compared with healthy control subjects. In addition, we examined whether higher anhedonia levels were associated with a diminished impact of emotion on behavioral and brain activation responses. In the present study, 38 individuals with schizophrenia and 32 healthy individuals completed blocks of a 2-back WM task in a functional magnetic resonance imaging scanning session. Blocks contained faces displaying either only neutral stimuli or neutral and emotional stimuli (happy or fearful faces), randomly intermixed and occurring both as targets and non-targets. Both groups showed higher accuracy but slower reaction time for negative compared to neutral stimuli. Individuals with schizophrenia showed intact amygdala activity in response to emotionally evocative stimuli, but demonstrated altered dorsolateral prefrontal cortex (DLPFC) and hippocampal activity while performing an emotionally loaded WM-task. Higher levels of social anhedonia were associated with diminished amygdala responses to emotional stimuli and increased DLPFC activity in individuals with schizophrenia. Emotional arousal may challenge dorsal-frontal control systems, which may have both beneficial and detrimental influences. Our findings suggest that disturbances in emotional processing in schizophrenia relate to alterations in emotion-cognition interactions rather than to the perception and subjective experience of emotion per se.

Key words: emotion-cognition interaction/hippocampus/dorsolateral PFC/amygdala/anhedonia/fMRI

Introduction

Emotional disturbances have long been recognized as a core feature of schizophrenia, related to social[1–3] and adaptive[4] disabilities in this illness. To understand how emotional disturbances may affect function, course, and outcome in schizophrenia, it is critical to make distinctions among the different components of emotional processing and to determine which of these are impaired in schizophrenia. The focus of this study was on understanding the interaction between cognition and emotional processing in schizophrenia by examining the influence that the emotional valence of a stimulus exerts on working memory (WM) in individuals with schizophrenia (SCZ) compared with healthy control subjects (CON).

Previous research on emotional processing in schizophrenia suggests a disconnection between the expression of emotion, which seems to be diminished, and the subjective response to affective stimuli "in the moment," which seems to be relatively intact (reviewed in Kring and Moran[5]). Although the majority of this work suggests intact subjective experience of emotion in schizophrenia, it is also clear that there are important individual differences. Notably, a number of studies suggest that high levels of anhedonia can predict diminished subjective affective responses in individuals with this illness.[6–9]

Neuroimaging evidence provides a somewhat different picture of emotional processing in schizophrenia, though research in this area has been mixed. A number of studies have found reduced activation in brain regions associated with emotional processing in response to emotionally evocative stimuli in SCZ compared with CON (reviewed in Russell et al[10]), though others have not.[9,11–13] Further, some studies have shown a differential deficit in processing positive affect in schizophrenia,[14,15] while others have shown a differential deficit in processing negative affect.[16] However, a recent study from our laboratory testing a wide range of affective stimuli and different modalities found comparable neural responses to positive and negative stimuli in SCZ and CON.[9] Discrepancies across studies may in part reflect task differences, with the use of

mood induction and implicit emotion processing paradigms being more associated with reduced amygdala activity[14,17–19] than explicit emotional evaluation tasks.[9,11–13] Importantly, individual differences in anhedonia and amotivation levels may also impact functional brain responses to emotionally evocative stimuli. For example, Taylor et al[13] found that negative symptom severity was negatively correlated with amygdala activity. Similarly, a recent study from our laboratory found a negative correlation between clinical measures of anhedonia and responses to affective stimuli in the amygdala among SCZ.[9] Furthermore, in a study examining the neural correlates of primary reinforcement in SCZ, higher clinical avolition ratings were negatively correlated with responses in regions involved in the processing of reinforcers.[20]

The influence of emotion on cognition is another critical area to examine, but this has received relatively less attention in the schizophrenia literature. Research on healthy individuals has consistently shown that emotional stimuli attract more attention than neutral stimuli and as such can facilitate the processing of affective stimuli.[21–24] Damage to the amygdala can impair this facilitation process,[25] indicating that the amygdala may play a key role enhancing attention to emotional stimuli. Consistent with such suggestions, studies examining episodic memory indicate that emotional stimuli are more likely to be remembered than neutral stimuli, with the magnitude of amygdala activity at encoding predicting the likelihood of subsequent memory for such emotional stimuli.[26–29] It has been proposed that the amygdala responds to stimulus salience (emotional significance) very early in information processing and can enhance stimulus perception through its feedback connections to sensory cortical regions, resulting in increased perceptual encoding of emotional events.[30–32] Further, animal models suggest that the release of stress hormones after an emotional event activates adrenergic receptors in the basolateral amygdala, modulating the consolidation of hippocampal dependent memories (reviewed in Cahill et al[33]). In support of this view, it has been shown that in humans amygdala damage,[34,35] as well as the administration of β-adrenergic blockers,[36] eliminates the enhancement of episodic memory for emotional events. At the same time, evidence from the animal literature suggests that the hippocampus is a key structure for learning and/or retrieving information about the emotional valence of stimuli in different contexts[37] that can in turn influence amygdala function, potentially providing contextual restraints on emotional responses.

In contrast to the studies described above (in which the emotional stimuli are relevant to the task), in paradigms where emotional salience is irrelevant or conflicts with task demands, the presentation of emotional stimuli can hurt performance as the demand for cognitive control increases.[38–41] This work has implicated the DLFPC as a key player in the integration of emotional and cognitive

information.[41] Thus, depending on task relevance, the emotional content of the stimuli can both facilitate and impair cognitive processing, with a number of brain regions (eg, dorsolateral prefrontal cortex [DLPFC], hippocampus, amygdala) critical for these interactions. In theory, the same mechanisms (both facilitatory and inhibitory) can operate for both positive and negative emotionally valenced stimuli. For example, the amygdala responds to positive as well as negative salient stimuli (see Kensinger and Schacter[42] and Ball et al[43]). However, empirically, more work has been devoted to the study of negative affect on cognition, and studies with negative stimuli have tended to produce more robust results, potentially due to the highly arousing nature of threat-relevant information, which can elicit strong responses in emotion-related systems.[37] Further, factors such as WM capacity, WM load, and basal DLPFC function may influence the degree to which the emotional content of stimuli can influence WM performance and brain activity.[44–46] Thus, it is possible that individuals with lower WM capacity (for whom the task may be more challenging, such as SCZ) may demonstrate a greater influence of emotional stimuli and greater activation in PFC regions when processing emotional information.

In schizophrenia, there are competing factors driving predictions about the relationship between emotion and cognition. First, SCZ have well-known deficits in a range of cognitive domains.[47,48] As such, one might expect that if SCZ demonstrated intact emotional responses (as suggested by the self-report literature), the influence of emotion on their cognitive processing may be greater than in CON, given their more vulnerable cognitive systems. Consistent with this hypothesis, Docherty and Sponheim[49] found that the typical disorganization of speech observed after the induction of laboratory stress is stronger in SCZ than in CON. Docherty and others have also documented that SCZ produce more speech errors when discussing negative as compared to positive or neutral topic.[50–53] In addition, Pauly et al[54] presented negative and neutral odors to SCZ and CON while they performed a verbal n-back task. The SCZ demonstrated greater sensitivity to the negative odors (larger performance decrements) than CON, consistent with the hypothesis that a more vulnerable cognitive system in this illness may lead to a stronger influence of emotion on cognition. In contrast, the neuroimaging literature reviewed above could be interpreted as suggesting that SCZ—especially those with high levels of anhedonia—might show reduced responses to emotionally evocative stimuli. If so, then SCZ may experience less modulation of cognition as a function of emotion, even if they have vulnerable cognitive systems.

The goal of this study was to address these mixed findings and further characterize how the emotional valence of stimuli (both negative and positive) in a WM task (n-back) impacts behavioral responses and brain activity

in schizophrenia. In our WM task, the task-relevant stimuli themselves had emotional valence. Thus, based on the findings from the episodic memory literature, we would expect emotional valence to facilitate memory performance if emotional valence enhances attention to and encoding of such stimuli. In terms of brain activity, emotional valence may then serve to reduce demand on regions involved in WM (eg, DLPFC) if the emotional content of stimuli enhances the encoding, maintenance, or retrieval of such stimuli. Thus, if SCZ are as sensitive (by which we mean as able to detect and react to) the emotional valence of stimuli, as CON, we would expect to see: (1) intact or even increased activity in brain regions involved in emotional processing, such as the amygdala and/or basal ganglia (regions involved in signaling stimulus salience in early processing stages); (2) greater facilitation of behavioral performance in patients as a function of emotion, given the known vulnerability of their cognitive systems; and (3) greater modulation of activity in dorsolateral prefrontal and hippocampal regions during task-blocks with emotional stimuli.

On the other hand, if SCZ are not as sensitive as CON to the emotional valence of stimuli in a cognitive task (as might be predicted by the imaging literature in schizophrenia using implicit emotional processing tasks), then we would expect to see (1) less activation in emotional processing regions such as the amygdala and/or basal ganglia, (2) less facilitation of behavioral performance in patients as a function of emotion, and (3) less modulation of cognitive control regions (DLPFC, hippocampus) as a function of emotional valence in schizophrenia. Further, we hypothesized that higher anhedonia levels would be associated with (1) less activation in emotional processing regions (amygdala, basal ganglia), (2) less facilitation of behavioral responses by emotional valence, and (3) less modulation of cognitive control regions by emotional valence.

Methods

Participants

Participants were recruited through the clinical core of the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St Louis and included (1) 38 individuals with *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) schizophrenia (SCZ: 13 females, 25 males) and (2) 32 CON (11 females, 21 males). Exclusion criteria included (*a*) substance abuse or any type of dependence within the past 3 months, (*b*) the presence of any clinically unstable or severe medical disorder, (*c*) present or past head injury with documented neurological sequelae and/or causing loss of consciousness, (*d*) meeting *DSM-IV* criteria for mental retardation, and (*e*) pregnancy or any contraindication to MR. CON were excluded if they had any lifetime history of, or first-order

family member with, an Axis I psychotic disorder, or any personal current mood or anxiety disorder other than specific phobias. All participants provided written informed consent in accordance with Washington University Human Subjects Committee's criteria. Participant diagnoses were based on a Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition Text Revised)[55] performed by a trained masters-level clinician. The clinician also had access to past and present medical records and to corroborative personal sources (eg, family) and combined all data to arrive at a diagnosis. This rater regularly participated in clinical interview and reliability training sessions as part of the CCNMD. Clinical symptoms were rated using the Scale for the Assessment of Positive Symptoms[56] and Negative Symptoms.[57] Based on previous factor analytic studies of the Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive symptoms,[58] we created the following symptom domain scores: (1) positive symptoms—hallucinations and delusions; (2) negative symptoms—alogia, anhedonia, avolition, affective flattening, and attentional impairment; and (3) disorganization—bizarre behavior, positive thought disorder, and inappropriate affect. In addition, we collected self-reports of anhedonia levels from all participants using the Chapman Physical[59] and Social[60] Anhedonia Scales. All SCZ were taking medications at the time of participation in the study. Please see table 1 for demographic information.

Tasks and Materials

Participants performed 3 runs of a nonverbal "2-back" version of the "*n*-back" task while being scanned. Each run included 4 initial fixation trials followed by alternating "fixation" and "task" blocks in alternating order (3 task, 4 fixation). Stimuli consisted of unfamiliar faces displaying happy, neutral, or fearful expressions matched in lighting, location, distance, exposure, and arousal ratings (taken from Ekman and Friesen[61] and Gur et al[62]). To avoid confusion, the same actor always had the same emotional expression. Stimuli appeared one at a time on a screen, and participants were instructed to press the target button if the stimulus currently on the screen was the same as the one seen 2 trials previously or the nontarget button if it was any other stimulus. The presentation of the critical "emotional" stimuli was manipulated to create a negative, a positive, and a neutral block condition. During each task block, participants saw 32 stimuli, each displayed for 2.5 seconds followed by a 500-millisecond interstimulus delay (see figure S2 in Supplementary material for task diagram). Depending on block condition, 16 of these stimuli were neutral, negative, or positive (occurring both as targets and nontargets) and the remaining 16 were always neutral fillers (also occurring both as targets and nontargets), which prevented habituation to emotional stimuli

Table 1. Demographics

Characteristics	SCZ ($n = 38$)	CON ($n = 32$)	t or χ^2	P
Age (y)	36.66 (9.12)	36.19 (10.86)	0.197	.84
Gender (%)			0.00	.99
Female	34	34		
Male	66	66		
Ethnicity (%)			0.07	.79
African American	50	47		
Caucasian	50	53		
Handedness	32R/4L	29R/3L	1.19	.24
Parental education	14.03 (3.16)	13.03 (2.32)	1.45	.15
Education years	13.03 (2.34)	15.66 (4.23)	3.27	<.05
Smoker (%)	55%	16%	11.69	<.001
Social Anhedonia scores	4.92 (2.1)	2.35 (2.2)	4.9	<.001
Physical Anhedonia scores	6.76 (4.17)	3.71 (3.1)	3.4	<.001
Negative Symptoms rating	1.84 (0.95)	0.26 (0.31)	8.8	<.001
Positive Symptoms rating	1.62 (1.4)	0.02 (0.09)	6.4	<.001
Disorganization symptoms rating	1.07 (0.78)	0.46 (0.46)	3.8	<.001
Age onset	19.2 (7.7)	N/A		
Illness duration (y)	17.4 (11.2)	N/A		
Atypical medications only (%)	92	N/A		
Combination typical/ atypical (%)	2.6	N/A		

Note: SCZ, individuals with schizophrenia; CON, healthy control subjects; R, right; L, left

and allowed us to directly compare global context effects on behavioral responses. During fixation blocks (90 s), a crosshair appeared continuously, and subjects were told to fixate. Visual stimuli were generated by a G3 Macintosh computer and PsyScope and projected onto a computer screen behind the subject's head within the imaging chamber. Participants saw the screen through a mirror positioned approximately 8 cm above their face.

Behavioral Data Acquisition and Analysis

A fiber-optic, light-sensitive key press interfaced with a PsyScope button box was used to record subjects' responses. To examine accuracy and reaction time (RT) separately for emotional vs neutral items within the emotional blocks, we conducted $2 \times 2 \times 2$ repeated-measures analyses of variance (ANOVAs) with block type (negative, positive) and stimulus valence (emotional, neutral) as within-subject factors and group as a between-subject factor.

Functional Magnetic Resonance Imaging and Analysis

Functional scanning was performed on a 3T Siemens Allegra head-dedicated system at the Research Imaging Center of the Mallinckrodt Institute of Radiology at the Washington University Medical School. For details on scanning parameters, please see Supplementary materials.

Functional magnetic resonance imaging (fMRI) data were analyzed combining the use of the general linear model (GLM) with ANOVA-based mixed- and random-effects models using inhouse software (FIDL). A GLM including regressors for linear trends within runs and baseline shifts between runs was computed for every subject. Blood oxygenation level–dependent (BOLD) responses to each block type (positive, negative, and neutral) were modeled as "boxcar" functions and then convolved with a canonical hemodynamic response function to generate separate estimates for each condition. The estimates from the individual subject GLMs were analyzed using appropriately designed ANOVAs and post hoc contrasts that treated participants as a random factor.

Regions of Interest Identification. We used a priori defined regions of interest (ROIs) including bilateral amygdala, hippocampus, basal ganglia, and DLPFC. The DLPFC ROIs were defined on an atlas-representative image (following Rajkowska et al[63]). The amygdala, basal ganglia, and hippocampal formation ROIs were defined based on manual tracing in individual participants enrolled in an ongoing study of brain structure and schizophrenia conducted by the CCNMD[64] and later warped into atlas-based space. We identified significant regions of activation within our a priori ROIs using a threshold criterion of $P < .01$ in voxel-wise comparisons and a cluster size of 10 voxels. This cluster size requirement provides further protection against type I error[65,66] and was chosen based on Monte Carlo simulations.

Whole-Brain Analyses. To look for nonpredicted effects in regions outside the a priori ROIs, we conducted whole-brain voxel-wise repeated-measures ANOVAs. These whole-brain maps were thresholded for significance to obtain a whole-brain false positive rate of 0.05 based on Monte Carlo simulations. The results of the whole-brain analyses are presented in Supplementary materials.

Correlational Analyses. To examine whether individual differences in self-reports of anhedonia predicted individual differences in behavior and brain activation, we correlated scores on the Chapman Physical and Social Anhedonia Scales with behavioral performance and
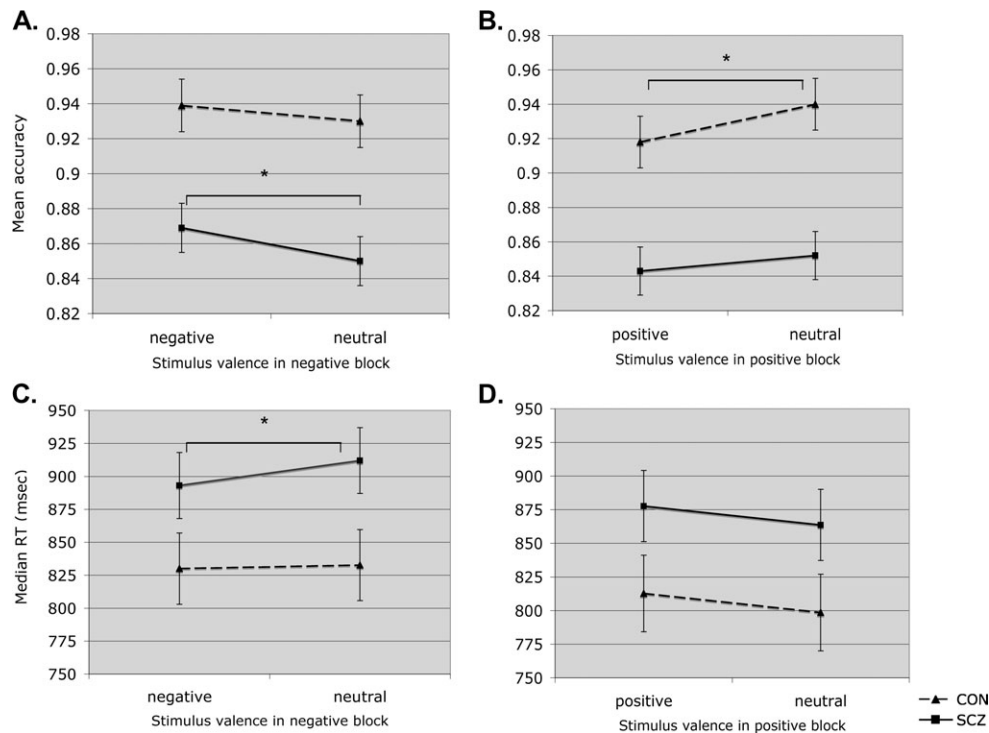
Fig. 1. Accuracy and Reaction Time as a Function of Stimuli Emotional Valence. *(A)* Graph depicting accuracy as a function of stimulus valence within negative block. *(B)* Graph depicting accuracy as a function of stimulus valence within positive block. *(C)* Graph depicting reaction time as a function of stimulus valence within negative block. *(D)* Graph depicting reaction time as a function of stimulus valence within positive block. Asterisk indicates a significant difference within group (*$P < .05$).

brain activation in regions showing an effect of valence during the emotionally loaded WM task separately for each group. The Revised Physical Anhedonia Scale[59] assesses a self-reported deficit in the ability to experience pleasure from typically pleasurable physical stimuli such as food, sex, and settings. The Revised Social Anhedonia Scale[60] assesses self-reported deficits in the ability to experience pleasure from nonphysical stimuli such as other people, talking and exchanging expressions of feelings. We examined correlations between these measures and activation in regions showing an effect of stimulus valence during the WM task.

Results

Behavioral Results

Overall, SCZ were less accurate than CON, $F_{1,68} = 17.1$ $P < .001$, and took longer to respond at a trend level, $F_{1,68} = 3.36$, $P = .07$ (see figure 1). In addition, we found a trend-level main effect of block type on accuracy, $F_{1,68} = 3.1$, $P = .08$, which was modified by a significant interaction with stimulus valence, $F_{1,68} = 11.8$, $P < .001$. Post hoc contrasts indicated that subjects were significantly more accurate for emotional than neutral stimuli in negative blocks, $F_{1,68} = 6$, $P < .05$, but more accurate for neutral than emotional stimuli in positive blocks, $F_{1,68} = 5.1$, $P < .05$ (see figure 1A,B). Although this was the tendency for

both groups and we found no evidence of an interaction with group, within-group contrasts revealed the difference in accuracy between negative and neutral stimuli was significant for SCZ alone, $F_{1,68} = 6.29$, $P < .05$, but not for CON alone, $F_{1,68} = 1.04$, $P = .31$. In contrast, the difference between positive and neutral stimuli was significant for CON, $F_{1,68} = 4.96$, $P < .05$, but not SCZ, $F_{1,68} = 0.83$, $P = .36$ (see figure 1A,B). Similarly, in the RT data, we found a significant main effect of block type $F_{1,68} = 18.05$, $P < .001$, modified by a significant interaction with stimulus emotional valence, $F_{1,68} = 6.97$, $P < .05$. Post hoc contrasts showed that responses tended to be faster for emotional compared with neutral stimuli in the negative block, $F_{1,68} = 3.1$, $P < .09$ but faster for neutral compared with emotional stimuli in the positive block, $F_{1,68} = 3.64$, $P < .06$ (see figure 1C,D). This was the tendency for both groups, but within-group contrasts indicated the difference in RT between negative and neutral stimuli was significant for SCZ alone, $F_{1,68} = 5.13$, $P < .05$, but not for CON alone, $F_{1,68} = 0.09$, $P = .77$. The difference in RT between positive and neutral stimuli was not significant in either group in within-group contrasts. In summary, we found that responses to negative stimuli were faster and more accurate than responses to neutral stimuli (including among SCZ) but tended to be less accurate for positive than neutral stimuli.
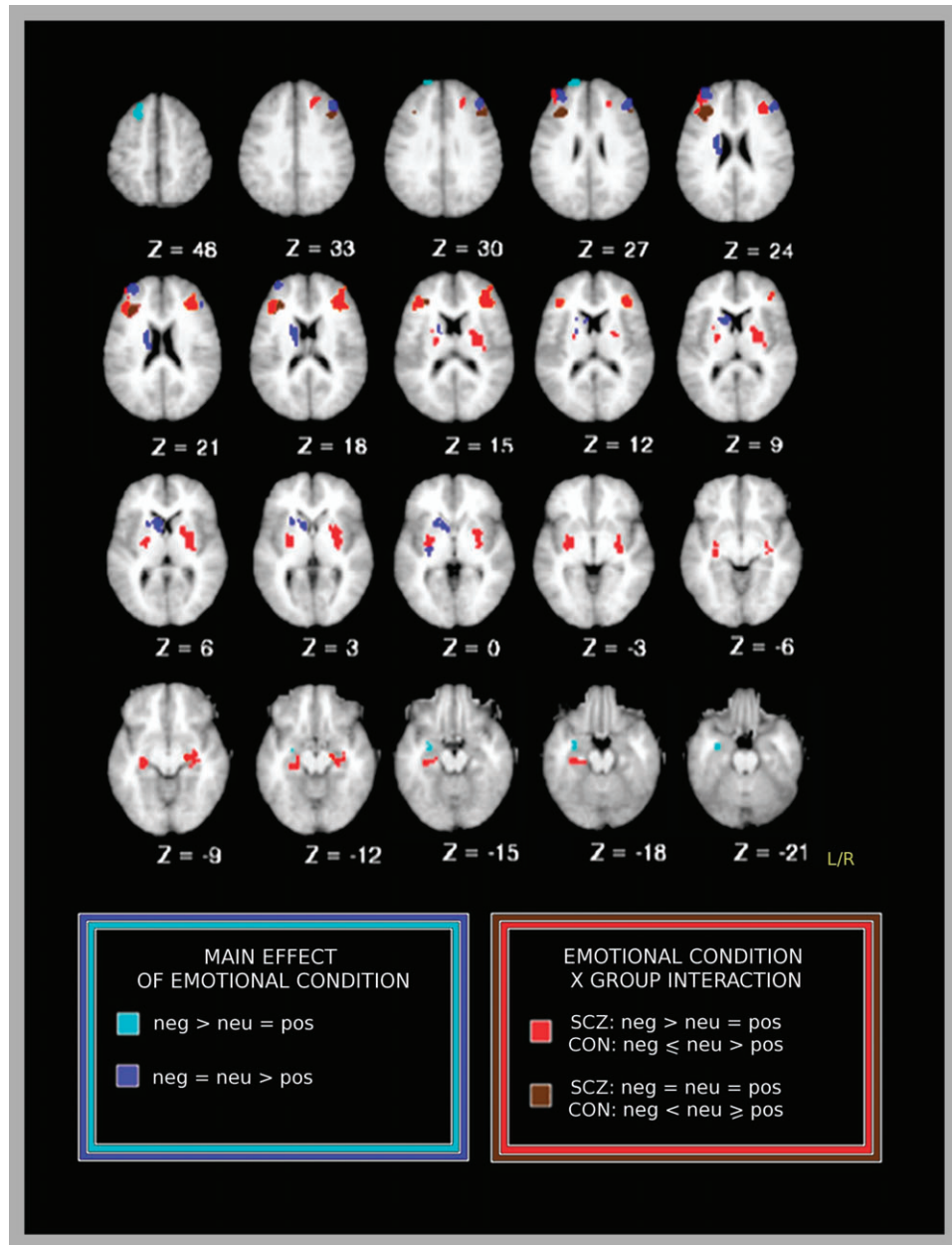
Fig. 2. Regions Showing a Significant Main Effect of Emotional Condition (Cold Colors) or a Group by Emotional Condition Interaction (Warm Colors).

Correlations Between Self-reports of Anhedonia and Behavioral Performance

As shown in table 1, mean scores on both physical and social anhedonia measures were higher among SCZ than CON. However, anhedonia scores were not significantly associated with accuracy or RT in either group.

fMRI Results

ROI-Based Analyses. We computed voxel-wise ANOVAs using block condition (positive, negative, neutral) as a within-subject factor and group (CON, SCZ) as a between-subject factor. As shown in figure 2 and table 2,

we found a number of regions that demonstrated a main effect of block condition that did not further interact with group. Post hoc contrasts separately comparing activation between negative and neutral and between positive and neutral block conditions revealed that, as expected, several regions showed greater activation in the negative as compared with neutral or positive conditions. These included the left amygdala and left superior frontal gyrus (Broadmann areas [BAs] 8 and 9). There were also several regions that showed less activation in the positive conditions than either the negative or neutral condition, including regions in the basal ganglia and the middle

Table 2. Functional Magnetic Resonance Imaging Results of Analyses for A Priori Regions of Interest

Talairach Coordinates

Brain Region	BA	x	y	z	Voxels	z Value	Activity Pattern
Main effect of group							
No significant regions							
Main effect of condition							
L amygdala		−27	−09	−19	28	2.69	neg > neu = pos
L superior frontal gyrus	9	−15	57	29	10	2.39	"
L superior frontal gyrus	8	−22	28	49	20	2.61	"
L caudate nucleus		−18	−01	20	24	2.72	neg = neu > pos
L caudate nucleus		−14	−11	18	15	2.67	"
L caudate nucleus[a]		−11	09	04	37	3.17	"
L putamen		−21	13	05	22	2.82	"
L putamen		−27	−04	−03	10	2.63	"
L putamen		−28	−18	−02	19	2.55	"
L middle frontal gyrus	10	−32	45	25	48	3.01	"
R middle frontal gyrus	46	42	31	29	54	2.83	"
Group (CON, SCZ) × condition (negative, neutral, positive)							
L hippocampus	N/A	−27	−22	−07	15	3.05	SCZ: neg > neu = pos; CON: neg < neu > pos
R hippocampus		28	−22	−11	16	2.89	"
L hippocampus		−24	−28	−15	28	3.28	"
R putamen		27	−13	07	43	2.83	"
R putamen		18	03	07	20	2.55	"
R putamen		26	00	01	36	2.71	"
L putamen/globus pallidus		−25	−10	01	51	2.89	"
R putamen/globus pallidus		29	−19	−06	26	3.21	"
L middle frontal gyrus	10	−39	45	24	23	2.66	"
R middle frontal gyrus	9	18	35	35	34	2.53	"
L putamen		−21	−05	10	15	2.68	SCZ: neg > neu[a] = pos; CON: neg < neu[a] > pos
R hippocampus		19	−19	−11	8	3.05	SCZ: neg > neu = pos; CON: neg = neu > pos
R middle frontal gyrus	10	41	44	13	21	2.65	"
L middle frontal gyrus	46	−40	29	15	48	2.94	"
R middle frontal gyrus	46	35	31	18	88	2.96	"
L middle frontal gyrus	9	−32	26	21	71	3	SCZ: neg = neu = pos; CON: neg < neu > pos
R middle frontal gyrus	9	42	24	32	31	2.45	SCZ: neg = neu = pos; CON: neg < neu = pos

Note: BA = Brodmann area; CON = control subjects; SCZ = participant with schizophrenia; L = left; R = right; neg = negative; neu = neutral; pos = positive; " = same as line above.
[a]Trend-level significance in post hoc analysis.

frontal gyrus (BAs 10 and 46). Within-group analyses confirmed that these effects were present in both groups in all regions, except for BA 46 in SCZ and the amygdala and BA 8 in CON (see table S1 in Supplementary material). Although amygdala BOLD responses did not reach a statistically significant difference between block conditions in CON alone, comparing activity in the amygdala to emotional vs neutral stimuli on an item-by-item basis within negative task blocks (using a repeated-measures ANOVA with stimulus valence (negative, neutral) as within-subject factor and group as between-subject factor) revealed that both CON and SCZ demonstrated significantly increased responses to negative as compared with neutral items (see table S2 in Supplementary Mate-

rial). There was no main effect or interaction with group in this region.

There were also several regions that did show a group × condition interaction. Somewhat surprisingly, we found a number of regions that showed greater activation in the negative condition than either the neutral or positive condition in SCZ but not in CON. As shown in figure 2 and table 2, these regions included the putamen and globus pallidus, the hippocampus, and the middle frontal gyrus. Thus, SCZ appeared to show evidence of greater modulation of brain activity in response to negative stimuli than did CON but in the direction of enhanced rather than reduced activity. We also found 2 regions in the more posterior and medial portion of the middle frontal

gyrus that showed modulation-by-block condition in CON but not in SCZ (see figure 2, table 2). In summary, both patients and CON showed increased amygdala activity in negative compared with neutral or positive block conditions, but only SCZ showed increased activity in the negative compared with neutral conditions in the basal ganglia and hippocampus. The modulation of activity within the DLPFC showed a more complex pattern, with some regions showing greater activation in negative block conditions in SCZ compared with CON and other regions failing to show a modulation of activation as a function of block condition in SCZ. See Supplementary material for a description of the relationship between brain activity and behavior across groups and conditions.

Correlations Between Individual Differences in Self-reports of Anhedonia and Brain Activity

We focused our correlations on the ROIs that demonstrated a main effect of valence to determine if we would find individual difference relationships with anhedonia even if there were no main effects of group. Importantly, as shown in table 3, higher scores on social anhedonia in SCZ correlated with diminished activation in the amygdala during positive blocks and with a smaller increase in amygdala activation in both the positive and negative blocks compared to the neutral blocks (see table 3). Further, both higher physical and social anhedonia scores in SCZ demonstrated a positive correlation with a region in the right DLPFC in the positive and neutral block conditions (see table 3). In CON, there were no significant correlations between anhedonia scores and functional task related activity in these regions. However, including anhedonia scores as covariates did not eliminate group differences in these regions.

Discussion

The goal of this study was to examine the influence that the emotional valence of a stimulus exerts on WM in SCZ compared with CON by assessing both behavioral and neural responses in an emotionally loaded 2-back WM task. Our results support the hypothesis that SCZ are at least as sensitive as CON to the emotional content of stimuli while performing a WM task. However, our results also suggest that this emotional information interacts with WM-related brain systems in a different way in SCZ than it does in CON. Each of these results will be discussed in more detail below.

Behavioral Performance During an Emotionally Loaded WM Task

Though SCZ performed overall worse than CON, we found no behavioral evidence for group differences in the influence of emotion on behavioral performance. As would be predicted by the episodic memory literature,

Table 3. Correlation Between BOLD Responses in A Priori ROIs Demonstrating an Effect of Emotional Valence and Anhedonia Measures

Talairach Coordinates

Brain Region	BA	x	y	z	Block Condition	r	z Score
Social anhedonia							
CON							
No regions							
SCZ							
R middle frontal gyrus	46	42	31	29	Neutral	0.41	2.65
L amygdala		−27	−09	−19	Positive	−0.45	−2.93
R middle frontal gyrus	46	42	31	29	"	0.42	2.67
L amygdala		−27	−09	−19	Negative-neutral	−0.44	−2.86
L amygdala		−27	−09	−19	Positive-neutral	−0.47	−3.13
Physical anhedonia							
CON							
No regions							
SCZ							
R middle frontal gyrus	46	42	31	29	Neutral	0.50	3.32
R middle frontal gyrus	46	42	31	29	Positive	0.49	2.86

Note: BA = Brodmann area; CON = healthy control subjects; SCZ = individuals with schizophrenia; L = left; R = right; " = same as line above.

stimuli with emotional content were better remembered than neutral stimuli. The strongest effect was observed for the comparison of negative to neutral stimuli, where accuracy was overall better. The finding that negative stimuli are better remembered than neutral stimuli is consistent with a number of prior studies (eg, Cahill et al,[67] Hamann et al,[68] Ochsner,[69] Buchanan et al,[70] and Sergerie et al[71]) and supports the hypothesis that there are neural systems specialized for detecting and enhancing memory for salient events. Further, although the same basic patterns of memory for emotionally evocative stimuli were present in both groups, some of the effects were significant within the SCZ group alone but not in the CON. Thus, the modulation of WM performance by emotional, and in particular negative stimuli, was somewhat stronger within the SCZ group, though not significantly so. This result is consistent with the self-report literature described in the introduction suggesting intact emotional experience—in the moment—among SCZ.

Emotion-Related Brain Activity During an Emotionally Loaded WM Task

We found evidence of intact amygdala responses to the emotional content of task stimuli in the SCZ group,

suggesting that the detection of emotionally salient stimuli during a cognitive task is preserved in individuals with this illness. Our findings demonstrated that amygdala activity was greater during negative as compared with both positive and neutral blocks. Importantly, this effect was present in both SCZ and CON (see table S1). As with the behavioral data, these results are consistent with the hypothesis that SCZ show intact responses to emotionally evocative stimuli. In our task, the emotion processing was implicit rather than explicit. Thus, unlike some of the prior literature,[14–19] our data provide evidence for relatively intact amygdala activity even during implicit emotion processing conditions in schizophrenia. This result could reflect enhanced power to detect emotion-relevant brain activity in the current study compared with some prior studies given our larger sample size.

Despite relatively intact responses in the amygdala, we also found evidence for group differences in BOLD responses as a function of the emotional condition of the WM task. Specifically, we found the predicted decreased activity in bilateral regions of the hippocampus and middle frontal gyrus (including DLPFC) for negative as compared with neutral task blocks in CON, but we found the opposite pattern in SCZ, despite the fact that SCZ showed as much behavioral facilitation from the negative stimuli. Our blocked analyses reflect activity associated with both item processes and any maintenance in WM that spans items. Prior studies have found reduced maintenance-related activity in SCZ.[72–74] Thus, an intriguing hypothesis is that the increased activity during the negative condition in SCZ reflected better active maintenance of such items due to enhanced encoding. The location of the DLPFC regions showing different patterns in SCZ vs CON was generally consistent with this hypothesis as they extended more ventrally than those only showing a main effect of condition. These ventral regions have been previously associated with the active maintenance of information in WM.[75,76] Alternatively, the observed increase in activity during the negative condition in schizophrenia could be due to an inefficient use of mental resources. In the context of a more vulnerable cognitive system, SCZ may be more reactive to the emotional content of stimuli and in need to recruit cognitive resources to a greater extent. Regardless of the correct interpretation, our findings suggest that disturbances in emotional processing in schizophrenia relate to alterations in emotion-cognition interactions, rather than to the perception and subjective experience of emotion per se.

Individual Differences in Anhedonia

Although we found no evidence of an association between anhedonia levels and behavioral responses, higher social anhedonia levels were associated with less of an increase in BOLD responses in amygdala in the positive and negative task conditions compared with the neutral conditions. In contrast, higher levels of social and physical anhedonia were positively correlated with BOLD responses in the DLPFC in the positive and neutral tasks blocks in SCZ. The negative correlation between anhedonia scores and amygdala responses to emotionally evocative stimuli is consistent with the hypothesis that high levels of anhedonia are associated with a diminished impact of emotion on neural processing. These results are particularly interesting given that the emotional stimuli were faces. As such, the correlation with social anhedonia may reflect a relative lack of engagement with key social stimuli (faces) that convey emotional information in those individuals with high social anhedonia. The positive correlation between DLPFC activation and both social and physical anhedonia scores could reflect the fact that the emotional content of the faces is less facilitatory on WM processing in the individuals with high social anhedonia, leading to a higher demand on cognitive control resources. However, the fact that we also saw a correlation between anhedonia scores and DLPFC activation in the neutral condition suggests a more general interpretation, perhaps indicating that those with high anhedonia scores have overall more alterations in activation of cognitive control regions regardless of task condition. The use of a more challenging task (or a task of a different nature), in which cognitive systems cannot as easily rescue performance, may unmask an effect of high levels of anhedonia on behavioral performance as well. However, including anhedonia scores as covariates did not eliminate group differences in these regions, suggesting that something in addition to anhedonia severity is driving group differences in the responses of these regions to emotional stimuli during WM. Nonetheless, our results contribute to the growing literature highlighting the importance of examining individual differences in symptom severity in schizophrenia.

An important limitation in this study is that all participants with schizophrenia were taking antipsychotic medications, which may interact with task performance and brain activity. To control for the effect of medication, we converted all medication dosages to chlorpromazine equivalents.[77–80] When correlating medication dosage with brain activation in regions showing an effect of group or emotional valence, we found no evidence of a significant association between medication and brain activation. Furthermore, an important proportion of SCZ are chronically medicated; thus, we believe it is important to assess the functioning of patients on medications if this is their typical state. Another limitation is that in this study we used only 2 types of emotion, which limits whether our findings can be generalized to other emotion types, such as anger or sadness. In addition, future studies may need to employ tasks that better recreate the emotional processing and content encountered in day-to-day cognitive tasks to increase the ecological validity of stimuli.

Conclusions

Taken together, the results from this study are consistent with the hypothesis that the subjective experience of emotion is relatively intact in schizophrenia and suggest that the emotional salience of stimuli can guide behavioral performance in WM tasks in SCZ as it does in CON. However, our results also indicate that SCZ show reduced DLPFC activity in neutral conditions but increased activity in negative conditions as compared with CON. We conclude that the emotional arousal caused by stimuli may challenge dorsal-frontal control systems and have both beneficial and detrimental influences on cognitive processing. If SCZ have vulnerable cognitive and neural systems that support WM and other cognitive control processes, then emotional processing may exert a greater modulatory effect than in CON. Further, our results also point to the importance of examining individual differences in symptom severity in schizophrenia. We found that higher levels of social anhedonia were associated with a diminished impact of emotion on cognitive and neural processing, suggesting that more severe anhedonia levels may prevent the use of emotional salience to guide WM and other cognitive processes in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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