



Impaired regulation of emotional distractors during working memory load in schizophrenia



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ABSTRACT

Schizophrenia (SZ) patients exhibit deficits in emotion regulation that affect their daily functioning. There is evidence that the prefrontal cortex plays an important role in emotion regulation. However, it remains unclear how this brain region is involved in emotion regulation deficits in SZ, and how such deficits impact performance on cognitively demanding tasks.

We examined how happy and fearful emotional distractors impact performance on working memory (WM) tasks of varying difficulty (0-back, 2-back), and brain activity using fMRI. Participants were 20 patients with SZ and 20 healthy controls (HC) matched on age, sex, race, and IQ.

A significant 3-way interaction showed that SZ patients had lower performance compared to HC when exposed to fearful and happy distractors, but only during the 2-back task. Second-level fMRI between-group analysis revealed that compared to SZ patients, HC showed significantly greater increase in brain activity with WM load in the left IFG (BA 45) when exposed to fearful distractors. Less brain activity in this region was also associated with reduction in SZ patients' performance during higher WM load and the presence of fearful distractors.

SZ patients had difficulty in performing a WM task when regulating emotions, and they failed to show the emotion-specific modulation of the left IFG observed in HC. These results suggest that SZ patients have difficulty with emotion regulation demands during effortful cognitive tasks. This also provides us with potential insight on how emotion regulation could be rehabilitated in SZ using cognitive training.

1. Introduction

Emotion regulation refers to the effortful control of experience in response to goal-unrelated or irrelevant emotional stimuli (Gross, 1998; Gyurak et al., 2011; Phillips et al., 2008). Emotion regulation is impaired in schizophrenia (SZ), and these deficits interfere with social life and daily functioning (Henry et al., 2008; O'Driscoll et al., 2014). Furthermore, it has been suggested that difficulties in emotion regulation could lead to psychotic symptoms, while adaptive emotion regulation could protect against symptom formation (Grezellschak et al., 2015). Thus, understanding the neural underpinnings of emotion regulation deficits in SZ is critical and may help develop more targeted

interventions.

Emotional working memory (WM) paradigms are often used to investigate emotion regulation processes and require participants to ignore emotional distractors while performing a WM task such as the N-back test (Erk et al., 2007; Phillips et al., 2008). Medial and lateral regions of the prefrontal cortex (PFC), as well as the dorsal anterior cingulate cortex (ACC, BA 32) are specifically active during effortful emotion regulation processes in healthy individuals (see Phillips et al., 2008, and Ochsner and Gross, 2005, for reviews). More specifically, when performing an emotional WM task, healthy subjects demonstrate robust activation in the inferior frontal gyrus (IFG, BA 45) and orbito-frontal gyrus (BA 47) when exposed to fearful distractors (Ladouceur

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et al., 2013). Hence, the modulation of the activity in these PFC regions seems important for normal regulation of emotional distractors.

There is some evidence that abnormal PFC function plays a role in emotion regulation deficits in SZ as advanced by fMRI studies during the performance of emotional WM tasks (Anticevic et al., 2012; Becerril and Barch, 2011; Eack et al., 2016; van der Meer et al., 2014). Yet, it remains unclear which regions of the PFC are involved and whether abnormal WM activation is dependent on emotional regulation ability. When required to memorize negative emotional faces in a WM task, SZ patients show increased activity in the dorsolateral PFC (Becerril and Barch, 2011). However, in an earlier study using an independent sample, our team observed reduced ventromedial PFC activity in SZ patients relative to healthy controls (HC) when fearful vs. happy faces are used as irrelevant distractors during a WM task (Eack et al., 2016). SZ patients have also demonstrated weaker dorsolateral PFC-amygdala connectivity when fielding irrelevant emotional distractors during WM (Anticevic et al., 2012) and none of these previous studies observed abnormal activity in the dorsal ACC in SZ.

We aimed to further explore these initial findings using a fMRI emotional WM paradigm with 2 different levels of difficulty or WM “load” (0-back, 2-back), and examine how different types of emotional distractors (happy and fearful) impact performance and brain activity in SZ. As SZ individuals have difficulty regulating emotions during emotional WM task compared to HC, we hypothesized that SZ will show abnormal decreased accuracy and an increased response time during the 2-back task with emotional distractors compared to HC. Moreover, we hypothesized that fearful distractors during the 2-back task will increase activation in the IFG (BA 45) and orbitofrontal gyrus (BA 47) in HC, but that SZ individuals will fail to show this normal modulation.

2. Methods

2.1. Participants

Twenty patients with SZ and 20 HC were recruited from the Early Course Treatment Program and the community referral networks, and selected as part of the baseline assessment of an ongoing two-site (Boston and Pittsburgh) randomized-controlled study (NCT #01561859) investigating the effect of cognitive enhancement therapy in early course SZ. We used data from the Pittsburgh site because of an inadequate number of HC available in the Boston site. All participants provided written consent to the study approved by the University of Pittsburgh IRB. Inclusion criteria for patients were (1) a diagnosis of schizophrenia or schizoaffective disorder verified using the SCID interview (First, 1998); (2) a duration of psychotic symptoms less than eight years; (3) clinically stabilized on antipsychotic medication (assessed via SCID and available medical history in consensus conferences); (4) age 18–45 years; (5) current IQ greater than 80 as assessed using the WASI-II (Hays et al., 2002); and (6) the ability to read (sixth grade level or higher) and speak fluent English. Exclusion criteria were (1) significant neurological or medical disorders that may produce cognitive impairment (e.g., seizure disorder, traumatic brain injury); (2) persistent suicidal or homicidal behavior; (3) a recent history of substance abuse or dependence (within the past 3 months); (4) any MRI contraindications such as ferromagnetic objects in the body and those people too large to fit into the scanner (shoulder width larger than 25 inches); and (5) decisional incapacity requiring a guardian. HC were also excluded if they had family history of psychosis or another major psychiatric illness.

2.2. Clinical measures

Patients' negative and positive symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Emotion recognition performance was assessed

using the PENN Emotion Recognition Task (Kohler et al., 2003). Medication data was collected by treating clinicians from medical records and confirmed when necessary with the treating psychiatrist.

2.3. Emotional faces N-back working memory task

Each participant performed an emotional face N-back (EFNBACK) task during functional magnetic resonance imaging (fMRI). The EFNBACK is a modified version of the N-back WM task, which consists of visually presenting a pseudo-random sequence of letters while participants respond to a pre-specified letter appearing on the computer screen. The N-back task includes two memory load conditions: a no-memory load condition (0-back; e.g. press the button when letter ‘M’ is presented) and a higher memory load condition (2-back; e.g. press the button whenever the current letter is identical to the letter present two trials back [M–X–M]). In the emotional N-back task, either fearful, happy, or neutral face distractors appeared on each side of the letter stimuli. A no-distractor condition was also included, but for the current study's purpose, this condition was excluded from further analysis.

Detailed instructions were provided during task practice prior to the MRI scanning session, and instructions were presented on the screen at the beginning of each block. The task was divided into 3 runs each lasting 7 min and 4 s. Each run was comprised of 8 blocks representing all combinations of memory load conditions and distractor conditions. The blocks were presented in a pseudo-randomized order. Each block included 12 trials of 500 ms. Inter-trial interval was a jittered fixation cross (mean duration = 3500 ms). Participants were instructed to respond as quickly as they could with their index finger to the target letter. Consequently, response time was solely computed when participants were responding correctly to the target letter.

2.4. Behavioral analysis

To analyze the response time and accuracy during the task, a $2 \times 3 \times 2$ ANOVA was performed to analyze 1) the effect of WM load across all distractor types (2-back vs. 0-back), 2) the effect of emotional distractors across all WM loads (neutral vs. happy vs. fearful), 3) the effect of group across all conditions (SZ vs. HC), and 4) the 3-way interaction (groups \times WM loads \times emotional distractor types). Post-hoc repeated-measures ANOVAs, and between-group independent *t*-tests were then performed to localize the specific interaction effect.

2.5. Neuroimaging analysis

2.5.1. MRI acquisition

The MRI study was performed on a 3.0T Siemens Trio Imaging Systems at the University of Pittsburgh. A T1-weighted 3D MPRAGE sequence was collected (voxel size of $1.0 \times 1.0 \times 1.2$ mm, TR 2300 ms, TI = 900 ms, TE = 2.89 ms, flip angle = 90° , FOV = 256 mm, 256×256 matrix, 160 slices, slice thickness = 1.2 mm). We also used a double echo-spin echo sequence to obtain T2 images in the axial plane to screen for neuroradiological abnormalities. fMRI images were acquired during the EFNBACK task using a gradient echo T2*-weighted sequence (voxel size of $3.2 \times 3.2 \times 3.2$ mm, TR 2000 ms, TE = 30 ms, bandwidth = 2298, flip angle = 79° , FOV = 205 mm (excluded part of the dorsal somatosensory-motor cortex), 64×64 matrix, 36 slices).

2.5.2. Preprocessing

First, the T1 anatomical image for each participant was segmented using the “New Segment” routine in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Next, the fMRI time series images were realigned to the first volume to correct for interscan movement, and coregistered to the participants' own anatomical image. The deformation field map obtained from the segmentation step was then applied to the fMRI images to normalize them into the standard MNI space (voxel size $2 \times 2 \times 2$ mm). Finally,

Table 1
Demographic and clinical results.

	Healthy controls			Schizophrenia patients			p-value
	(N = 20)			(N = 20)			
	Mean	SD	Range	Mean	SD	Range	
Age (years)	25.05	4.05	19–48	26.9	7.63	18–32	.35
SANS w/o attention total	1.35	2.49	0–7	20.37	13.68	6–47	.00
SAPS total	0.45	0.75	0–2	8.47	6.23	0–21	.00
IQ score	107.7	13.85	82–134	108.05	9.62	97–139	.93
PENN emotion recognition (total)	33.65	2.56	29–37	32.33	3.33	26–38	.18
Medication (mg chlorpromazine)				511.7	393.5	100–1560	–
Duration of illness (years)				4.37	2.39	1–8	–
	N	%		N	%		
Gender							.50
Male	15	75		12	60		
Female	5	25		8	40		
Level of education							.16
Partial high school	1	5		2	13		
Completed high school	3	15		3	19		
Attended college	3	15		7	44		
Completed college	8	40		3	19		
Completed post grad	5	25		1	6		
Race							1.00
Asian	1	5		1	5		
White	13	65		13	65		
African-American	5	25		5	25		
Hispanic	1	5		1	5		

Note: SD = Standard deviation, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, w/o = without, mg = milligrams, IQ = Intelligence quotient. Information about the level of education was missing for 4 patients. SANS and SAPS total scores were missing for one patient. PENN emotion recognition total scores were missing for 2 patients.

the images were smoothed with an isotropic 8-mm full width at half maximum (FWHM) Gaussian kernel. Low frequency drifts were removed by applying a high-pass filter with a cut-off of 128 s. We examined the realignment parameters for all participants to ensure head motion was not greater than 4 mm in any direction during the fMRI acquisition. Moreover, maximum translational absolute motion (in mm) for patients (mean = 1.17, SD = 0.97) and HC (mean = 0.92, SD = 0.60) as well as the mean translational relative motion for patients (mean = 0.09, SD = 0.04) and HC (mean = 0.08, SD = 0.05) did not significantly differ between the groups (all $p > .35$).

2.5.3. fMRI statistics

A general linear model (GLM) in which individual conditions were modeled with the canonical hemodynamic response function (HRF) implemented in SPM8 was used at first-level analysis. More precisely, a subject-specific fixed-effects model was used to estimate the effect of each 8-block condition, and the motion parameters were entered as covariates in the model. Five contrasts of interests were generated for each subject to investigate the effect of WM load across all distractor types (2-back > 0-back), the effect of emotional distractor across all WM loads (happy > neutral; fearful > neutral) and the interaction between emotional distractor types and the WM load (2-back_happy > 2-back_neutral – 0-back_happy > 0-back_neutral; 2-back_fearful > 2-back_neutral – 0-back_fearful > 0-back_neutral). Each contrast weight is described in detail in [Appendix A](#).

We then submitted these contrasts to a second-level analysis to examine differences between groups in task related brain activity. We conducted 2-sample t-tests to investigate the following between-group differences (HC > SZ; SZ > HC) for each contrast of interest using a random-effects model. In an attempt to strike a balance between the risk of false-positives ([Eklund et al., 2016](#)) and false-negatives ([Lieberman and Cunningham, 2009](#)) we applied a cluster extent threshold determined by a non-parametric Monte Carlo simulation to correct for multiple comparisons ([Slotnick et al., 2003](#)). Statistical

significance was defined at the cluster level, using an uncorrected p -value of 0.001 at the single voxel level. Results of a Monte-Carlo simulation with 10 000 iterations indicated that a cluster of 41 contiguous voxels in the normalized image corresponded to a cluster significance of $p < 0.05$, corrected for multiple comparisons. Mean beta values were also extracted using spheres of 10 mm around the local maxima of the significant clusters using WFU_PickAtlas for illustrative purposes only ([Maldjian et al., 2003, 2004](#)). Finally, second-level within-group analyses were also performed separately for HC and SZ patients for each contrast using random-effects model. These analyses and results are presented in [Appendix A](#).

2.6. Brain activity and WM performance

To further investigate if the WM performance was related to the fMRI findings, we performed exploratory non-parametric Spearman rank correlations between the reduction in accuracy with the increase in WM load for fearful distractors (0-back minus 2-back) and the HRF β values from the significant cluster.

2.7. Effect of symptoms severity and medication in patients

We performed post-hoc non-parametric Spearman rank correlations to explore the potential relationship with positive and negative symptoms severity in patients and the behavioral measures (accuracy and response time for each condition) as well as the brain activity (using HRF β values from the significant clusters). We also used post-hoc non-parametric Spearman rank correlations to investigate any possible association with the amount of antipsychotic medication used by patients, as measured by chlorpromazine equivalents, on the same measures.

Table 2
EFNBACK behavioral results.

	Healthy controls			<i>p</i> -value	Schizophrenia patients			<i>p</i> -value
	(N = 20)				(N = 20)			
	Neutral	Happy	Fearful		Neutral	Happy	Fearful	
Mean accuracy % (SD)								
0-back	99 (3)	99 (2)	99 (4)	.40	97 (6)	98 (5)	98 (4)	.33
2-back	95 (6)	96 (6)	95 (7)	.86	92 (10)	*87 (12)	*87 (11)	.03
Mean response time ms (SD)								
0-back	637 (90)	642 (73)	637 (89)	.90	627 (133)	639 (110)	629 (102)	.69
2-back	697 (197)	697 (205)	721 (246)	.73	740 (246)	656 (110)	641 (210)	.11

Note: SD = Standard deviation, ms = milliseconds, *significant post-hoc *t*-test compared to healthy controls ($p < .02$).

3. Results

3.1. Demographic and clinical results

As shown in Table 1, the groups of HC and SZ patients were matched on age, sex, race, and IQ. Moreover, no significant between-group difference was observed on the level of education nor on the emotion recognition performance.

3.2. Behavioral results

Response time. We observed a main effect of WM load on the response time, showing that all participants were taking more time to answer during the 2-back versus 0-back task, $F_{(1,38)} = 4.12$, $p = .05$ (see Table 2). However, no significant main effect of group or emotional distractors was found, nor any group by condition interactions (all $p > .05$).

Accuracy. Globally all participants had lower performance on the 2-back compared to 0-back task, $F_{(1,38)} = 43.89$, $p = .000$. We also observed a significant 3-way interaction (groups x emotional distractor types x WM loads) on the accuracy during the task $F = 3.57_{(1.7,64.18)}$, $p = .041$. Post-hoc analyses showed that SZ patients had lower accuracy compared to HC when exposed to fearful and happy distractors, but only during the 2-back task ($p < .02$). No significant effect of the emotional distractors was observed for any memory load task in HC ($p > .05$). The emotional distractors had no significant effect on the performance for the 0-back task in SZ, but a significant decrease in accuracy for the 2-back task was observed in SZ patients when there were emotional distractors (happy and fearful) compared to neutral distractors (see Table 2).

3.3. Between-group fMRI results

We observed a significant group difference (SZ > HC) for the WM load effect across all distractors (2-back > 0-back) in the right superior frontal gyrus (SFG, BA 10), showing that SZ had greater SFG activity than HC during increased WM load. The examination of the HRF beta values suggested that this between-group difference was mainly driven by greater deactivations of this brain region in HC for the 2-back

Table 3
Between-group fMRI results.

Contrast	Region	BA	k	Local maxima (MNI coordinates)			Voxel-level		Direction
				x	y	z	<i>t</i> -value	<i>p</i> -value	
				2-back > 0-back	R SFG	10	113	18	
2-back_fearful > 2-back_neutral – 0-back_fearful > 0-back_neutral	L IFG	45	80	–50	26	8	4.01	< .001	HC > SZ

Note: Only significant clusters ($p < .05$) corrected for multiple comparisons are presented. SZ = Schizophrenia patients, HC = Healthy controls, L = left, R = right, SFG = Superior frontal gyrus, IFG = Inferior Frontal Gyrus, k = cluster size, BA = Brodmann area.

condition (see Table 3 and Fig. 1a). Moreover, the between-group comparison (HC > SZ) showed a significant cluster in the left IFG (BA 45) for the interaction between fearful versus neutral distractor types and the WM load (2-back_fearful > 2-back_neutral – 0-back_fearful > 0-back_neutral). Thus, compared to SZ patients, HC showed a greater increase in brain activity in the left IFG (BA 45) during increased WM load with the presence of fearful distractors. The examination of the HRF beta values suggests that SZ patients failed to show this normal brain modulation for the fearful distractor with the increase in WM load (see Table 3 and Fig. 1b).

No other significant clusters were observed for any between-group comparison with the other contrasts of interest.

3.4. Brain activity and accuracy

We explored the impact of brain activity in the IFG (BA45) on participant's performance during increased WM load and the presence of fearful distractors. For this analysis, only participants that did not reach a ceiling effect at the 2-back task were included. A total of 3 SZ patients and 8 HC had a perfect performance in presence of neutral and fearful distractors and were excluded from this analysis. As presented in Fig. 2a, less IFG activity during fearful distractors was significantly associated with greater reduction in task performance in higher WM load ($r_s = -.42$, $p = .02$). Looking at each group separately, SZ patients showed a strong negative relationship between these two variables ($r_s = -.64$, $p = .006$), and the negative correlation was strong but marginal in HC because of the small sample size ($r_s = -.41$, $p = .18$) (see Fig. 2b and c).

3.5. Effect of symptoms severity and medication in patients

Post-hoc analysis revealed a marginal negative correlation between the response time during the 2-back_neutral condition and the severity of positive symptoms in patients ($r_s = -.51$, $p = .023$ uncorrected). However, this finding disappeared after correction for multiple comparisons. No other post-hoc correlations showed marginal nor significant association with positive nor negative symptoms on any other behavioral measures (accuracy and response time for each condition) nor brain activity, $p > .10$ for all correlations. The specific effect of flat

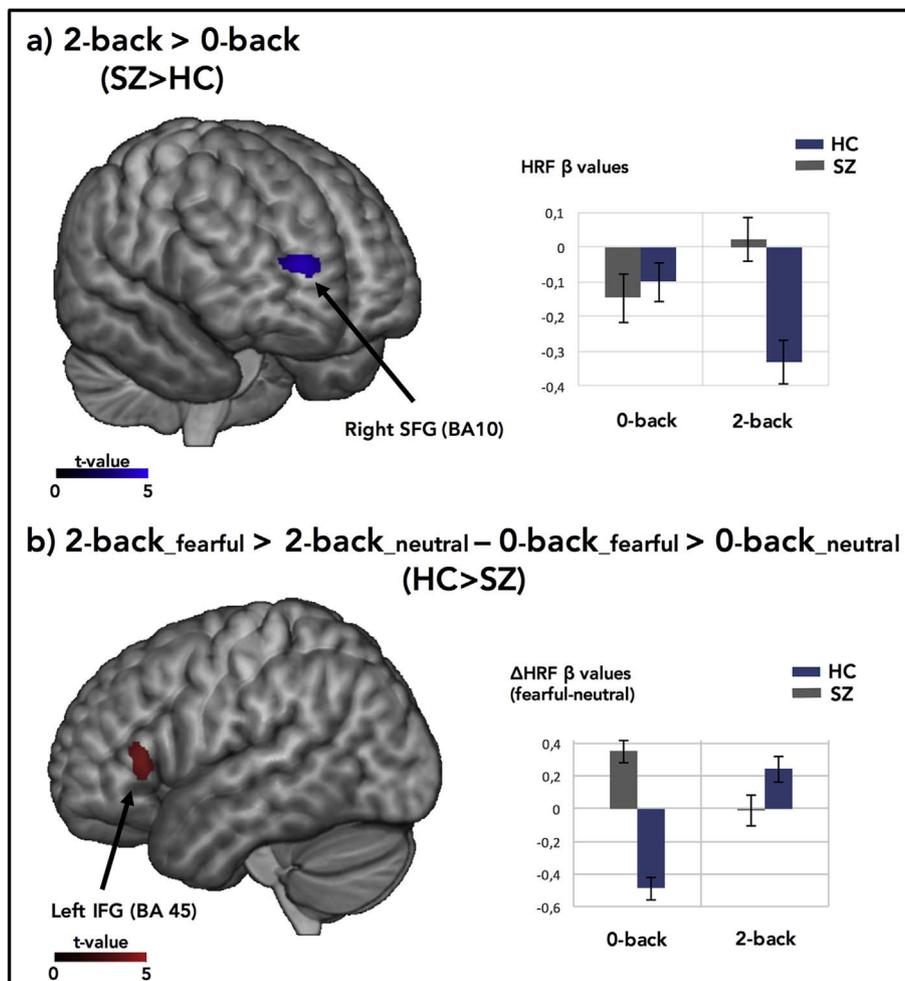


Fig. 1. Significant clusters from the second-level fMRI analysis examining the between-group difference for a) the working memory load effect across all emotional distractors, and b) the effect of fearful distractors in interaction with the working memory load. Error bars represent standard errors. SFG = superior frontal gyrus, IFG = inferior frontal gyrus, BA = Brodmann area, SZ = schizophrenia patients, HC = healthy controls, HRF = hemodynamic response function.

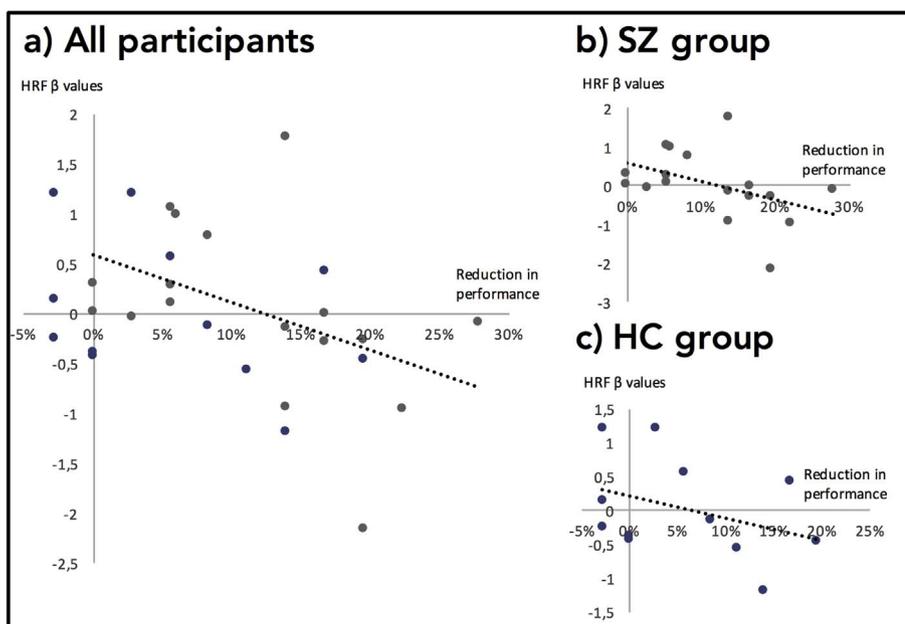


Fig. 2. Association between decreased brain activity in the left inferior frontal gyrus (IFG, BA45) and greater reduction in performance at the task for the 2-back condition with fearful distractors in a) SZ and HC combined, b) only SZ, and c) only HC. Note: Only participants who did not reach a ceiling effect in their performance during the 2-back task were included. SZ = schizophrenia patients, HC = healthy controls, HRF = hemodynamic response function.

affect in patients was also examined on these same measures in post-hoc analysis, and there was no significant correlation ($p > .10$). Finally, post-hoc analysis also revealed no significant association with antipsychotic medication dose on any behavioral measures (accuracy and response time for each condition) nor brain activity, $p > .10$ for all correlations.

4. Discussion

Taken together, the behavioral and fMRI findings in our study show that effortful emotion regulation during a WM task is impaired in SZ. Patients showed decreased performance during the 2-back task when confronted with emotional distractors and the IFG (BA 45) seems to play a key role in this deficit. Impairment in emotion regulation is an important treatment target in SZ because it is related to poorer outcomes (Henry et al., 2008; Horan et al., 2013; Kimhy et al., 2012; O'Driscoll et al., 2014; Tabak et al., 2015). A better understanding of the processes by which the PFC contributes to impaired emotion regulation in SZ could lead clinicians to develop better treatments that target adaptive coping mechanisms of emotion regulation, and potentially improve clinical outcome.

When looking at the WM effect across all distractors, we observed abnormal increased brain activity in SZ with WM load in the right SFG (BA 10) compared to HC. Interestingly, in a previous study, Thermenos et al. (2005) also observed that when IQ is controlled, subjects with SZ showed significantly greater activation than HC in the right frontal gyrus (BA 10) when performing a 2-back task. A potential explanation for these findings is that healthy individuals usually show increased deactivation in this region when performing a WM task, because their default-mode network (DMN) deactivates when performing a cognitive effortful task (Tomasi et al., 2006). The examination of the HRF beta values in the current study suggests that the difference in the right SFG (BA10) was mainly driven by greater deactivations of this brain region in HC for the 2-back condition. Our findings are in line with previous studies showing failure of deactivation in the prefrontal region part of the default-mode-network, including the BA 10 region, when SZ patients are performing a WM task (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009).

We also observed that compared to SZ patients, HC showed greater increase brain activity in the left IFG (BA 45) with increased WM load when regulating fearful distractors. SZ patients failed to show this normal pattern of activation suggesting that the increase in WM load may have placed a high demand on their executive network and interfere with their ability to regulate the emotional distractors. The IFG (BA45) plays an important role in inhibition and attentional control (Hampshire et al., 2010), as well as in directing attention away from emotional information (Dolcos et al., 2006; Dolcos and McCarthy, 2006). Our results suggest that during an effortful cognitive task, such as the 2-back task, patients may have more difficulties to recruit these attentional control mechanisms and inhibit fearful distractors. Interestingly, less brain activity in the IFG (BA 45) was associated with significant reduction in patients' performance when they were exposed to fearful distractors in higher WM load. Further connectivity analysis could help better understanding the impaired IFG response in this context.

These findings provide us with potential insight on how emotion regulation could be rehabilitated in individuals with schizophrenia. For instance, intervention focusing on redirecting attention away from irrelevant emotional stimuli, such as the attentional-bias modification treatment, has been shown to be promising in individuals with anxiety disorders (Hakamata et al., 2010) and could be adapted to SZ patients. Moreover, van der Meer et al. (2009) suggested that teaching SZ patients how to reappraise emotional events could potentially diminish the impact of irrelevant emotional stimuli. Intervention focusing on cognitive bias (Steel et al., 2010) could also potentially be adapted to treat emotion regulation deficits in SZ.

The results should be viewed in light of some limitations of this study. First, our sample consisted of medicated early course SZ individuals that show stable positive symptoms before participating in the study and had comparable IQ and emotion recognition abilities to HC. Therefore, the conclusions cannot be extended to unmedicated patients or to patients in more acute stages of their illness. Future studies should investigate if similar processes are impaired in individuals in all stages of the illness. Furthermore, while comparing a group of SZ patients having similar IQ and emotion recognition abilities to HC provides assurance that our results are not due to a general low level of cognition or to an incapacity to recognize emotions, our findings cannot be generalized to SZ patients with low IQ or with deficits in emotion recognition. It remains difficult to separate the role of impaired emotion regulation processes in SZ from possible difficulty to distinguish between emotions (Chan et al., 2010; Strauss et al., 2010). Some could argue that a lack of emotional expression may also explain how patients perceived the different emotional distractors (Gur et al., 2006). However, in the current study, no significant relationship between flat affect and neither patients' performance nor brain activity during the task were observed. Nonetheless, hemodynamic response to the emotional distractors may reflect voluntary emotion regulation during the task, but possibly also the general processing of the emotional distractors. Future studies should aim to disentangle such processes by assessing how accurate participants are when asked to identify emotion on distractors before performing the EFNBACK task, and using this information as a further covariate. Finally, our sample size was modest, and it is possible that we failed to detect smaller effects in other brain regions. For example, the amygdala is known to play a role in normal emotional processing and to show altered activation in SZ (Pankow et al., 2013; Sergerie et al., 2008). Thus, it is possible that our lack of findings in this brain region for the effect of emotional distractors across all WM loads can be explained by the size of our sample.

In conclusion, the current study suggests that impaired voluntary emotion regulation in SZ relates to alterations in emotion-cognition interaction processes. Our findings indicate that SZ patients have more difficulty in performing a WM task when regulating emotion, and fail to show the emotion-specific modulation of the left IFG (BA45) that was seen in HC. The abnormal activity in this brain region reflects how SZ patients have difficulty using attentional control mechanisms to regulate fearful distractors during an effortful cognitive task. Improving strategies for efficient emotion regulation is a critical therapeutic target for improving recovery outcomes in schizophrenia.

Disclosures

All authors reported no relevant financial interests or potential conflicts of interest.

MK, HT, SE, and SG contributed to the design of the study. SP and OL were involved in the data collection and helped SG with the behavioral analysis. SG undertook all fMRI analysis and wrote the first draft of the manuscript. All authors significantly contributed to the interpretation of the data and to the revisions of the manuscript, and have approved the final article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2018.02.028>.

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