Altered emotional modulation of associative memory in first episode schizophrenia: An fMRI study

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ABSTRACT

Alterations of associative memory, resulting from perturbations within the medial temporal lobe, are well established in schizophrenia. So far, all the studies having examined associative memory in schizophrenia have limited ecological validity, as people experience various emotional stimuli in their life. As such, emotion must be taken into account in order to fully understand memory. Thus, we designed an fMRI study aimed at investigating neural correlates of the effects of emotions on associative memory in schizophrenia. Twenty-four first episode schizophrenia (FES) patients and 20 matched controls were instructed to memorize 90 pairs of standardized pictures during a scanned encoding phase. Each of the 90 pairs was composed of a scene and an unrelated object. Furthermore, trials were either neutral or emotional as a function of the emotional valence of the scene comprising each pair. FES patients exhibited lower performance for both conditions than controls, with greater deficits in regard to emotional versus neutral associations. fMRI analyses revealed that these deficits were related to lower activations in mnemonic and limbic regions. This study provides evidence of altered associative memory and emotional modulation in schizophrenia, resulting from dysfunctions in the cerebral networks underlying memory, emotion, and encoding strategies. Together, our results suggest that all these dysfunctions may be targets for new therapeutic interventions known to improve cognitive deficits in schizophrenia.

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1. Introduction

Difficulty to establish coherent associations is considered a central feature of specific positive (e.g. hallucinations, delusions) and cognitive (e.g. episodic memory, autobiographic awareness) symptoms in schizophrenia (Boyer et al., 2007; Danion et al., 1999). Among them, episodic memory dysfunction is one of the most pronounced (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; Pelletier et al., 2005), and has a profound effect on vocational, social and clinical outcome (Lepage et al., 2014). Episodic memory refers to the memory of personal events associated with the spatial-temporal and emotional contexts in which they occurred (Kensinger, 2009; Tulving, 1983). In other words, information is not stored separately in memory but is integrated into a unique and coherent whole. The severity of deficits seems to vary from one task to another in schizophrenia (Pelletier et al., 2005), which suggests that particular memory processes may be selectively compromised, while others are preserved. For example, it has been established that patients with psychosis had more difficulties to memorize the pairing between common objects than memorizing objects themselves

(Lepage et al., 2006; Luck et al., 2009), and that deficits for associations are related to medial temporal and prefrontal abnormal activity (Achim et al., 2007; Lepage et al., 2006).

All the studies that examined associative memory in psychosis used neutral materials so far, limiting their ecological validity, as people experience various emotional stimuli in their life. Thus, emotion must be taken into account to fully understand memory. Similar to disturbances in associative memory, deficits in emotion are heterogeneous and some processes are more affected than others in patients with schizophrenia. Patients with schizophrenia rate valence and arousal characteristics of emotional stimuli like healthy controls (Hall et al., 2007; Sergerie et al., 2010), have preserved responses to emotional stimuli (Herbener et al., 2008), but altered memory for emotional stimuli (Hall et al., 2007; Lakis et al., 2011). This discrepancy led some authors to suggest that patients have intact emotional processing but ineffective integration with cognitive processes (Herbener et al., 2007, 2008). Such integration can be assessed when examining the effects of emotions on memory. Emotion may enhance the likelihood that information is remembered and this effect reflects in part the influence of the amygdala on encoding and consolidation processes occurring in the hippocampal region (Dolcos et al., 2004; McGaugh, 2004). These cerebral structures are of great importance to psychosis, as they are morphologically and functionally perturbed (Aleman and Kahn, 2005; Heckers, 2001),

Table 1
Sociodemographic and clinical data in the full sample of FES patients, healthy controls, and the restricted sample of FES patients.

Characteristic	FES patients	FES patients	Controls	Analysis (P)	
	N = 24	N = 18	N = 20	Full sample vs. controls	Restricted sample vs. controls
Sociodemographic characteristics					
Age at scan (years)	24.71 (0.92)	23.00 (0.96)	23.75 (0.66)	0.42	0.51
Gender (M/F)	19/5	16/2	14/6	0.48	0.15
Handedness [a]	91.11 (2.49)	92.51 (2.41)	81.82 (12.03)	0.47	0.53
Parental SES score [b]	44.94 (3.35)	43.38 (4.05)	39.25 (3.28)	0.24	0.43
IQ [c]	100.10 (3.63)	102.23 (5.36)	111.75 (3.65)	0.05	0.14
Clinical characteristics					
Antipsychotic dose (CPZ equivalents)[d]	264.24 (25.00)	206.55 (12.57)			
PANSS					
Positive	27.25 (1.70)	29.13 (1.87)			
Negative	19.33 (1.37)	20.06 (1.75)			
General	40.29 (1.95)	41.00 (2.53)			

All data are presented as mean (and SEM).
[a] Edinburgh Handedness Inventory.
[b] Hollingshead Parental Socio-Economic Status.
[c] Evaluated with the WAIS-III.
[d] Expressed in CPZ equivalent.

and may constitute a neural marker of outcome (Bodnar et al., 2010, 2011, 2012).

Thus, this fMRI study aimed to investigate neural correlates of the effects of emotions on associative memory in schizophrenia. We hypothesized a deficit of both associative memory and emotional modulation in patients, resulting from abnormal activation of hippocampal and prefrontal regions.

2. Methods

2.1. Subjects

Demographic and clinical data are summarized in Table 1. Twenty-four first-episode of schizophrenia (FES) patients were recruited through the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) at the Douglas Mental Health University Institute in Montreal, Canada. All were diagnosed according to the DSM-IV criteria (American Psychiatric Association, 1994), based on the Structured Clinical Interview for DSM-IV (First et al., 1998). Symptom severity was determined using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All but three patients were taking 2nd generation antipsychotic medication.

Additionally, 20 healthy controls were recruited. The FES and control groups were matched on age, gender, handedness, parental socio-economic status, but differed significantly from each other on IQ (see Table 1). Controls were excluded if they reported current or past history of any Axis I disorders, any neurological diseases, head trauma causing loss of consciousness, or if a first-degree family member had sought help for a psychiatry diagnosis.

The McGill University Faculty of Medicine Ethical Review Board approved the study. Each participant signed an informed consent form prior to the experiment and received financial compensation for their participation.

2.2. Procedure

A detailed description of the procedure is given in Luck et al. (2014). Briefly, participants had to memorize 90 pairs of standardized images presented during 3000 ms, and preceded by a fixation cross (3000 ms). Each pair was composed of a picture depicting a complex scene and a common object. Of these scenes, 30 were negatively valenced, 30 were positively valenced and 30 were neutral. The objects were conceptually unrelated to the pictures with which they were presented. Each object was placed in a white box delimited by gray borders to dissociate the object from the scene. The corner designated for object location was equally distributed among the four corners, across valence. On each trial, participants had to indicate whether the object was located on the left or on the right side, regardless of its vertical location (top or bottom) on the screen. This task, in combination with intentional associative-encoding instructions, ensured that the participants focused on both stimuli during their presentation.

Approximately 10 minutes after completing the encoding session, participants were required to make a pair recognition memory judgment. No functional scanning was conducted during the associative recognition test. Participants were presented with 90 consecutive trials (45 intact pairs and 45 rearranged pairs), and were instructed to indicate whether pairs were intact (objects and scenes presented in the same pairing as in the encoding session) or rearranged.

Table 2
Mean (and SEM) proportions of hits (H), false alarms (FA), Pr index as a function of associative recognition (emotional vs. neutral) for the full sample of FES patients, healthy controls, and the restricted sample of FES patients.

	Emotional			Neutral		
	H	FA	Pr	H	FA	Pr
FES patients (N = 24)	0.62 (0.04)	0.31 (0.04)	0.29 (0.05)	0.63 (0.04)	0.34 (0.04)	0.29 (0.05)
Healthy controls (N = 20)	0.77 (0.04)	0.20 (0.03)	0.57 (0.06)	0.77 (0.05)	0.25 (0.04)	0.50 (0.07)
FES patients (N = 18)	0.61 (0.04)	0.31 (0.05)	0.30 (0.07)	0.71 (0.03)	0.29 (0.03)	0.42 (0.04)

Table 3
Mean (and SEM) ratings of valence and intensity for the positive, negative and neutral pictures in FES patients and healthy controls.

	Valence			Intensity		
	POS	NEG	NEU	POS	NEG	NEU
FES patients ($N = 24$)	6.77 (0.24)	3.45 (0.25)	5.37 (0.21)	2.81 (0.17)	3.08 (0.18)	2.01 (0.18)
Healthy controls ($N = 20$)	7.07 (0.19)	2.93 (0.16)	5.25 (0.09)	3.28 (0.22)	3.47 (0.21)	2.17 (0.18)
FES patients ($N = 18$)	6.75 (0.31)	3.48 (0.31)	5.46 (0.30)	2.81 (0.25)	3.02 (0.24)	2.09 (0.22)

After scanning, participants were invited to rate valence and intensity of emotional pictures. Thus, the central scenes were presented again but without any objects. Participants were asked to rate the emotional valence of each visual scene using a 9-point Likert scale ranging from 1 (extremely negative) to 9 (extremely positive), with 5 indicating a neutral valence.

2.3. fMRI scanning protocol

Scanning was carried out on a whole-body 1.5 T Siemens Sonata System, using gradient-echo EPI sequences. The head was stabilized with a moldable vacuum cushion to minimize head movements. First a localizer scan was acquired followed by the functional run consisting of 214 T_{2*}-weighted images acquired with a blood oxygenation level-dependent contrast (TR = 2540 ms; TE = 50 ms; Flip angle = 90°; 30 interleaved slices; voxel size $4 \times 4 \times 4$ mm). Functional scans were acquired parallel to the anterior-posterior commissural plane. After completing the functional run, a 3D-T_1 MDEFT sequence was used for the acquisition of anatomical images (voxel size $1 \times 1 \times 1$ mm).

2.4. Data analysis

2.4.1. Behavioral analyses

Behavioral performance was analyzed using Statistica 6.0 (Statsoft). Hits (H) and false alarms (FA) cannot be assessed independently in an old/new task, because they are influenced by the participant's response bias. To determine accuracy separately from response bias, the Pr index (H − FA) was estimated as it provides an unbiased estimate of accuracy (Snodgrass and Corwin, 1988). Repeated measure analyses of variance (ANOVA) were performed for Pr index, valence and intensity ratings. Two sets of analyses were conducted. First, analyses were conducted with the full sample of patients. In a subsequent analysis, we excluded six patients whose performance was around the chance level (50% correct responses) for the neutral association condition. This additional analysis was motivated by the fact that an overall deficit of associative memory may have overshadowed subtle alterations of the emotional modulation of associative memory. When needed, Fisher's least significant difference (LSD) test comparisons were performed for post hoc analyses.

In all behavioral analyses, the alpha level was set at 0.05.

2.4.2. Neuroimaging analyses

Functional images acquired during memory encoding were pre-treated with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The T_{2*} images were first realigned to the 29th image in their respective run and normalized to the Echo Planar Imaging (EPI) template. Images were then spatially smoothed with an 8-mm full width half maximum (FWHM) isotropic Gaussian kernel. Prior to individual analyses, the movement correction logs were examined to ensure that none of the participants presented movements greater than 5 mm or 5°.

To assess the effects of emotion on associative memory, four event types[1] were modeled: positive, negative, and neutral associations, and the fixation cross (baseline). Functional images were analyzed in two steps. In a first-level analysis, a general linear model was created for [Emotional–baseline], [Neutral–baseline], [Emotional–Neutral], and [Neutral–Emotional] contrasts, for each subject. In a second-level analysis, [Emotional–Neutral] and [Neutral–Emotional] contrasts were pooled for main effects into one-sample t-tests of within-group effects (random effect analysis). Main effects were performed at the whole-brain level, and between-group analysis was restricted to the regions involved in the main effect, i.e. masked by the main effect in the control group (e.g. when contrast in controls > patients was masked with activation in the control group). Activation was considered significant at a voxel extend threshold of 10 or more voxels, with p < 0.001 uncorrected for multiple comparisons. Masks for group comparisons were set at a threshold of p < 0.01, with a minimum cluster size of 10 contiguous voxels. Thus, a voxel was considered active if it surpassed the statistical threshold for both contrasts (conjunction threshold $p < 1.00 \times 10^{-5}$).

3. Results

3.1. Behavioral analyses

3.1.1. Analyses of Pr scores

Pr scores are summarized in Table 2. The group X conditions ANOVA showed a significant effect of group ($F(1,42) = 10.99$; $p = 0.002$) with patients' overall performance being lower than that of controls. There was no significant effect of conditions ($F(1,42) = 1.14$; $p = 0.29$), nor group X conditions interaction ($F(1,42) = 1.06$; $p = 0.31$).

In a subsequent analysis, six patients were excluded given their low performance. Groups of patients and controls remained matched on age, handedness, and parental SES but also on IQ (see Table 1). Again, the group X conditions ANOVA showed a significant effect of group ($F(1,36) = 4.34$; $p = 0.05$), but no significant effect of conditions ($F(1,36) = 0.89$; $p = 0.35$). However, the analysis showed a significant group X conditions interaction ($F(1,36) = 12.78$; $p = 0.001$). Post-hoc comparisons revealed that both groups differed for emotional associations ($p = 0.03$; $d = 0.96$), but not for neutral associations ($p = 0.49$; $d = 0.32$). Within-group comparisons revealed that controls performed better for emotional than neutral associations ($p = 0.05$; $d = 1.75$). Conversely, patients performed more poorly for emotional than neutral associations ($p = 0.005$; $d = 0.94$).

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[1] Positive and negative trials were pooled into a single condition named 'emotional' condition, as analyses revealed no significant differences between positive and negative valence conditions for either behavioral performance (t < 1) or brain activations ([Positive – Negative]) analysis threshold at p < 0.001 uncorrected in both groups.
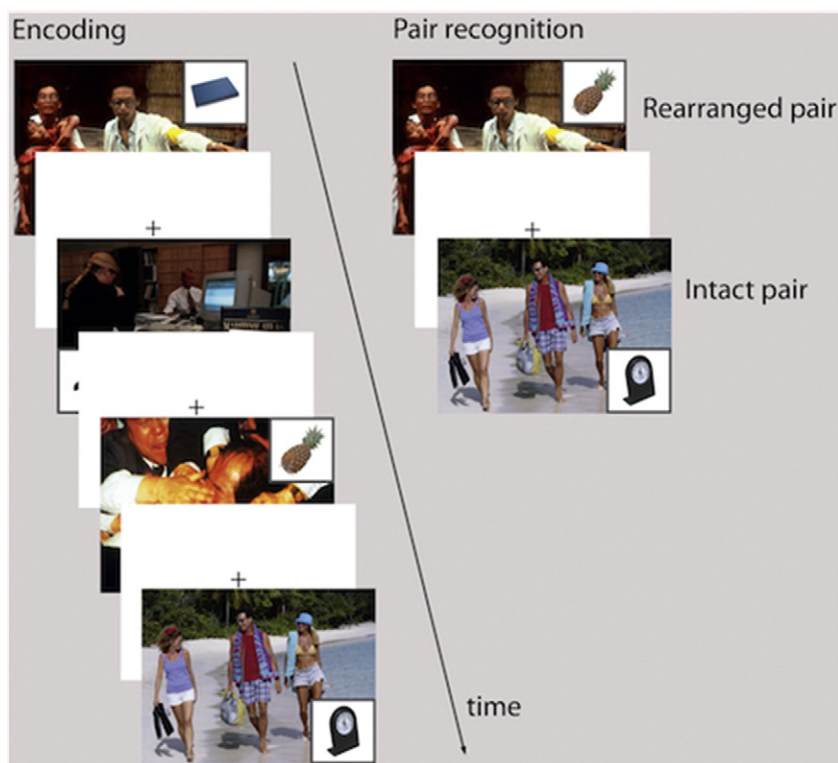
Fig. 1. Illustration of the behavioral task. The left part represents a segment of the encoding session, with pairs composed of a scene and an unrelated common object presented in one of the four corners. The right part represents the pair recognition test during which intact and rearranged pairs were presented.

3.1.2. Analyses of valence and intensity ratings

Valence and intensity ratings were not collected in three patients and two controls due to technical problems. Analyses for both the full sample of patients (n = 24) and a subset of 18 patients showed a similar pattern of results. Here, only results for the subset of 18 patients were presented, but Table 3 contains the data for the two groups of patients.

The repeated-measure ANOVA of the valence ratings showed no main effect of group ($F(1,36) = 1.70$; $p = 0.41$) or interaction between conditions and group ($F(2,72) = 1.60$; $p = 0.21$), but a significant main effect of conditions ($F(2,72) = 150.40$; $p < 0.001$). Subsequent LSD tests revealed that the three conditions differ from each other ($p < 0.001$ in all cases). Similarly, the analysis of the intensity ratings showed no main effect of group ($F(1,36) = 1.30$; $p = 0.26$) or interaction between conditions and group ($F(2,72) = 2.44$; $p = 0.10$), but a significant main effect of conditions ($F(2,72) = 70.76$; $p < 0.001$). Subsequent LSD tests revealed that the ratings for positive and negative pictures did not differ from each other ($p = 0.13$), but both significantly differ from neutral pictures ($p < 0.001$ in both cases).

3.1.3. Neuroimaging analyses

3.1.3.1. fMRI analyses[2]. The regions activated by emotional associations relative to neutral associations are reported in Table S1 and illustrated in Fig. 2. In controls, greater activations for emotional associations were found in a large panel of cortical structures, including parietal regions (supramarginal gyrus and postcentral gyrus), temporal regions (fusiform, superior, and inferior gyri), and occipital regions (precuneus, cuneus and middle occipital gyrus),

as well as in the anterior part of the right parahippocampal regions (i.e. the entorhinal cortex). Between-group comparisons revealed greater activations in most of these regions in controls relative to FES patients. By contrast, patients showed no greater activations for emotional associations when compared to neutral associations, and no greater activations than controls. (See Fig. 1.)

The regions activated by neutral associations relative to emotional associations are reported in Table S2 and illustrated in Fig. 3. Controls exhibited greater activations in frontal regions (precentral, inferior and middle gyri), parietal regions (postcentral gyrus and inferior parietal lobe), temporal regions (fusiform and superior gyri), as well as in the cerebellum, the anterior cingulate gyrus and in the right parahippocampal gyrus. When compared to patients, most of these regions showed greater levels of activity in controls. In FES patients, greater activations for neutral associations were found in frontal regions (inferior, precentral and middle gyri), parietal (inferior gyrus), temporal (fusiform and superior gyri, left parahippocampal gyrus), occipital (precuneus and middle gyrus), and in the cerebellum. Group comparisons revealed greater activation in patients relative to controls in the right fusiform gyrus.

4. Discussion

This fMRI study yielded three main results. First, we replicated results from previous studies by showing altered associative memory encoding in FES patients. Second, we extended these findings by revealing that the emotional modulation of associative memory is altered as well. Third, these deficits may have resulted from lower activations in cerebral networks involved in associative memory, emotion, and encoding strategies.

At the behavioral level, our results are in line with previous studies we conducted on associative recognition memory, and that revealed a massive deficit for processing associations between multiple

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[2] fMRI analyses were conducted on the restricted sample of FES patients to provide neurobiological validation for the behavioral distinctions.
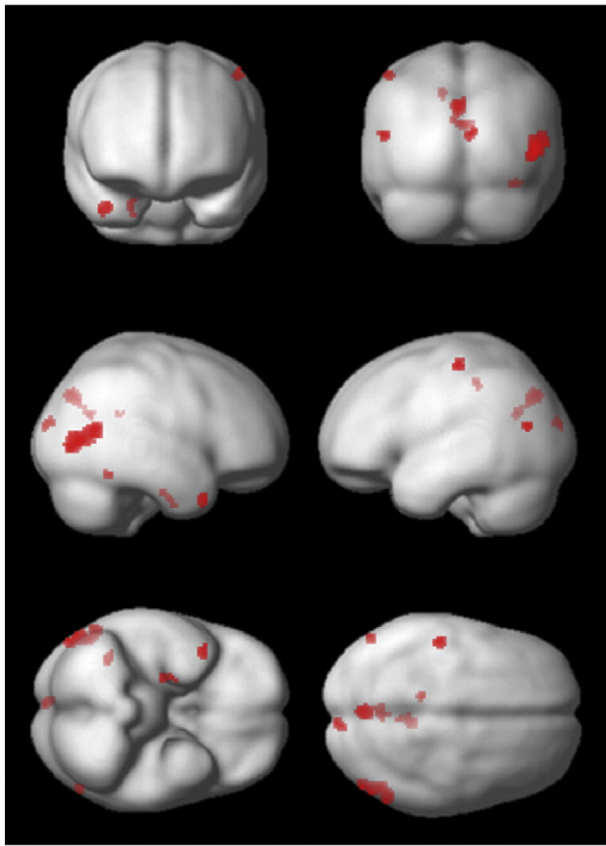
Fig. 2. Between-group comparisons contrasting emotional–neutral associations. Greater activations in controls relative to FES patients are shown in red.

Fig. 3. Between-group comparisons contrasting neutral–emotional associations. Greater activations in controls relative to FES patients are shown in red. Greater activations in FES patients relative to controls are shown in blue.

information in patients with psychosis (Achim et al., 2007; Lepage et al., 2006; Luck et al., 2009). It has also been recently suggested that associative memory deficits may constitute a reliable marker of psychosis and of patients' outcome (Lepage et al., 2015; Ragland et al., 2015). What is new in the present study is that patients exhibited an alteration of the emotional modulation of associative memory as well. Our results showed that controls performed better for emotional than neutral associations, while patients exhibited the reverse pattern of results. Such dissociation may not rely on a perturbed response to emotional stimuli in patients, as their subjective evaluation of both valence and arousal of emotional picture was similar to that of controls, suggesting that these memory perturbations may result from altered cognitive processes. This is consistent with similar previous findings that reported cognitive deficits with relatively normal emotional experience (Lakis et al., 2011; Sergerie et al., 2010).

Two opposing theories have been proposed to explain the effects of emotion on associative memory (see (Mather, 2007) for a review). The attention-narrowing hypothesis (Easterbrook, 1959), predicts that emotional stimuli attract attention, and thus reduce attentional resources allocated to associated non-emotional stimuli. As a consequence, associations comprising emotional stimuli are more poorly remembered than associations composed of neutral stimuli. Alternately, the priority-binding theory stated by MacKay and Ahmetzanov (2005) and MacKay et al. (2004) suggests that arousing stimuli evoke emotional reactions that give priority to the binding mechanisms, strengthening the association between emotional stimuli and associated non-emotional stimuli. As a result, associations between emotional information and neutral information are better remembered than associations between solely neutral information.
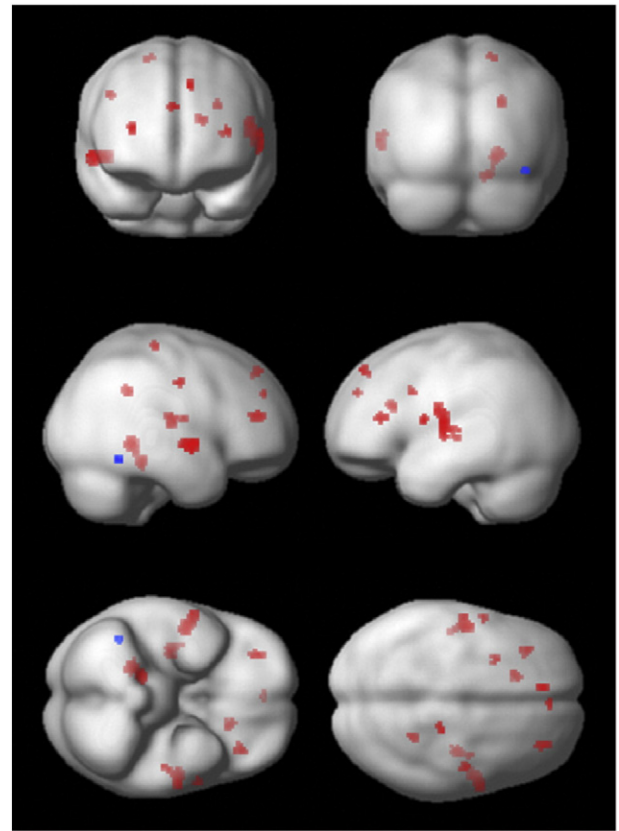
Our results suggest that patients and controls may have used opposite strategies: controls may have processed emotional central scenes faster than neutral scenes, then allocating more attentional resources to the association with the peripheral object. As a consequence, controls performed better for associations comprising an emotional stimulus than associations composed of neutral stimuli exclusively. By contrast, and in light of the attention-narrowing hypothesis (Easterbrook, 1959), patients may have focused on the central emotional picture, thus disturbing encoding processes or reducing attentional resources needed to process the association with the peripheral neutral picture (Mitchell et al., 1998). Such an explanation is compatible with studies that showed that patients with psychosis spend more time watching emotional stimuli than controls (Quirk and Strauss, 2001; Streit et al., 1997). Another explanation may rely on the use of efficient strategies to encode associations between multiple information. For example, Murray and Kensinger (2012) showed better performance for emotional associations over neutral associations when participants use an encoding strategy (i.e. the participants were told to generate a mental image that combined the two words of a pair). Although we did not explicitly asked participants to use encoding strategies, they were instructed to memorize the combination of both images. Some evidence suggests that healthy people are more prone than patients with schizophrenia to use efficient self-initiated strategies to encode associations (Kirchhoff, 2009). Thus, we could not exclude the possibility that controls, unlike FES patients, used such encoding strategies.

At the brain level, functional perturbations were observed in networks underlying associative memory, emotion, and encoding strategies in FES patients. Between-group comparisons revealed

lower level of activations in FES patients in MTL structures. However, they exhibited high levels of activation in the left posterior parahippocampal gyrus when encoding neutral associations, probably explaining why they performed equally well as controls. Together, our results may suggest dissociation between anterior and posterior parts of MTL in patients, and/or dissociation between the left and the right MTL. Our first hypothesis is compatible with structural studies that showed volume reductions in the anterior part but preserved volume of the posterior part of the hippocampal region (Baiano et al., 2008; Pegues et al., 2003; Szeszko et al., 2003). However, there is only limited evidence about greater alterations in the right than in the left hemisphere in psychosis. Indeed, most studies found no laterality effect (Sim et al., 2006), or greater left than right anatomical modifications (Razi et al., 1999), thus contradicting our second hypothesis. Besides medial temporal activations, hypoactivations were found in FES patients in posterior regions usually considered to be involved in visual imagery such as the middle occipital gyrus, the middle temporal gyrus, the precuneus, or the fusiform gyrus (Leshikar et al., 2012). As previously stated, we hypothesized that deficit for emotional associations in FES patients may result from the inefficient use of encoding strategies, such as visual imagery, known to improve memory performance in healthy people (Dunlosky and Hertzog, 2000; Richardson, 1998), and suggested as perturbed in patients with psychosis (Bonner-Jackson and Barch, 2011; Bonner-Jackson et al., 2005).

To conclude, we observed evidence for altered association memory and its modulation by emotions in FES patients. At the brain level, these alterations result from abnormal activity in mnemonic and limbic regions, as well as from their perturbed connectivity. Our fMRI data revealed dysfunction in the cerebral network underlying encoding strategies. Together, our results suggest that all these dysfunctions may be targets for new therapeutic interventions, such as cognitive remediation, known to improve cognitive deficits in schizophrenia (Danion et al., 2007; Demily and Franck, 2008).

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Contributors

D.L. designed the protocol, analyzed the data, interpreted results, and wrote the first draft of the manuscript. R.J. and A.M. conceptualized the longitudinal study, conducted clinical assessments, provided laboratory space and resources for data collection, and collaborated in the writing of the final version of the manuscript. M.L. conceptualized the longitudinal study, supervised the analyses, provided laboratory space and resources for data collection, and collaborated in the writing of the manuscript. All the authors have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.
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