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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.

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),

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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)