Clinical Imaging 44 (2017) 27–32

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Comparative functional neuroanatomy between implicit and explicit memory tasks under negative emotional condition in schizophrenia

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ARTICLE INFO

Article history:
Received 16 September 2016
Received in revised form 1 February 2017
Accepted 29 March 2017
Available online xxxx

Keywords:
Negative emotion
Implicit memory task
Explicit memory task
Schizophrenia

ABSTRACT

Purpose: To evaluate the brain activation patterns in response to negative emotion during implicit and explicit memory in patients with schizophrenia.
Material and methods: Fourteen patients with schizophrenia and 14 healthy controls were included in this study. The 3.0T fMRI was obtained while the subjects performed the implicit and explicit retrievals with unpleasant words.
Results: The different predominant brain activation areas were observed during the implicit retrieval and explicit with unpleasant words.
Conclusion: The differential neural mechanisms between implicit and explicit memory tasks associated with negative emotional processing in schizophrenia.

1. Introduction

Schizophrenia is a complex neurological disorder that involves a disturbance of coupling or disconnection between large-scale cortical systems. The cognitive deficits in schizophrenia are involved in more than one domain, including working memory (WM), verbal learning and memory, and executive functions [1,2]. In the last two decades, a considerable number of reports [2–4] have declared that patients with schizophrenia displayed greater impairment in the evaluation of the negative emotion relative to the positive emotion. Therefore, understanding of the neural mechanism of negative affective pathology is an important step towards improving treatment for patients with schizophrenia. The commonly used imaging modalities for gleaning information regarding the brain function in schizophrenia included single photon emission tomography (SPECT) and positron emission tomography (PET) which are invasive imaging techniques [5,6]. Instead, the functional magnetic resonance imaging (fMRI) has provided a new opportunity to gain insight to neuronal activity and neural circuitry without exposing to radiation for clinical application [7–11].

Recently, much of the empirical evidence comes from studies declared that the long-term memory (LTM) is significantly more impaired than short-term memory (STM) in schizophrenia [12]. Numerous studies [7,13] focusing on WM, a theoretical conception of STM, have been carried out to identify the neural centers related to emotional processing in patients with schizophrenia. However, few studies concerned the impact of LTM on emotional process. Both of implicit and explicit memories belong to LTM, the former is a type of memory in which previous experiences aid the performance of a task without conscious awareness of these previous experiences, while the latter is the conscious, intentional recollection of previous experiences and information [14].

So far, no neuroimaging study on negative emotional processing in both implicit and explicit memory retrievals with unpleasant words in patients with schizophrenia has been published. The aim of this study was to reveal the differential brain activation patterns in response to negative emotional processing during the implicit and explicit retrievals with unpleasant words in schizophrenia.

2. Materials and methods

2.1. Participants

This study included 14 patients with schizophrenia of (mean age = 29.1 ± 7.8 years) and 14 healthy controls (mean age = 29.1 ± 5.0 years). The duration of illness in patients with schizophrenia was 7.1 ± 4.6 years. All patients were diagnosed by DSM-IV-TR criteria [15] with results of the Positive and Negative Syndrome Scale (PANSS) for assessing the schizophrenia symptom severity (Table 1). 12 patients with schizophrenia were being treated with multiple psychotropic medications (Table 2). They submitted informed written consent before participating in this study. This study was approved by Institutional Review Board of the Chonbuk National University Hospital.

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http://dx.doi.org/10.1016/j.clinimag.2017.03.021
0899-7071/

Table 1
Demographic and clinical characteristics of patients with schizophrenia and healthy controls.

	Schizophrenia ($n = 14$)	Control ($n = 14$)	p
Age (years)	29.1 ± 7.8	29.1 ± 5.0	$p = 1.000$[a]
Sex (male/female)	7/7	7/7	$p = 1.000$[b]
Handedness (% of right)	100	100	$p = 1.000$[b]
Duration of illness (years)	7.1 ± 4.6	–	–
Age of onset (years)	22.0 ± 6.5	–	–
Clinical global impression	3.9 ± 1.1	–	–
Positive and Negative Syndrome Scale score (PANSS)			
Positive symptoms	15.0 ± 4.8	–	–
Negative symptoms	18.5 ± 5.4	–	–
General psychopathology	35.5 ± 6.1	–	–
Perceived negative scores for unpleasant words	7.2 ± 2.0	6.8 ± 1.5	$p = 0.520$[a]
Recognition task for words	87.5 ± 10.5 (10/14)	92.8 ± 9.4 (14/14)	$p = 0.079$[a]

[a] Independent sample t-test.
[b] χ^2 test.

2.2. Brain activation paradigm

Before the fMRI examination, 24 unpleasant words were selected by a psychologist, two psychiatrists, five graduate students and 15 individuals from a lexical database of the Korean language. The levels of perception for unpleasant words was defined by analog scale ranging from 0 to 10 (0 = no displeasure and 10 = maximal displeasure). The visual stimuli were presented to the subject to induce negative emotional response in participants through a mirror, angled 45° and located on the top of the head coil.

The stimulation paradigm for the implicit and explicit retrieval tasks consists of a string of five times rest condition (R), two times encoding of two-syllable unpleasant words (E), and two times implicit or explicit memory retrieval of the encoded words (I/ER), in which each condition lasted for 14, 18, and 18 s, respectively. Six different unpleasant words were presented for 3 s each in the encoding and retrieval tasks on a quartile coordinate. In the implicit retrieval task, the same words were presented in the encoding task, but with omission of the first positioned consonant presented (Fig. 1 A), and the participants were asked to complete the words. In the explicit retrieval task, the same words in the encoding task in a different order were presented (Fig. 1 B), and the participants pressed the right-hand button if the word was recognized.

2.3. Data acquisition

Subjects underwent 3 T Magnetom Verio MRI Scanner (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. The high-resolution T1-weighted images (repetition time (TR) / echo time (TE) = 1900 ms/2.35 ms) were acquired with field of view = 22 cm × 22 cm, matrix size = 256 × 256, NEX = 1, and slice thickness = 1 mm. Functional images were acquired from a total of 25 axial slices parallel to an AC-PC (anterior commissure to posterior commissure) with a gradient-echo planar pulse sequence with the following parameters: TR/TE = 2000 ms/30 ms, flip angle = 90°, field of view = 22 cm × 22 cm, matrix size = 64 × 64, number of averages (NEX) = 1, and slice thickness = 5 mm. In addition, two phases of dummy scans were supplemented to circumvent unstable fMRI signals.

Table 2
Psychotropic medicine in patients with schizophrenia.

Medicine	Dose range
Amisulpride ($n = 2$)	1200–1600 mg
Aripiprazole ($n = 1$)	10 mg
Benztropine ($n = 11$)	1–4 mg
Clozapine ($n = 1$)	300 mg
Fluoxetine ($n = 2$)	40–80 mg
Lorazepam ($n = 6$)	0.5–2 mg
Olanzapine ($n = 2$)	5–15 mg
Paliperidone ($n = 4$)	6–15 mg
Propranolol ($n = 6$)	40–80 mg
Quetiapine ($n = 1$)	100 mg
Risperidone ($n = 3$)	4–12 mg
Trazodone ($n = 2$)	50 mg

2.4. Data processing of fMRI and statistical analysis

Functional imaging data was analyzed using the SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). The image data were reconstructed using am optimized protocol described in our previous study [16]. Signal changes in the hemodynamic response function produced by the different experimental conditions (implicit/explicit retrieval and rest conditions) were assessed at each voxel through a generalized linear model (GLM). To analyze the individual BOLD signal in a voxel with a dimension of 2 mm × 2 mm × 2 mm, an independent t-test was performed under the rest and activation conditions (encoding, implicit or explicit retrieval conditions). The mean images of the implicit and explicit memory retrieval with unpleasant words were obtained using two-sample t-test at $p < 0.001$ in patients with schizophrenia versus normal controls. Paired t-test at $p < 0.001$ was used to compare the differential brain activation patterns between implicit and explicit memory retrievals tasks in schizophrenia. For the group analysis of schizophrenia vs. normal controls, the following regions of interest (ROIs), which are associated with pathophysiology of schizophrenia [4,7,11], were created using Wake Forest University Pick Atlas (Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, NC, USA) [17]: superior parietal gyrus (SPG), middle occipital gyrus (MOG), lingual gyrus (LiG), calcarine gyrus (CcG), parahippocampal gyrus (PHG), amygdala, superior temporal gyrus (STG), insula, precuneus, supramarginal gyrus (SMG), and dorsolateral prefrontal cortex (dlPFC). The ROI mask was applied to the evaluation of the contrasting areas between the groups using statistical analysis. The x, y and z coordinates of the maximum t-value were based on MNI brain space provided by SPM8 software. Anatomical labeling for the activation areas was implemented through MRIcron software (http://www.mricro.com). The correlation between BOLD signal changes and PANSS-negative symptoms scores was analyzed using the SPM statistical package. Two-sample t-test was used to compare the scores of perceived negative emotion with unpleasant words and the accuracy for recognition tasks between two groups, and the chi-square ($\chi 2$) test was used to compare the sex and handedness between the two groups using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Perceived negative scores and recognition accuracy for unpleasant words

The results of PANSS [18] are as follows: positive, 15.0 ± 4.8; negative, 18.5 ± 5.4; and general psychopathology, 35.5 ± 6.1. The average scores of perceived negative emotionality for the unpleasant words was 6.8 ± 1.5 and 7.2 ± 2.0 in healthy controls ($n = 14$) and patients with schizophrenia ($n = 14$) ($p = 0.520$), respectively (Table 1). The accuracies (%) of the recognition task with unpleasant words were 92.8 ± 9.4 and 87.5 ± 10.5 in the healthy controls ($n = 14$) and patients with schizophrenia ($n = 10$) ($p = 0.079$) (Table 1).