Psychiatry Research: Neuroimaging 183 (2010) 99–104

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Functional magnetic resonance imaging response to experimental pain in drug-free patients with schizophrenia

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ARTICLE INFO

Article history:
Received 25 May 2009
Received in revised form 6 February 2010
Accepted 6 May 2010

Keywords:
fMRI
Nociceptive stimulus
Psychosis
Pain tolerance
Insula
Posterior cingulate cortex
S1

ABSTRACT

Clinical evidence suggests that there is decreased pain sensitivity in schizophrenia; however, the neurobiological mechanism of this decrease remains unknown. Using functional magnetic resonance imaging, we examined the blood oxygen level-dependent (BOLD) changes induced by experimental pain-tolerance (endure) hot stimuli vs. non-painful stimuli during an acute psychotic episode in 12 drug-free patients with schizophrenia and in 13 gender- and age-matched healthy controls. The analyses revealed that patients showed a greater BOLD response at S1 compared with controls but a reduced BOLD response in the posterior cingulate cortex (PCC), insula, and brainstem during pain-tolerance stimuli. Pain-tolerance temperature was higher in patients than in healthy controls. BOLD response in the insula positively correlated with unpleasantness and temperature in controls, but this effect was not observed in patients. S1 BOLD response positively correlated with unpleasantness in patients but not in controls. These initial results confirm that unmedicated patients with schizophrenia have a higher pain tolerance than controls, decreased activation in pain affective–cognitive processing regions (insula, PCC, brainstem), and an over-activation of the primary sensory-discriminative pain processing region (S1). These pilot results are the first to explore the mechanism driving altered pain sensitivity in schizophrenia.

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1. Introduction

Schizophrenia is a chronic mental illness characterized by psychotic symptoms, cognitive impairment, apathy and social withdrawal. Among other characteristics of the disease, altered pain sensitivity has been described in patients with schizophrenia since Bleuler and Kraepelin's early observational clinical reports (Bleuler, 1911/1950; Kraepelin, 1919). In addition, the majority of contemporary controlled experimental studies report reduction in pain sensitivity in schizophrenia (Blumensohn et al., 2002; Singh et al., 2006; Potvin et al., 2008).

Neuroimaging studies in healthy controls have mainly implicated the following areas associated with pain anticipation and processing: thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), primary (S1) and secondary (S2) somatosensory cortices, insula, dorsolateral prefrontal cortex, ventral striatum, inferior parietal cortex, primary and secondary motor cortices, brainstem, cerebellum, and hippocampus (Gelnar et al., 1999; Davis, 2000; Peyron et al., 2000; Becerra et al., 2001; Pridmore et al., 2003; Apkarian et al., 2005). However, no prior study has examined the brain structures involved during pain processing in schizophrenia. In the present study, we examine the blood oxygen level-dependent (BOLD) changes induced by an experimental pain-tolerance stimulus during an acute psychotic episode in drug-free patients with schizophrenia. Gender- and age-equated healthy controls also completed the functional magnetic resonance imaging (fMRI) protocol with the experimental pain-tolerance stimulus as a comparison group.

2. Methods

2.1. Participants

The study was approved by the Ethics and Scientific Committees of the National Institute of Neurology and Neurosurgery of Mexico (NINN), and subjects were included following successful completion of an informed consent procedure.

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doi:10.1016/j.pscychresns.2010.05.003

Seventeen right-handed patients were diagnosed as suffering from schizophrenia on the basis of the Structured Clinical Interview for DSM-IV (First et al., 1997) at the inpatient and outpatient psychiatric services of the NINN from January, 2004 to September, 2006. Further inclusion criteria were as follows: duration of illness less than 4 years; a minimum Positive and Negative Syndrome Scale (PANSS) total score of 60; score above 3 on at least two PANSS psychosis items (P1, P2, P3, P5, or P6) score above 4 on one psychosis item; antipsychotic drug-free for at least 1 month (or 6 months if treatment by by depot injection); and competency to grant informed consent and to follow the procedures. Patients were excluded if they had any concomitant medical or neurological illness; current substance abuse or a history of substance dependence (excluding nicotine); comorbidity of any other axis I disorders; high suicidal risk; or psychomotor agitation. Use of psychotropic medications was not allowed for the duration of the study. From the 17 initially recruited patients, 12 patients completed all the inclusion criteria and successfully completed all the procedures in the study.

Thirteen right-handed age- and gender-equated healthy controls met the inclusion criteria and completed all the procedures in the study. The control subjects were assessed in the same manner as the patients, and any subject with a history of psychiatric illness or positive family history for schizophrenia was excluded.

All the participants were tested for drugs of abuse (e.g. cannabis, cocaine, heroin, opioids and benzodiazepines) prior to the fMRI scan.

2.2. Stimuli and task design

Painful and non-painful thermal stimuli were administered to the dorsal aspect of the left hand using an electrically controlled Peltier contact cell (2×2 cm). Prior to the functional neuroimaging, individual pain tolerance was assessed. Tolerance was defined as the temperature perceived as painful and endured for at least 30 s. The temperature was determined for each subject using a staircase approach, starting with a temperature of 39 °C with 0.5 °C increments. The temperature set for each subject for the experiment had to fulfill the following two conditions: 1) endured for at least 30 s, and 2) perceived as painful by the subject at the end of the 30-s block. According to previously collected data from healthy controls, the upper limit was set at 46 °C in order to avoid any physical injury to the patients with abnormal pain perception. The maximum temperature tolerated by the subjects (heat-pain-tolerance limit) was not used for this experiment because it would not be tolerated for the required 30 s by the participants and it was much higher than the temperature limit established in our pain-tolerance procedure in controls. While the temperature employed was lower than the heat-pain tolerance limit, the temperature was overall qualified as painful at the end of the 30s block.

The temperature to be used during the scanning was determined 1 hour before each fMRI scan along with the perceived intensity and unpleasantness (visual analogue scales). The thermodes were placed at a new skin site for the experimental session in order to reduce any skin sensitization at that site. Non-painful stimuli were delivered at a temperature of 37 °C.

The fMRI stimuli were presented in a periodic block design, semi-randomly between a pain-tolerance stimulus, a non-painful stimulus, and a rest period. The subjects were stimulated by seven blocks for each of the three conditions (pain-tolerance stimuli, non-painful stimuli, and rest period), with each block lasting 30 s. The pain tolerance and non-painful stimuli were administered with different thermodes.

2.3. MRI scan acquisition

Images were acquired on a 3 T GE (General Electric Co, Milwaukee, Wisconsin) whole-body scanner with a high-resolution four-channel head coil. The participant's head was positioned along the cantho-meatal line and immobilized by means of a forehead strap. T1-weighted sagittal images were used to select 25 contiguous oblique axial slices parallel to the anterior–posterior commissure plane. During the session, 210 volumes (25 slices each) covering the whole brain were acquired using a T2*-sensitive EPI sequence (TE = 60 ms, TR = 3000 ms, flip = 90°, FOV = 24 cm, 64×64, slice thickness = 5 mm).

2.4. Image analysis

Image pre-processing and analysis were performed using statistical parametric mapping version SPM2 (Friston et al., 1995) (SPM2, Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) and MRIcro software (by Chris Rorden, Version 1.36). All images were transformed to analyze format for their further automatic realignment with SPM2 (6-parameter rigid body), and during this procedure 6 linear regressors were obtained describing the correction parameters applied at each volume. Data from subjects who showed movement of greater than two voxels on any axis were discarded. Subsequently, images were spatially normalized to the EPI image template in the SPM system from the Montreal Neurological Institute (MNI). The voxel size was interpolated to 2×2×2 mm. The normalized images were smoothed with a Gaussian filter in each coordinate direction with a kernel of 8 mm. Individual analysis (first level) was performed with a general linear model (GLM) including the six rigid body correction parameter regressors as a nuisance covariate in the design matrix. *T*-contrast was performed between the nociceptive tolerance stimuli and non-painful somatosensory stimuli for each subject (first level analysis). Then, a random effect analysis (second level) was performed with the contrast images from each subject obtained during the first level analysis. Two-sample *T*-tests were performed between controls and patients (Table 1). Also, one-sample *T*-test was performed within each group in order to describe the areas of activation for patients and controls (Table 2). The threshold for significance during the second level analysis for the pain-related regions (thalamus, ACC, PCC, S1, S2, insula, dorsolateral prefrontal cortex, ventral striatum, inferior parietal cortex, primary and secondary motor cortices, brainstem, cerebellum, and hippocampus) was a *P*-corrected<0.01 (false discovery rate (FDR) approach) and clusters of at least 10 voxels.

2.5. Statistical analysis

Results are presented in using means and standard deviation (±S.D.). Demographic, clinical characteristics and pain measures were compared between patients and controls using chi-square (χ^2) on categorical data, and *t* tests on continuous data. The significance level for tests was established at $P<0.05$. Pearson product-moment correlations between

Table 1
Statistical parametric mapping results (SPM2) showing clusters of voxels having differences (two-sample *T*-test) during pain tolerance vs. non-painful stimuli among patients and healthy controls.

	Coordinates (MNI)			Region	Cluster size	Values		
	X	*Y*	*Z*			*T*	*P*-corr.	*P*-no corr.
Control>Patients	−3	−39	−33	L. brainstem (Pons)	11	3.43	0.035	0.001
	−6	−30	−18	L. brainstem (Midbrain)	18	3.19	0.035	0.002
	45	0	6	R. insula	21	3.61	0.030	0.002
	−4	−30	33	L. PCC	57	4.01	0.018	<0.001
Control<Patients	42	−30	51	R. S1	37	4.57	0.004	<0.001

Coordinates correspond to Montreal Neurological Institute brain atlas related to the Talairach–Tournoux system (Talairach and Tournoux, 1988). *T* values correspond to the maximal voxel of each cluster. P-corr, *P*-corrected. R, Right. L, Left. PCC, posterior cingulate cortex. S1, postcentral gyrus. Cluster size, number of voxels in the cluster. Voxel size = 2×2×2 mm.

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