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Lack of insula reactivity to aversive stimuli in schizophrenia

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ABSTRACT

Patients with schizophrenia may have altered pain perception, as suggested by clinical reports of pain insensitivity, and recent neuroimaging findings. Here, we examined neural responses to an aversive electrical stimulus and the immediate anticipation of such a stimulus using fMRI and a classical conditioning paradigm, which involved pairing an electrical shock with a neutral photograph. Fifteen men with schizophrenia and 13 healthy men, matched for demographic characteristics, electrical stimulation level and scan movement, were studied. The shock induced robust responses in midbrain, thalamus, cingulate gyrus, insula and somatosensory cortex in both groups. However, compared to controls, the schizophrenic patients displayed significantly lower activation of the middle insula ($p_{FWE} = 0.002$, $T = 5.72$, cluster size = 24 voxels). Moreover, the lack of insula reactivity in the schizophrenia group was predicted by the magnitude of positive symptoms ($r = -0.46$, $p = 0.04$). In contrast, there were no significant differences between the two groups in the magnitude of neural responses during anticipation of the shock. These findings provide support for the existence of a basic deficit in interoceptive perception in schizophrenia, which could play a role in the generation and/or maintenance of psychotic states.

1. Introduction

It has long been observed that some patients with schizophrenia are relatively insensitive to pain. Kraepelin reported that *dementia praecox* patients could burn themselves with cigarettes and experience needle pricks or injuries without showing adaptive withdrawal reactions (Kraepelin and Robertson, 1919; Bonnot et al., 2009). More recently, a meta-analysis of experimental pain studies indicated that schizophrenic patients show a blunted response to experimental pain (Potvin and Marchand, 2008), a finding confirmed in a detailed review of cases, and clinical and experimental studies (Bonnot et al., 2009). Pain insensitivity in schizophrenia is associated with increased morbidity and mortality, but the underlying pathophysiology is poorly understood (Singh et al., 2006). Although antipsychotic medications may have an analgesic effect (Seidel et al., 2010), alterations in pain perception in schizophrenia cannot be solely explained by medication effects (Potvin and Marchand, 2008). Recent neuroimaging studies in schizophrenia found greater somatosensory activation, but diminished insula, posterior cingulate cortex and brainstem responses to thermal pain (de la Fuente-Sandoval et al., 2010; de la Fuente-Sandoval et al., 2012). These reports provide initial evidence that painful stimuli are processed differently in schizophrenia. But pain is a highly subjective experience, and emotional, anticipatory and/or sensory aspects of noxious processing may drive alterations in sensitivity. Considering the communicative and social impairments associated with schizophrenia, a more detailed dissection of aversive experiences in the disorder is warranted.

Here we examined fMRI responses evoked by an aversive electrical shock stimulus in schizophrenic patients and healthy controls. Using a Pavlovian fear-conditioning protocol (Milad et al., 2007; Holt et al., 2009) we examined neural and autonomic responses to conditioned (CS+) and unconditioned stimulus (US, an electrical shock) presentations in a partial reinforcement paradigm. The US was delivered at a 62.5% reinforcement rate, allowing us to compare neural responses to the US with responses to the immediate anticipation of the US (the moment just prior to the offset of unreinforced CS+ trials). In this way, the sensory component of a US response may be isolated from its expectancy related components (Linnman et al., 2011a; Linnman et al., 2011b; Dunsmoor and Labar, 2012). Responses to an electrical (Linnman et al., 2011a) or auditory (Dunsmoor et al., 2007, 2008; Knight et al., 2010; Dunsmoor and Labar, 2012) US in healthy subjects are accompanied by increased activity in the brainstem and thalamus, as well as in the cingulate, sensory and insular cortices, structures also known to respond to noxious stimuli (Apkarian et al., 2005). In the current investigation, we hypothesized, based on previous evidence (de la

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Fuente-Sandoval et al., 2010; de la Fuente-Sandoval et al., 2012), that schizophrenic patients would display impaired responses of the insula and brainstem and elevated responses of somatosensory cortex, compared to controls. We further sought to disentangle the sensory and anticipatory aspects of this response, and relate any observed alterations to the symptoms of schizophrenia.

2. Methods

2.1. Subjects

For all subjects, exclusion criteria included severe medical illness, significant head trauma, neurologic illness, substance abuse during the past six months and contraindications for MRI scanning (e.g., implanted metal objects, claustrophobia). Twenty male patients with DSM-IV diagnosed schizophrenia were recruited and characterized by the Massachusetts General Hospital Schizophrenia Program. 17 healthy male subjects were recruited from the community via advertisements. The healthy subjects were without psychiatric disorders as determined by a structured clinical interview (SCID) (First et al., 1995). All subjects gave informed consent, in accordance with the procedures of the Partners Healthcare System Human Research Committee. In the patients, levels of positive and negative symptoms of schizophrenia were evaluated in each patient by one trained rater using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on the first day of the experimental protocol. Also, symptoms of anxiety and depression were measured on Day 1 of the protocol in all subjects using the Spielberger State and Trait Anxiety Inventory (Spielberger, 1988) and the Beck Depression Inventory (Beck et al., 1961), respectively.

An analysis of the neural correlates of fear and extinction learning and memory in these participants has been published (Holt et al., 2012); however the responses to the US during the fear conditioning phase of the study have not previously been reported. After matching for subject (scan-to-scan) head movement (Friston et al., 1996; Weinberger et al., 1996; Van Dijk et al., 2012) and individual US shock levels, the final sample here consisted of 15 patients (9 antipsychotic-treated and 6 antipsychotic-free) and 13 controls. Mean age, parental education and handedness did not differ between these two groups. See Table 1 for the demographic information and symptom levels for this cohort.

Table 1
Demographic, clinical and experimental information about the subjects.

	Patients (n = 15 ♂)	Controls (n = 13 ♂)
Age (±SD)	32 (±10)	36 (±10)
Race/ethnicity	10 Caucasian	8 Caucasian
	1 Latino	2 Latino
	2 African Am.	1 African Am.
	1 Asian	1 Asian
	1 mixed origin	1 no report
Handedness[a]	85 (±24)	72 (±47)
Premorbid IQ[b]	107 (±10)	110 (±6)
Mean parental education[c]	14 (±4)	14 (±2)
Beck Depression Inventory[d]	9.7 (±9)	1.4 (±2)
Spielberger Trait Anxiety[d,e]	42 (±14)	27 (±7)
Spielberger State Anxiety[d]	38 (±11)	25 (±4)
Age of illness onset	21 (±5)	n.a.
Duration of illness (years)	10 (±9)	n.a.
Current antipsychotic dose (in CPZ)	341 (±384)	n.a.
PANSS Positive Subscale	14 (±6)	n.a.
PANSS Negative Subscale	13 (±6)	n.a.
PANSS General Subscale	24 (±6)	n.a.
Experimental details:		
Shock level (mA at 500 V)	1.3 (±0.46)	1.6 (±0.46)
Scan–scan motion (mm)[f]	0.09 (±0.03)	0.07 (±0.03)
Maximum movement (mm)	1.20 (±1.06)	0.74 (±0.86)

CPZ, chlorpromazine equivalents; PANSS, Positive and Negative Syndrome Scale.
[a] Measured using the Edinburgh Handedness Inventory.
[b] Measured using the American National Adult Reading Test.
[c] Mean years of education for mother and father.
[d] Significantly higher in the schizophrenia group than in the control group, $p<.005$.
[e] Significantly correlated with shock level in the patient group ($r=-0.46$, $p=0.04$) but not in the control group ($r=0.09$, $p=0.39$).
[f] Calculated as per Van Dijk et al. (2012).

2.2. Fear conditioning procedure

While functional MRI (fMRI) data were simultaneously collected, subjects participated in a partial reinforcement classical conditioning paradigm that has been described in detail previously (Milad et al., 2007; Holt et al., 2012), see Fig. 1 for an overview. Briefly, each trial began with an image of a room (the "context") containing a lamp presented for 3 s in the "off" state. The lamp then "turns on" to one of three colors (blue, red, or yellow) for 6 s. Two of the colors (CS+) were followed by a 500 ms electric shock (US) in 62.5% of the trials, and the third color was never followed by a shock (CS−). The illuminated lamp was presented 32 times for a total of 16 safe trials (CS−): 10 CS+ trials followed by the shock, and six CS+ trials in which the shock was omitted. Between trials, a black screen was displayed for 12 to 18 s. The lamp color sequence was counterbalanced across subjects in pseudo-random order. The total length of the run was 13 min and 34 s.

2.2.1. Electric shock

The US consisted of a 500 ms train of 1 ms spikes at 50 Hz delivered to the second and third fingers of the right hand with currents ranging from 0.2 to 4.0 mA. Prior to the experiment, the level of the shock current was adjusted by the subject so that the subject perceived it as "highly annoying but not painful".

2.2.2. Skin conductance

Skin conductance responses (SCRs) were measured on the palm of the left hand. SCRs during the interval following the US, the omitted (non-delivered) US, and the CS− offset were calculated by subtracting the mean skin conductance level recorded during the first 2 s of this interval from the highest skin conductance level during the ensuing 3 s.

2.3. Image acquisition

MRI data were collected using a Trio 3.0 Tesla whole body, MRI system (Siemens Medical Systems, Iselin, New Jersey) equipped for echo planar imaging with a 12-channel head coil. Subjects were instructed to lie as still as possible and head movement was restricted with foam cushions. After an automated scout image was obtained and automated shimming procedures were performed, a high-resolution, T1-weighted, three-dimensional, magnetization prepared rapid acquisition gradient echo (MPRAGE) volume was collected. Functional MRI images, sensitive to blood oxygenation level dependent (BOLD) contrast, were acquired with an interleaved gradient echo T2*-weighted sequence (TR = 3000 ms, TE = 30, flip angle = 90°), collected in 45 slices. The voxel size was $3.1\times3.1\times3$ mm.

2.4. fMRI data analysis

2.4.1. Preprocessing

SPM8 (Wellcome Trust Center for Neuroimaging, www.fil.ion.ucl.ac.uk) was used to process the fMRI data. Structural images were segmented and spatially normalized to the Montreal Neurological Institute (MNI305) T1 template. Functional images were realigned, corrected for slice timing, co-registered with the structural volume, resampled to $2\times2\times2$ mm, normalized into MNI space using parameters obtained from the structural normalization process, and smoothed with an 8 mm full-width-half-maximum Gaussian kernel to reduce spatial