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Brain activation induced by psychological stress in patients with schizophrenia

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ABSTRACT

Environmental influences are critical for the expression of genes putatively related to the behavioral and cognitive phenotypes of schizophrenia. Among such factors, psychosocial stress has been proposed to play a major role in the expression of symptoms. However, it is unsettled how stress interacts with pathophysiological pathways to produce the disease. We studied 21 patients with schizophrenia and 21 healthy controls aged 18 to 50 years with 3T-fMRI, in which a period of 6 min of resting state acquisition was followed by a block design, with three blocks of 1-min control-task, 1-min stress-task and 1-min rest after-task. Self-report of stress and PANSS were measured. Limbic structures were activated in schizophrenia patients by simple tasks and remained active during, and shortly after stress. In controls, stress-related brain activation was more time-focused, and restricted to the stressful task itself. Negative symptom severity was inversely related to activation of anterior cingulum and orbitofrontal cortex. Results might represent the neurobiological aspect of hyper-reactivity to normal stressful situations previously described in schizophrenia, thus providing evidence on the involvement of limbic areas in the response to stress in schizophrenia. Patients present a pattern of persistent limbic activation probably contributing to hypervigilance and subsequent psychotic thought distortions.

1. Introduction

In most cases of schizophrenia, heritability seems to result from a large number of predisposing single nucleotide polymorphisms, each with a very small contribution to increased risk, and also very prevalent in the general population (Schizophrenia Working Group, 2014). This pattern of heritability probably explains the observation that the environment has long been recognized as a critical factor, at different developmental steps, for the expression of the behavioral and cognitive phenotypes of the disease. Among such environmental factors, psychosocial stress is a major determinant in the onset and worsening of schizophrenia symptoms. For example, Myin-Germeys and van Os (2007) observed an increased emotional reactivity to daily stress in patients with schizophrenia and first-degree relatives, whereas Castro et al. (2008, 2009) demonstrated the presence of a cardiac autonomic response to acute mental stress which in contrast to healthy controls, was protracted beyond stressful stimulus cessation. These observations suggest that vulnerability to stress may be a trait marker of schizophrenia. However, it is unsettled how stress interacts with pathophysiological pathways related to gene variants to produce the disorder, and most research has focused on neurotransmitter systems—especially dopamine (e.g. Lataster et al., 2014). In healthy persons, fMRI and PET studies have identified several cortical and subcortical areas as being activated or deactivated in response to stress (e.g., Dedovic et al., 2009a; Pruessner et al., 2008). Stressors which require the completion of demanding and uncontrollable cognitive challenges in the context of negative social evaluation induce increased activity at the medial prefrontal cortex (Urry et al., 2006; Kern et al., 2008), anterior cingulate cortex—which may be of particular importance for generating autonomic responses (Critchley et al., 2000a,b, 2005; Critchley, 2005), insula—which probably works together with anterior cingulum, as both are components of a system underlying self awareness (Medford and Critchley, 2010) and deactivation of the hippocampus–amygdala complex (Kern et al., 2008), which probably results in disinhibition of the hypothalamus; the latter in turn commands hyphotalamic-pituitary and autonomic responses (McEwen and Gianaros, 2010).

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Some authors have used a variety of tests to induce stress by generating a social evaluative threat combining an arithmetic task with a social evaluative component (Dedovic et al., 2005). They found a deactivation of diverse limbic system components, including hippocampus, hypothalamus, medial orbitofrontal cortex, and anterior cingulum, concluding that such deactivation would permit the initiation of the stress response by the hypothalamic–pituitary system (Dedovic et al., 2009a; Pruessner et al., 2008). However, we are not aware of studies systematically probing the functional brain correlates of acute stress in patients with clinically stable schizophrenia using fMRI techniques, which have a more favorable time definition than PET, thus permitting the observation of brain activity changes during, and immediately after psychological stress. This is indeed an important step to fully characterize the neurobiological mechanisms operating the diathesis-stress model of disease, formulated three decades ago (Nuechterlein and Dawson, 1984; Kendler et al., 2004; Kendler and O'Donovan, 2014). On the basis of the aforementioned observations made by our group and others on psychological and autonomic reactions to acute stress, we hypothesized that patients would have a pattern of brain activation during acute stress that would be similar to healthy controls, but that in contrast to them, this pattern would persist beyond stimulus termination, hence providing a basis for both the subjective stress experience and its bodily correlates. To test this hypothesis, we used a functional MRI paradigm of stress induction, and compared brain activation in patients with schizophrenia and healthy subjects during and after acute mental stress. In addition to performing a whole-brain analysis of functional images, and based on previous findings about this topic, we also focused on five regions of interest relevant to stress physiology (Medford and Critchley, 2010; Dedovic et al., 2009a; Kern et al., 2008; Pruessner et al., 2008; LeDoux, 1995), namely: amygdala, hippocampus, anterior cingulate, orbitofrontal cortex, and insula.

2. Methods and materials

All participants were assessed at the Psychiatry Section, FLENI Institute, Buenos Aires. All participants gave written informed consent as approved by the local bioethics committee, performed in accordance with the ethical standards set by the 1964 Declaration of Helsinki.

2.1. Participants

2.1.1. Patients (SZ)

Psychiatry outpatients were invited to participate in the study if they (a) received a DSM-IV-TR (American Psychiatric Association, 1994) diagnosis of schizophrenia (any subtype), confirmed with a Composite International Diagnostic Interview (Robins et al., 1988) administered by a consultant psychiatrist (SMG or MNC), (b) were aged 18–65 years, and (c) had been on the same medications for at least two weeks. Exclusion criteria: (a) misuse or addiction to illegal substances in the previous 6 months, (b) active symptoms having warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment, in the preceding 2 weeks, (c) a history of mental retardation, or (d) a history of active cardiovascular symptomatology and head trauma resulting in loss of consciousness. We obtained a structural MRI to exclude any underlying anatomical abnormality. Twenty-one SZ (9 females, aged 29 ± 7 years) were recruited for this study.

2.1.2. Healthy controls (HC)

Healthy volunteers were recruited from local community; they were offered no financial compensation for their participation. Exclusion criteria: (a) the lifetime presence of any DSM-IV-TR Axis I anxiety, mood, or psychotic disorder diagnosis as detected by a psychiatric interview with a consultant psychiatrist and (b) a medication history of antidepressants, antipsychotics, or mood stabilizers. Twenty-one subjects (8 females, aged 27 ± 7 years, range years) were studied.

2.2. Procedures

2.2.1. Screening tests

All participants were screened for premorbid intelligence with the Word Accentuation Test (WAT; Del Ser et al., 1997; de Achával et al., 2012) and for depressive symptoms with the Hamilton depression test (HAM-D; Hamilton, 1960). All patients were evaluated using Positive and Negative Symptoms Scale (PANSS; Kay et al., 1987) to measure psychotic symptom severity.

2.2.2. fMRI stimuli

All subjects were evaluated between 17:00 and 20:00 h. We used a stress paradigm based on previous studies (Ewing, 1992; Dedovic et al., 2005). A period of 6 min of resting state (PRE) acquisition was followed by a block-design which had three blocks of 1-minCONTROL-task, 1-minSTRESS-task and 1-minrest post-stress (POST). CONTROL-task consisted in a one-digit sum of three terms, which had a very low difficulty level (Fig. 1). STRESS-task consisted of two subtractions of two-digit, or one subtraction plus one sum of two-digit, therefore making it more stressful. During stress-task, the screen displayed the remaining time with a countdown timer. The allocated time was calculated using information from a previous training session (done inside the fMRI device), from which we subtracted 20% of allotted time to generate more stressful conditions; thus this time was specific to each subject. Participants picked their response from a row of numbers (from 0 up to 9) using a two-button response box. With one button, they moved the cursor along the numbers, and with the other button they selected the chosen number; equations were designed so that all correct results were between 0 and 9. During POST-task the screen displayed a black fixation cross in a white background. All participants were advised to perform as accurately as possible and told that the evaluator would be controlling their responses, so as to generate a social negative evaluation.

We evaluated the performance during each condition measured as the percentage of correct responses. After scan, subjects were required to report a scale of subjective stress, with items including self-report of stress and anxiety level during resting inside scan and during the stress task, the level of effort, task difficulty and frustration generated by the stress task (on a scale of 1 to 10; adapted from Wang et al., 2005).

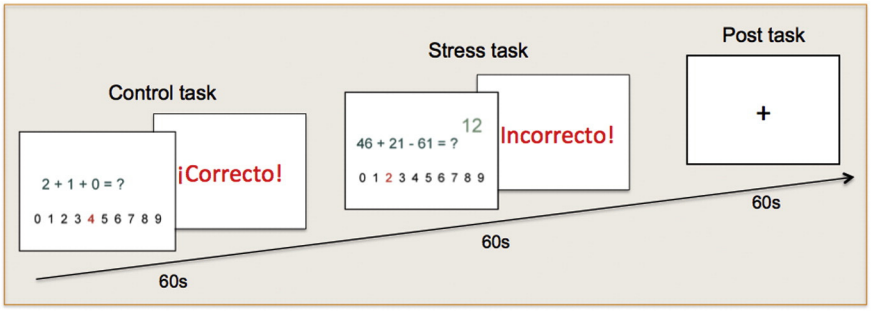

Fig. 1. Block design paradigm with three blocks of 1-minute CONTROL task, 1 minute STRESS task and 1 minute rest after task (POST).

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