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Limbic response to psychosocial stress in schizotypy: A functional magnetic resonance imaging study

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ABSTRACT

Psychological stress causes dopamine release in the striatum and is thought to play a role in susceptibility to psychotic illness. Previous work suggests that an elevated dopaminergic response to stress may index vulnerability to psychosis in certain individuals. With functional magnetic resonance imaging, we measured stress-induced changes in brain activity in healthy individuals at elevated risk of developing psychosis. Participants were 15 controls and 25 psychometric schizotypes: 12 with positive symptom schizotypy (perceptual aberrations) and 13 with negative symptom schizotypy (physical anhedonia), as determined by questionnaires (Chapman et al., 1976; Chapman and Chapman, 1978). In the scanner, participants performed the Montreal Imaging Stress Task and a matched sensory-motor control task. Measures of self-reported stress and salivary cortisol levels were taken throughout the experiment.
All three groups showed significant increases in self-reported stress and significant fMRI signal change in the striatal, limbic and cortical regions. However, the Physical Anhedonia group showed greater stress-induced striatal and limbic deactivation than the other two groups. Deactivation in the striatum was significantly correlated with Physical Anhedonia score across all subjects. Our findings suggest the presence of abnormalities in striatal response to stress in negative symptom schizotypy.

1. Introduction

Stress is thought to play a role in development and maintenance of schizophrenia symptoms (Walker and Diforio, 1997). Elevated sensitivity to stress is also thought to relate to vulnerability to schizophrenia (e.g. Myin-Germeys et al., 2001). Schizophrenia patients report higher stress-arousability than controls (Dinzeo et al., 2004). High-risk populations also show differences in stress appraisal and response (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005). Increased stress reactivity is seen in a dose dependent fashion as degree of familial risk increases from controls to relatives to patients (Myin-Germeys et al., 2001), which suggests that biological response to stress may index genetic vulnerability to schizophrenia. Differences in stress appraisal and emotional reactivity have been proposed as a means to classify negative and positive schizophrenia symptoms (Docherty, 1996; Docherty et al., 2001) and genetic risk (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005). Negative symptoms are linked to a more familial form of the disorder, and in such patients stress or negative affect is more likely to exacerbate thought disorder or impair information processing than in other patients (Asarnow et al., 1978; Docherty, 1996; Docherty et al., 1996).

Here, we chose to focus on both the positive and negative dimensions of schizotypy as markers of vulnerability, since these have been associated in longitudinal studies with elevated rates of psychosis and social dysfunction (Erlenmeyer-Kimling et al., 1993; Chapman et al., 1994; Kwapil et al., 1997; Freedman et al., 1998). "Psychometric schizotypes", that is, healthy individuals with elevated scores on positive or negative symptom schizotypy scales are at elevated risk of developing psychosis (Chapman et al., 1994) and thus are thought to have some of the biological risk factors for schizophrenia.

Our previous study examined positive (Perceptual Aberration, PerAb) and negative (Physical Anhedonia, PhysAn) schizotypes' response to stress using [^{11}C]raclopride positron emission tomography (PET), which allows imaging of striatal dopamine release (Soliman et al., 2008). We demonstrated that PhysAn individuals show increased stress-induced striatal dopamine release, something not observed in PerAb or control subjects (Soliman et al., 2008). Our data were consistent with aforementioned studies linking stress sensitivity and

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negative symptoms. However, the PET technique we used is only sensitive to dopamine release, and then only to signal changes in the striatum. Because stress affects many brain regions and neurotransmitters, we carried out the current study using functional magnetic resonance imaging (fMRI) to get a more complete picture of the stress response in schizotypy, and to confirm our previous findings. In fMRI, the psychosocial stress task used here and in our previous work has been shown to induce deactivation in limbic regions in healthy individuals (Pruessner et al., 2008). The deactivation is thought to index stress effects as it correlates with saliva cortisol, and is only seen in individuals who respond to the stress with an increase in cortisol.

Thus, we compared fMRI responses to a psychosocial stress task in healthy individuals at elevated risk for psychosis, i.e. schizotypes, and demographically similar normal controls who did not differ in age, sex, or ethnicity. Psychometric schizotypes were selected based on the presence of significant elevations of either positive or negative symptom schizotypy as assessed by the Chapman scales (Chapman et al., 1976; Chapman et al., 1978; Chapman and Chapman, 1978). Because our previous findings have suggested a role for perceived maternal care in the stress response (Pruessner et al., 2008; Soliman et al., 2008), this was assessed using the Parental Bonding Inventory (Parker et al., 1979).

We hypothesized that stress would result in striatal and limbic deactivation. Based on our previous PET study (Soliman et al., 2008), we anticipated the greatest striatal deactivation in the PhysAn group.

2. Methods

2.1. Subjects

Subjects were undergraduates in ten of the largest classes at McGill University who completed a 300-item questionnaire including the 35 items from the Perceptual Aberration Scale (Chapman et al., 1978), the 61 items from the Physical Anhedonia Scale (Chapman et al., 1976), and distracter items from the Minnesota Multiphasic Personality Inventory-2 (MMPI-2, Hathaway and McKinley, 1989). We identified schizotypal subjects who scored >1.95 S.D. above the mean of their sex on either the PerAb or PhysAn scale but not both, to allow these two dimensions of risk to be compared (only 1% of subjects scored above 1.95 S.D on both measures). Control subjects scored 0.5 S.D. below the mean on both scales as per previous studies (O'Driscoll et al., 1998; Gooding et al., 2000). Potential subjects had spent the majority of their lives in North America or Europe to limit the potential effects of cultural variation on the schizotypy questionnaire responses (Chmielewski et al., 1995).

Potential subjects were screened for Axis I diagnoses using the Diagnostic Interview Schedule Screening Instrument (DISSI) (Robins et al., 1981); possible diagnoses were followed up with the Structured Clinical Interview for DSM-IV (First et al., 1996). Current DSM-IV Axis I diagnosis, neurological condition, prescription medication other than oral contraceptives, pregnancy, claustrophobia or metal in the body were exclusion criteria.

Forty healthy demographically similar volunteers participated in the fMRI experiment: 15 control, 12 PerAb and 13 PhysAn. There were no significant group differences in age, sex, ethnicity or handedness. The study was approved by the Research Ethics Boards of the Montreal Neurological Institute and of the Institut Universitaire de Gériatrie de Montréal. All subjects gave written informed consent and were compensated for their participation.

2.2. Procedure

2.2.1. Stress task

Psychological stress was induced using the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2005), a mental arithmetic task similar to that used in our previous PET study (Soliman et al., 2008) and adapted for fMRI. The MIST uses a block design, and consists of mental arithmetic challenges that must be answered under time pressure (see Dedovic et al., 2005, for full description). It induces psychosocial stress using elements of uncontrollability and social evaluative threat. The MIST algorithm continuously varies task difficulty based on user performance by adjusting the time constraints per question and the complexity of the arithmetic problems, to yield a 45–50% correct performance for all subjects. Subjects receive correct or incorrect feedback from the computer after each math question and a performance bar shows their cumulative performance as well as the expected performance of the 'average subject', which is artificially set to 80% success. There is also verbal feedback from a confederate, which emphasizes the need to improve performance, after each scanning run. This task has been shown to induce behavioral and physiological stress and anxiety responses (Pruessner et al., 1999), striatal dopamine release in vulnerable individuals measured by [^{11}C] raclopride PET (Pruessner et al., 2004; Soliman et al., 2008) and striatal and limbic deactivation on fMRI (Pruessner et al., 2008).

Each scanning session had three 7-minute runs containing three stimulus conditions presented in block format (Fig. 1, and Supplementary methods): the static arithmetic interface screen (0.5 min), control arithmetic questions presented without feedback, progress bar or time constraint (1 min), and stressful arithmetic questions with a time limit and a visible progress bar (2 min), always in this order. This series of stimulus blocks was repeated twice for a total of 7 min of scanning per fMRI run (see Fig. 1 and Supplementary methods). Thus, subjects performed the stress arithmetic six times, 12 min in all. After each 7-minute scanning run, a confederate entered the scanning suite to deliver the scripted negative verbal feedback for about one minute. After the testing session, subjects were debriefed, told that the task was designed to be impossible to accomplish and that it did not assess their ability to perform mental arithmetic.

2.2.2. Psychological and physiological measures

Subjects completed the Spielberger State-Trait-Anxiety inventory (Spielberger et al., 1893), the Parental Bonding Index (PBI), a validated self-report scale of parenting style with a maternal care subscale (Parker et al., 1979; Parker, 1981), and the Rosenberg self-esteem scale (Rosenberg, 1989). Perception of stress was assessed immediately before and after the imaging session by asking subjects to complete the State Anxiety questionnaire (Spielberger et al., 1983) and visual analog scales (VAS) (Pruessner et al., 2004) to assess feelings of negativity and uncontrollability. The final assessment was done prior to debriefing.

Six saliva samples were collected with the Salivette sampling device (Sarstedt Inc., Montréal, Canada) throughout the experiment, starting approximately 30 min before the first MIST run and ending after the final run. Saliva-derived cortisol was analyzed using a time-resolved fluorescence immunoassay (Dressendorfer et al., 1992) and the area under the curve (AUC; μg/dl/min) was calculated for each subject and each scanning session (Pruessner et al., 2003).

2.2.3. MRI data acquisition and analysis

Imaging was conducted on a 3.0T Siemens Magnetom TRIO at the Unité de Neuroimagerie Fonctionelle, University of Montreal. Blood oxygen level dependent (BOLD) data were acquired using an echo-planar imaging sequence (repetition time 2 s, echo time 30 ms, flip angle 90, voxel size 4 mm^3, 32 slices covering the whole brain). Each 7-minute run consisted of rest, control and stress blocks completed twice, and was followed by a salivary cortisol collection and a one-minute verbal feedback period. Scanning time and question presentation were synchronized with a trigger signal generated by the MRI scanner at the start of each frame; a new question was presented at the beginning of every third 2-second frame (i.e. every 6 s), to ensure all subjects received the same number of arithmetic problems regardless of speed of response. Each subject also underwent a 3D