



Functional neural substrates of self-reported physical anhedonia in non-clinical individuals and in patients with schizophrenia

Philippe-Olivier Harvey^{a,b}, Jorge Armony^{a,b,c}, Ashok Malla^{a,c}, Martin Lepage^{a,b,c,*}

^a Douglas Mental Health University Institute, Montreal, Quebec, Canada

^b Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

^c Department of Psychiatry, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Background: Anhedonia is a negative symptom of schizophrenia that has a detrimental impact on functioning and quality of life. Anhedonia also represents a vulnerability marker for schizophrenia when measured in non-clinical individuals. The investigation of the neural correlates of anhedonia in schizophrenia and non-clinical individuals could provide key insights on the pathophysiology of negative symptoms, as well as on the characterization of neural markers of vulnerability.

Methods: Thirty patients with schizophrenia and twenty-six non-clinical individuals were recruited. We used an event-related functional Magnetic Resonance Imaging paradigm involving an emotional picture viewing task. For each group, separately, we correlated the regional BOLD signal changes during hedonic processing with the Chapman Physical Anhedonia Scale scores. An interaction analysis identified the neural correlates of anhedonia specific to schizophrenia.

Results: We found that anhedonia severity in both groups was inversely correlated with the activity of a limited number of emotion-related regions, including the medial prefrontal cortex. The orbitofrontal cortex and putamen/ventral striatum activity was negatively correlated with anhedonia severity in people with schizophrenia only.

Conclusions: The data first suggest that anhedonia severity is linked to a poor modulation of emotional/attentional brain regions during the processing of hedonic information. The link between anhedonia and the activity of the ventral striatum and orbitofrontal cortex found in schizophrenia could reflect the specific impairment of indirect factors, such as reward anticipation deficits, that influence the measurement of anhedonia severity through self-report questionnaires.

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1. Introduction

The NIMH-MATRICES consensus statement on negative symptoms in schizophrenia concluded that persistent and clinically significant negative symptoms represent an unmet therapeutic need (Kirkpatrick et al., 2006). It was also suggested that the subdomains of negative symptoms may have separate neurobiological substrates and may represent separate therapeutic targets. Only scant attention however, has been devoted to the neural correlates of specific subdomains of negative symptoms. Among these subdomains, the symptom of anhedonia, defined as the reduced capacity to experience pleasure, may be of particular interest given its strong relationships with various measures of functioning (Horan et al., 2008).

The brain circuits underlying reward and pleasure are well identified. Animal studies have suggested that reward processing strongly depends on the mesolimbic dopaminergic circuit (i.e. brain reward system), which includes the basal ganglia, ventral tegmental area, and medial prefrontal cortex (mPFC) (Wise, 1982). In humans, neuroimaging studies have demonstrated that different types of pleasures and rewards, including money (Knutson et al., 2001), appetitive foods (O'Doherty et al., 2002; Waltz et al., 2009), beautiful pictures (Lane et al., 1997), and music (Blood and Zatorre, 2001), primarily activate the striatum, insula, mPFC, and orbitofrontal cortex (OFC). Thus, evidence suggests that anhedonic symptoms, both in clinical and non-clinical populations, may originate from dysfunctions of the brain reward system. However, only few studies thus far have directly correlated brain activity to individual differences in anhedonia severity. In a study from our group that focused exclusively on non-clinical individuals, we found significant correlations between trait anhedonia severity and brain activity in the ventromedial prefrontal cortex, insula, temporal areas, and visual-related regions during the observation

* Corresponding author. Address: Douglas Mental Health University Institute, 6875 LaSalle Boulevard, F.B.C. Pavilion, Verdun, Canada QC H4H 1R3. Tel.: +1 514 761 6131x4393; fax: +1 514 888 4064.

E-mail address: martin.lepage@mcgill.ca (M. Lepage).

of positively-valenced pictures (Harvey et al., 2007). Among the neuroimaging studies on anhedonia that recruited patients with schizophrenia, Juckel and colleagues found in 10 schizophrenic patients that the striatal activity during monetary reward processing was inversely correlated with the severity of the negative symptoms (Juckel et al., 2006). This study exclusively focused on the basal ganglia and as such it cannot be ruled out that cortical areas also play a key role in anhedonia. In another recent study, Park et al. found that physical anhedonia severity in patients with schizophrenia was negatively correlated with resting state activity in the supplementary motor area, mPFC, insula, and precuneus (Park et al., 2009). Linking resting state brain activity to anhedonia severity in schizophrenia has the potential of providing key information on the relation between negative symptoms and default-mode brain function. At the same time, resting state imaging in people with schizophrenia always raises the question of what the participants may be doing during such a state. Moreover, the absence of a reward/pleasure-related activation task likely reduces the possibility of identifying meaningful associations between anhedonia severity and dysfunctions of the brain reward system.

To overcome these limitations, we investigated the functional neural substrates of self-reported anhedonia in patients with schizophrenia and in non-clinical individuals using an emotional valence categorization task and neural activity for the whole brain was systematically examined in relation to anhedonia severity. We expected anhedonia severity to be correlated with mPFC and ventral striatum activity during the observation of positively-valenced pictures. A secondary objective was to directly compare the neural correlates of anhedonia in patients vs. non-clinical individuals, using an interaction analysis. Findings from recent studies indirectly suggest that self-reported anhedonia severity in schizophrenia patients is not only *quantitatively* (i.e. magnitude of severity) different from non-clinical individuals, but possibly *qualitatively* (i.e. nature of what exactly is measured by self-reported anhedonia questionnaires) different as well (Gard et al., 2007; Gold et al., 2008). If this is indeed the case, potential differences in the neural correlates of self-reported anhedonia in patients vs. non-clinical individuals could reflect this qualitative difference.

2. Method

2.1. Participants

Subjects were 20–56 years of age and had an estimated IQ of at least 75. All participants were screened to exclude the following: (1) past or current neurological condition that could affect cognition; (2) current drug or alcohol abuse; and (3) family history of hereditary neurological disorders. After a complete description of the study to the subjects, written informed consent was obtained from all participants. The protocol was approved by the institutional review boards of the Douglas Mental Health University Institute.

Thirty right-handed outpatients with schizophrenia were recruited from various outpatient clinics of the Douglas Hospital. Diagnosis was established with the Structured Clinical Interview for DSM-IV (Spitzer et al., 1992) conducted by trained interviewers (Kappa of at least 0.75) and confirmed through consensus between 2 senior psychiatrists. Positive and negative symptoms were assessed with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984), respectively. All patients had been clinically stable for at least 4 weeks and had been on a fixed medication regimen for at least 6 weeks. All but three of the patients were taking antipsychotic medication. Twenty-four were on second-generation antipsychotics (8 Olanza-

pine, 10 Risperidone, 3 Quetiapine, and 3 Clozapine) and 3 on conventional antipsychotics (1 Loxapine and 2 Zuclopenthixol). The mean dose of antipsychotic medication was equivalent to 313 mg/day of chlorpromazine (sd = 334) (Woods, 2003). Importantly, none of the patients had a concurrent mood disorder at the time of the study. No patients were taking benzodiazepines.

Twenty-six right-handed non-clinical individuals were recruited through advertising in local newspapers and were examined with the Non-Patient Edition of the SCID-I to rule out a current or past Axis I psychiatric disorder. Efforts were made to match non-clinical individuals with people with schizophrenia based on their sex, age and education.

We measured the severity of anhedonia using the Revised Physical Anhedonia Scale (PAS) (Chapman et al., 1976). In both patient and non-clinical samples, internal reliability for the PAS is consistently very good, with the alpha coefficient exceeding .80 (Horan et al., 2006).

2.2. Procedure

The fMRI data were acquired at the Montreal Neurological Institute (MNI) while participants underwent an emotional memory task. The task included three hundred color pictures selected from the International Affective Picture System (IAPS) (Lang et al., 1995) and the Empathy Picture System (EPS) (Geday et al., 2003). Stimuli were divided into three emotional conditions (positive, negative or neutral), based on the original valence ratings of the IAPS and EPS. Our event-related design was divided in two parts: (1) an emotional valence categorization task and (2) a memory recognition test. During the emotional valence categorization task, 150 pictures (fifty for each condition) from pre-generated list I, II or III (counterbalanced across subjects) were pseudo-randomly presented to the subjects, one at the time. Each picture was presented for 3 s, followed by a fixation cross presented for 2 s. Stimulus presentations were de-synchronized with respect to the onsets of volume acquisitions to increase the effective sampling rate and thus get a better estimate of the hemodynamic response (Rees et al., 1997). Participants were required to categorize each picture into the proper emotional valence condition using a three-button computer mouse. This task was followed by the recognition memory test. However, the memory component of the task was not analyzed and discussed for the purpose of the present article. Within one week after the scanning session at the MNI, participants were invited to the Douglas Hospital for further evaluation. Participants first completed the PAS and were then assessed with the Wechsler Abbreviated Scale of Intelligence, to estimate Full-Scale IQ (WASI, 1999). Three non-clinical individuals refused to be assessed with the WASI. Finally, subjects rated all the pictures seen in the scanner in terms of both valence and arousal on a PC laptop computer (300 pictures in total, including the new pictures presented during the recognition task). In order to get a more precise and idiosyncratic rating from subjects, each picture was accompanied by a continuous line with the label “very negative” at the left end of the line and the label “very positive” at the right end. Subjects were further told that the middle of the line was associated with neutrality. Using a mouse, subjects moved an arrow on this line and clicked the left button once the arrow was well-positioned on the line according to the emotional valence of the picture. The continuous line was in fact an ordinal scale ranging from “1” (very negative) to “323” (very positive). Rating data from one non-clinical individual and three patients were not available due to technical problems.

2.2.1. Imaging data acquisition

Functional MRI data were acquired using a 1.5 T Siemens Sonata scanner (Siemens, Germany). A vacuum cushion stabilized the subject's head. Stimuli were generated by an IBM PC laptop computer

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