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Abnormal effective fronto-limbic connectivity during emotion processing in schizophrenia

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ABSTRACT

Background: Schizophrenia is associated with core emotional dysfunctions. At the neural level, functional neuroimaging studies have highlighted fronto-limbic alterations during emotion processing in schizophrenia, as well as impaired connectivity between the amygdala and the prefrontal cortex. However, the direction of the impaired fronto-limbic connections remains largely unknown. To clarify this issue, we performed an effective connectivity study on emotion processing in schizophrenia.
Methods: Forty-one healthy individuals and 39 schizophrenia patients (DSM-IV criteria) viewed negative, positive and neutral images during an fMRI session. Effective connectivity between significantly activated regions was examined using Granger causality and psychophysical interaction analyses.
Results: Subjective ratings of emotionally neutral images were higher in schizophrenia patients than in controls. Across groups, significant activations were observed in the dorso-medial prefrontal cortex (dmPFC) and the bilateral amygdala. The Granger connectivity from the right amygdala to the dmPFC was significantly reduced in schizophrenia patients, relative to controls, during the negative and neutral conditions. The Granger connectivity from the left amygdala to the dmPFC was significantly reduced in schizophrenia patients, relative to controls, during the positive condition.
Discussion: The finding of a reduced lagged connectivity from the bilateral amygdala to the dmPFC in schizophrenia suggests that the bottom-up mechanisms involved in the processing of highly arousing emotional stimuli are impaired in this disorder. The finding of an impaired lagged connectivity from the right amygdala to the dmPFC during the processing of emotionally neutral stimuli in schizophrenia is novel and may explain why these patients tend to confer emotional significance to irrelevant stimuli.

1. Introduction

From a clinical standpoint, schizophrenia is associated with significant emotional dysfunctions, including blunting of affect, anhedonia and anxio-depressive symptoms (Buckley et al., 2009; Foussias et al., 2015). In addition, experimental studies have consistently shown that the recognition of emotional facial expressions is impaired in schizophrenia, and that these patients tend to experience negative emotions (aversion) when presented with neutral or even positive stimuli (Barkl et al., 2014; Cohen and Minor, 2010). Given that emotional dysfunctions are core features of schizophrenia, several functional neuroimaging studies have been performed in schizophrenia patients in order to better understand the pathophysiological bases underlying these emotional disturbances. Neuroimaging studies have consistently shown that frontal and limbic activations are reduced in schizophrenia patients presented with emotional stimuli (Li et al., 2010), suggesting that the emotional flattening frequently present in patients could be explained by these fronto-limbic hypo-activations. However, more recently, some authors have argued that the reduced fronto-limbic activations observed during emotion processing in schizophrenia are actually due to hyper-activations in response to emotionally neutral stimuli (e.g. the experimental control condition) (Anticevic et al., 2012).

In view of the accumulating evidence showing that schizophrenia is a brain dys-connectivity disorder (Coyle et al., 2016), a growing number of studies have examined the coupling between frontal and limbic regions during emotion processing in schizophrenia. Thus far, most studies have used the amygdala as the main seed region, due to its obvious role as a threat detector (Phelps and LeDoux, 2005). These connectivity studies have shown that the coupling between the amygdala and various sub-regions of the prefrontal cortex (Das et al., 2007; Fakra et al.,

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2008; Mukherjee et al., 2014; Vai et al., 2015) and the parietal cortex (Mukherjee et al., 2012; Satterthwaite et al., 2010) is disrupted in schizophrenia. Such results have been interpreted as disruptions between regions involved in spontaneous affective reactions and regions involved in more elaborate evaluative and/or regulatory processes (Diwadkar et al., 2012). Interestingly, preliminary studies performed in individuals at biological or clinical risk for psychosis have also shown that the connectivity between the prefrontal cortex and the amygdala in these individuals is impaired (Diwadkar et al., 2012; Gee et al., 2012; Modinos et al., 2010; Pulkkinen et al., 2015), suggesting that these fronto-limbic dys-connections are endophenotypic features of psychosis.

Despite these scientific advances, several important questions in the field remain unanswered. First of all, most functional connectivity studies have paid attention to negative emotions exclusively (Das et al., 2007; Fakra et al., 2008; Satterthwaite et al., 2010), although the processing of positive emotions is also disrupted in schizophrenia (Cohen and Minor, 2010). Likewise, none of the published studies have examined the connectivity between the prefrontal cortex and the amygdala during the processing of emotionally *neutral* material (at least, to our knowledge), despite increasing evidence showing that schizophrenia patients have aberrant activations in these circumstances (Hall et al., 2008; Modinos et al., 2015). Overall, most studies have enrolled relatively small samples of participants. Moreover, the precise prefrontal sub-regions displaying an impaired coupling with the amygdala remain to be determined. Indeed, whereas some studies showed impaired connections between the amygdala and the ventro-lateral prefrontal cortex (PFC) (Diwadkar et al., 2012; Modinos et al., 2010; Vai et al., 2015), in other studies, the impaired connections were observed in the case of the dorso-lateral PFC, the medial PFC or the orbito-frontal cortex (Das et al., 2007; Diwadkar et al., 2012; Gee et al., 2012; Modinos et al., 2010; Mukherjee et al., 2014; Pulkkinen et al., 2015). In addition, the directionality of the impaired coupling between these regions has only been examined in a few studies yielding somewhat ambivalent results (Diwadkar et al., 2012; Vai et al., 2015). Vai et al. (2015) reported reduced connectivity from the dorso-lateral PFC to the amygdala and increased connectivity from the amygdala to the ventral PFC in schizophrenia, whereas Diwadkar et al. (2012) observed reduced bidirectional coupling between fronto-limbic regions. Therefore, further inquiries are required to clarify the roles of bottom-up versus top-down processes in the emotional disturbances associated with schizophrenia. Finally, some studies used regions found to be impaired in schizophrenia as seeds to perform connectivity analyses (Fakra et al., 2008; Modinos et al., 2010), although this approach may produce a bias towards finding significant between-group differences in brain connectivity (Harvey et al., 2011).

In view of the current state of the literature, the main objective of the present functional magnetic resonance imaging (*f*MRI) study is to examine the *direction* of the impaired connectivity between the amygdala and the prefrontal cortex during emotion processing in schizophrenia, using a relatively large sample of participants, while considering positive, negative and neutral stimuli. We expected to observe impaired fronto-limbic connectivity in schizophrenia, regardless of emotional valence, and had no a priori hypothesis regarding the direction of the impaired connections.

2. Methods

2.1. Participants

Thirty-nine schizophrenia outpatients (DSM-IV criteria; age 18–45 years; 19 females) in a stable state (no hospitalization and no antipsychotic change within the last two months) were recruited from a general psychiatric hospital. Patients with schizoaffective or schizophreniform disorders were not included, as well as patients taking antidepressants. We also added 41 healthy controls (20 females) with no psychiatric disorder. Participants had to not present concomitant neurological disorders, substance use disorders (lifetime, for controls; in the last 12 months, for schizophrenia patients), MRI contraindications, and an estimated IQ lower than 70 (Wechsler Abbreviated Scale of Intelligence (WASI), 2007). Handedness was determined using the *Edinburgh Inventory* (Oldfield, 1971), and parental socio-economic status (SES) was assessed according to the *National Occupational Classification* (Human Resources and Skills Development Canada, 2001). In schizophrenia, psychiatric symptoms severity was evaluated with the *Positive and Negative Syndrome Scale* (Kay et al., 1987). Schizophrenia patients were treated with one or more of the following antipsychotics: clozapine ($n = 18$), olanzapine ($n = 11$), quetiapine ($n = 8$), risperidone ($n = 14$) and ziprasidone ($n = 2$). The influence of antipsychotics was examined by calculating chlorpromazine equivalents (Woods, 2003). Controls were screened with the non-patient edition of the *Structured Clinical Interview for DSM-IV* (Spitzer et al., 1992; Michael et al., 2002). In agreement with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The study was approved by the ethics committees of the *Centre de Recherche de l'Institut Universitaire en Santé Mentale de Montréal* and the *Regroupement Neuroimagerie Québec*.

2.2. Experimental procedure and task

After completing the clinical assessments, participants were placed inside a 3Tesla TIM Trio Siemens MR scanner where structural and *f*MRI data were collected. During the *f*MRI session, participants viewed blocks of emotionally positive, negative, and neutral pictures from the *International Affective Picture System* (IAPS) (Lang et al., 2008). These pictures were selected based on their normative valence and arousal ratings and were matched for content (e.g. people, animals, landscapes). They were grouped based on valence and arousal intensity, resulting in the following five experimental conditions: High arousal/positive content (HA+), High arousal/negative content (HA−), Low arousal/positive content (LA+), Low arousal/negative content (LA−) and Neutral (NTR). Each condition was presented in separate blocks in a pseudo-randomized fashion. To ensure that participants attended to the presented images, they were asked to indicate with a button press whether they saw a person (or part of a person) in the picture. Instructions before the scanning session made no mention of the emotional nature of the presented images.

The task consisted of viewing twelve blocks, 48.5-s in length each, separated by 16-s periods of rest from one another. Each block contained 10 images and was repeated 2 times (except NTR block, which was repeated 4 times). Each picture appeared for 3000 ms followed by a blank screen with a fixation point for an average of 1.75 s (average inter-stimulus interval: 4.75 s). Participants' subjective emotional response to the images was assessed at the end of the fMRI session. They were presented with images from each block and were asked to rate the block as a whole on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) the intensity of experienced emotion.

2.3. Neuroimaging acquisition parameters

Whole-brain fMRI was performed using an echo-planar imaging (EPI) sequence measuring blood oxygenation level dependent (BOLD) signal (TR = 3000 ms; TE = 30 ms; FA = 90°; matrix size = 64 × 64; voxel size = 3.5 mm^3; 41 slices). The functional slices were oriented in transverse plane and were angled to be parallel to the AC-PC line. An inline retrospective motion correction algorithm was employed while the EPI images were acquired. Individual high-resolution coplanar anatomical images were also acquired during the same scanning session (three-dimensional, spoiled gradient echo sequence; TR = 19 ms; TE = 4.92 ms; FA = 25°; matrix size: 256 × 256; voxel size = 1 mm^3; 176 slices).