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Short Communication

Emotion processing in treatment-resistant schizophrenia patients treated with clozapine: An fMRI study

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ABSTRACT

Objectives: To examine the neural correlates of emotion processing in treatment-resistant patients with schizophrenia (SCZ-TR).
Methods: Twenty-two SCZ-TR patients on clozapine, 24 schizophrenia patients on antipsychotics other than clozapine, and 39 healthy controls were scanned using functional neuroimaging while viewing positive, negative and neutral images.
Results: Emotionally-laden images (positive and negative) elicited hyper-activations in the dorso-medial prefrontal cortex and left cerebellum in SCZ-TR patients, compared to the two other groups. Similarly, neutral images prompted hyper-activations in the cingulate gyrus in SCZ-TR patients, relative to the two other groups.
Conclusions: Treatment resistance is associated with neuro-functional hyper-activations in schizophrenia patients during emotion processing.

1. Introduction

Despite substantial evidence demonstrating the efficacy of antipsychotics for the treatment of schizophrenia (Leucht et al., 2009), up to 30% of patients are treatment-resistant (Kennedy et al., 2014). Treatment resistance in schizophrenia is associated with increased rates of smoking, substance use disorder, suicide ideations, decreased quality of life and increased medication side effects (Kennedy et al., 2014). The annual costs are 3 to 11 times greater for treatment-resistant schizophrenia patients (SCZ-TR) than for those with adequate response (SCZ) (Kennedy et al., 2014). Unfortunately, treatment options remain limited for SCZ-TR patients, apart from clozapine (Muscatello et al., 2014).

Several neuroimaging studies have investigated the neural markers of treatment resistance in schizophrenia (Nakajima et al., 2015). The available evidence tentatively suggests that treatment-resistance is associated with frontal and striatal abnormalities in schizophrenia, but the results have been heterogeneous thus far. Neuroimaging studies on treatment resistance in schizophrenia have overlooked the role of emotion, although schizophrenia patients with persisting symptoms have increased depressive and negative symptoms and greater emotion recognition deficits (Elkis, 2007; Savla et al., 2013). A large number of functional neuroimaging studies found hypo-activations of medial prefrontal and limbic (amygdala) regions during emotion processing in schizophrenia (Li et al., 2010). Some of these findings may be partially explained by hyper-activations in response to neutral stimuli (Lakis and Mendrek, 2013), which are often disregarded in analyses. Unfortunately, it is unknown to what extent these results are associated with treatment resistance in schizophrenia. In the current study, we sought to identify the brain regions with greater neuro-functional alterations in SCZ-TR, relative to SCZ patients and healthy controls, during emotion processing.

2. Methods

1. Participants

Forty-six schizophrenia outpatients (DSM-IV criteria; age 18–55 years) were divided into two groups: 22 patients with treatment resistance (SCZ-TR) and 24 patients with adequate antipsychotic response

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(<3 antipsychotic trials). Treatment resistance was defined as ≥3 failed antipsychotic trials at chlorpromazine equivalents of ≥500 mg/day for ≥6 weeks (Suzuki et al., 2011). Treatment response was defined as ≥20% improvement in psychiatric symptoms, as measured with the *Positive And Negative Syndrome Scale* (PANSS) (Kay et al., 1987). SCZ-TR patients were all treated with clozapine, and half of them were treated with another antipsychotic. SCZ patients were treated with second-generation antipsychotics other than clozapine. Patients with schizo-affective or schizophreniform disorders were not included. Patients in a stable state (no hospitalization and no antipsychotic change within the last two months) were recruited from a general psychiatric and a forensic hospital. We also added 39 healthy controls with no psychiatric disorder. Participants had no concomitant neurological disorders, substance use disorders, MRI contra-indications, and had an estimated IQ over 70 (Wechsler Abbreviated Scale of Intelligence (WASI), 2007). Symptom severity was evaluated with the PANSS (Kay et al., 1987). 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). All participants signed a detailed consent form. The study was approved by the local ethics committees from the *Regroupement Neuroimagerie Québec*.

2. Experimental procedure and task

During the functional magnetic resonance imaging (fMRI) 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 matched for content (people, animals, landscapes), and grouped based on valence and arousal intensity, resulting in five experimental conditions: High arousal/positive, High arousal/negative, Low arousal/positive, Low arousal/negative and Neutral. Each condition was presented in separate blocks lasting 48.5 s, interceded by 16-s rest periods. To ensure that participants attended to the presented images, they were asked to press a button whenever they saw a person in the picture. Each block contained 10 images and was repeated 2 times (except neutral 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). At the end of the fMRI session, participants 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.

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 = 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 co-planar anatomical images were also acquired during the same scanning session (see Bourque et al., 2013).

4. Analysis of fMRI data

fMRI data was analyzed with Brain Voyager QX (Brain Innovation, Maastricht, Netherlands) software. Functional images were slice-time corrected, corrected for motion artifacts (≤2 mm), high-pass filtered (2 cycles per time course), co-registered to the corresponding anatomical image, spatially normalized to the Talairach space (Talairach and Tournoux, 1988), and spatially smoothed with a 3D isotropic Gaussian kernel (8 mm FWHM).

We used a standard block design approach and general linear model to identify the cerebral changes associated with emotion processing. Five predictors of interest, corresponding to the experimental conditions, were convolved with the hemodynamic response function estimated using the double-gamma model (Boynton et al., 1996). We undertook a first-level analysis to investigate individual brain-activation maps associated with our primary contrast of interest [(High Positive + High Negative) > Neutral; orthogonal] [Note: High Positive and High negative conditions were also analyzed separately, and results for these contrasts are described in Supplementary Table 2]. The [Neutral > Rest] contrast was also examined. A second-level random-effects model was then implemented to investigate the pattern of activations during emotion processing between both schizophrenia sub-groups (Penny and Holmes, 2003).

The statistical threshold for significance was determined by Monte Carlo simulation (Ward, 2000). Assuming a voxel-level threshold of $p < 0.001$ (10,000 simulations), a cluster size of 343 mm^3 was required to correct for multiple comparisons at $p < 0.05$. The clusters found to significantly differ between schizophrenia sub-groups were used as data-driven regions of interest for subsequent statistical analyses, comparing patients with control subjects. Finally, correlation analyses between regional BOLD responses and clinical variables (e.g. emotional ratings, positive and negative symptoms, age of onset, and clozapine dosage) were performed within schizophrenia sub-groups. The level of significance was set at $p < 0.05$, and Bonferroni correction was applied.

3. Results

1. Clinical data

The three groups did not differ in socio-demographic variables. Schizophrenia sub-groups did not differ in psychiatric symptoms. However, chlorpromazine equivalents were higher in SCZ-TR, compared to SCZ patients. Finally, both schizophrenia groups rated the neutral stimuli with a greater emotional intensity than did controls (Supplementary Table 1).

2. fMRI data

For the [(High Positive + High Negative) > Neutral] contrast, increased activations in the (posterior) mid-cingulate gyrus and the left cerebellum (culmen) were observed in SCZ-TR, relative to SCZ patients (Supplementary Table 2; Fig. 1). Subsequent volume of interest (VOI) analyses in these clusters revealed that SCZ-TR patients had greater activations than controls (cingulate gyrus: $F_{1,59} = 8.1$; $p = 0.006$; cerebellum: $F_{1,59} = 11.5$; $p = 0.001$). For the [Neutral > Rest] contrast, increased activations were observed in the left superior frontal gyrus in SCZ-TR, relative to SCZ patients (Supplementary Table 2; Fig. 2). VOI analyses in this cluster indicated that SCZ-TR patients had higher activations, relative to controls ($F_{1,59} = 16.9$; $p = 0.0001$). For all 3 clusters (mid-cingulate, cerebellum, superior frontal), results remained significant after controlling for chlorpromazine equivalents. Lastly, there were no differences in brain activations in all 3 significant clusters (mid-cingulate, cerebellum, superior frontal) between SCZ-TR patients treated with two antipsychotics and those treated solely with clozapine ($p > 0.05$).

In SCZ-TR patients, the activation level in the left cerebellum [(High Positive + High Negative) > Neutral] correlated positively with age of onset ($r = 0.463$; $p = 0.046$). In SCZ patients, the activation in the superior frontal gyrus [Neutral > Rest] correlated inversely with negative symptoms ($r = -0.479$; $p = 0.018$) and ratings of high-arousal positive and negative images ($r = -0.486$; $p = 0.022$). Please note that none of these correlation results would survive a strict Bonferroni correction ($p = 0.05 / 5$ analyses → $p < 0.01$), but they are nevertheless informative. Finally, no association was found between activations and positive and negative symptoms, and clozapine dosage ($p > 0.05$).

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