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Childhood trauma and emotional processing circuits in schizophrenia: A functional connectivity study

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ABSTRACT

Childhood trauma strongly impacts emotional responses in schizophrenia. We have explored an association between early trauma and the amygdala functional connectivity using generalized psychophysiological interaction during an emotional task. Twenty-one schizophrenia patients and twenty-five controls were included.

In schizophrenia patients, higher levels of sexual abuse and physical neglect during childhood were associated with decreased connectivity between the amygdala and the posterior cingulate/precuneus region. Additionally, patients showed decreased coupling between the amygdala and the posterior cingulate/precuneus region compared to controls.

These findings suggest that early trauma could impact later connectivity in specific stress-related circuits affecting self-consciousness and social cognition in schizophrenia.

1. Introduction

Childhood trauma is a major risk factor for psychosis, leading to long-term altered emotional responses in schizophrenia patients such as increased reactivity to daily-life stress (Lardinois et al., 2011; Lataster et al., 2012). This supports the idea of an affective pathway to psychosis (Isvoranu et al., 2016; Myin-Germeys and van Os, 2007). Given its cardinal role in emotion processing (for review, see: Ledoux, 2000) the amygdala has been extensively scrutinized in schizophrenia. Neuroimaging studies exploring the activity of the amygdala during emotional tasks have led to discrepant findings, showing either hyper or hypo activity in patients within this structure (Anticevic et al., 2012b). Aside from localized activation patterns, interactions between brain regions can offer crucial information on abnormal brain functioning in psychosis (Friston and Frith, 1995). The literature examining the interaction of the amygdala with other brain areas in schizophrenia indicates impaired functional connectivity of this structure (Anticevic et al., 2012a, 2014; Bjorkquist et al., 2016; Das et al., 2012; Hoptman et al., 2010; Liu et al., 2014; Mukherjee et al., 2012, 2016). There is also evidence of impaired anatomical connectivity in critical cortico-limbic circuits in schizophrenia patients. Interestingly, in schizophrenia patients, early trauma was correlated with diffusion tensor imaging (DTI) measures of white matter integrity, namely fractional anisotropy and mean diffusivity (Poletti et al., 2015). However, to our knowledge, no work has provided analogous findings with functional connectivity data.

Since childhood trauma is a central risk factor for schizophrenia which strongly impacts emotional responses and since schizophrenia patients present altered emotional processing, we proposed to study the association between childhood trauma and functional connectivity of the amygdala during an emotional valence task.

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2. Materials and methods

2.1. Participants

The analyses included data from a group of twenty-one schizophrenia patients described in detail in a previous study (Cancel et al., 2015). All patients fulfilled DSM-IV-TR criteria for schizophrenia (American Psychiatric Association, 2000) and were stabilized on antipsychotic monotherapy for at least 6 weeks prior to the study. Individuals were excluded if they had any MRI contraindications, any history of head trauma or neurological disorder, or any concomitant major medical disorder or drug abuse. Childhood trauma was estimated with the French long version of the Childhood Trauma Questionnaire (CTQ) (Paquette et al., 2004). Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Depression was determined in schizophrenia patients by a score above six at the Calgary Depression Scale for Schizophrenia (Addington et al., 1992).

A control group of twenty-five healthy subjects was included for comparison with the same exclusion criteria considered.

2.2. Experimental paradigm

The Variable Attention and congruency Task (VAAT) was used as the experimental fMRI task (see (Comte et al., 2016) and supplementary material for full description). Briefly, it consists of images displaying faces and scenes with a pleasant (positive condition) or unpleasant (negative condition) emotional content. A negative versus a positive valence condition was considered.

2.3. MRI acquisition

Data were acquired on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker) using a T2*-weighted gradient-echoplanar imaging sequence (TR = 3000 ms; TE = 30 ms; FOV = 19.2 × 19.2; 64 × 64 matrix; flip angle 84.8°; voxel size 3 × 3 × 3 mm^3). Four functional runs of 45 interleaved axial slices were acquired with a continuous slice thickness of 3 mm. Following the functional MRI scans, high-resolution anatomical images were acquired for the purpose of anatomical identification with a sagittal T1-weighted MP-RAGE sequence (TR = 9.4 ms; TE = 4.42 ms; TI = 800 ms; 256 × 256 × 180 matrix; flip angle 30°, voxel size 1 × 1 × 1 mm^3).

2.4. Statistical analyses

t-Tests were performed on socio-demographic and CTQ measures with PASW Statistics 18 (SPSS Inc. http://www.spss.com.hk/statistics/). Imaging data were analysed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). We performed standard preprocessing procedures as described in a previous article (Comte et al., 2015). A generalized form of psychophysiological interaction (gPPI, http://brainmap.wisc.edu/PPI) (McLaren et al., 2012) was used to assess context-dependent variations in the amygdala's whole-brain functional connectivity (see supplementary material for details). For each subject, the seed mask was created using a 3-mm radius sphere around the coordinates of the healthy group maxima and within the amygdala anatomical mask, as defined using the Automated Anatomical Labeling software implemented in the WFU PickAtlas (Maldjian et al., 2003). Within this amygdala seed region, the time series of the first eigenvariate of the blood oxygen level-dependent signal were temporally filtered, mean corrected, and deconvolved to generate the physiological variable.

Psychophysiological interaction (PPI) terms were computed as the cross product of the physiological variable and each task regressor (negative or positive valence). Finally, the physiological variable, the psychological regressors, and PPI variables were entered as regressors in a first level general linear model. In the second level analyses, the five CTQ sub-scales were entered as predictors into five whole-brain voxelwise multiple regressions with the first-level contrast images entered as the dependent variable.

Given the subtle nature of brain activity during emotion processing and the general tendency of PPI analyses to lack power and generate a high proportion of false negatives (O'Reilly et al., 2012), the primary threshold at the voxel level was set at $p < 0.005$ uncorrected, consistent with recent studies on emotional processing in psychiatric populations article (Comte et al., 2015; Bjorkquist et al., 2016; Voegler et al., 2016). Results were corrected for multiple comparisons with 1) a cluster-extent based threshold at $p < 0.05$ FWE-corrected (family wise error) and 2) Bonferroni procedure for the five CTQ sub-scales (pcluster <0.01 FWE-corrected).

To test whether findings could be influenced by confounding factors such as age, gender, parents' education level or antipsychotic medication, these variables were included as covariates in another set of regressions.

Additionally, we explored the differences between schizophrenia patients and the healthy controls in the regions in which functional connectivity with the amygdala was associated with the CTQ. We used two-sample *t*-tests and a region of interest approach with anatomical masks defined with WFU PickAtlas toolbox. The results were assessed at a statistical threshold of $p < 0.005$ voxel-wise with a minimum of 10 voxels per cluster.

3. Results

Controls did not differ from the patient group with regard to gender, age and education (Table 1). None of the schizophrenia patients met CDSS criteria for depression.

In schizophrenia patients, sexual abuse was negatively associated with the functional connectivity between: the amygdala seed region and the left precuneus (k = 249 voxels; pcluster = 0.006 FWE-corrected; T-score = 6.22 at [−12;−62;44]); the amygdala and the left posterior cingulate/precuneus (k = 234 voxels; pcluster = 0.009 FWE-corrected; T-score = 5.92 at [0;−50;20]); the amygdala and the right calcarine sulcus (k = 256 voxels; pcluster = 0.005 FWE-corrected; T-score = 5.97 at [18;−94;−8]). These clusters are represented in Fig. 1A. In addition, physical neglect was negatively associated with the functional connectivity between the amygdala and the left precuneus (k = 232 voxels; pcluster = 0.0097 FWE-corrected; T-score = 6.20 at [−10;−52;36]). This cluster is represented in Fig. 1B. There was no significant positive association between the CTQ sub-scores and the whole-brain connectivity of the amygdala. The addition of age, gender,

Table 1
Socio-demographic and clinical characteristics of participants (mean ± standard deviation). Effect sizes (η^2) are reported only for significant group comparisons ($p < 0.05$).

	Schizophrenia patients ($n = 21$)	Healthy controls ($n = 25$)	p (η^2)
Sex-ratio (M/F)	2.5	1.8	0.592
Age (years)	32.1 ± 8.3	33.1 ± 7.5	0.689
Educational level (years)	-0.3 ± 2.8	0.5 ± 2.2	0.282
CTQ			
Emotional neglect	46.1 ± 14.0	35.8 ± 10.2	0.006 (0.16)
Physical abuse	16.9 ± 7.9	12.1 ± 2.2	0.013 (0.14)
Emotional abuse	28.6 ± 11.0	22.5 ± 7.5	0.040 (0.09)
Physical neglect	12.4 ± 3.9	9.5 ± 1.8	0.004 (0.18)
Sexual abuse	7.1 ± 2.9	5.8 ± 1.1	0.076
Total score	9.8 ± 2.8	7.6 ± 1.4	0.002 (0.20)
Clinical status			
PANSS (total score)	46.9 ± 18.6		
Medication (Chlorpromazine)	275 ± 144		

CTQ: Childhood Trauma Questionnaire. PANSS: Positive and Negative Syndrome Scale. n: number of subjects.

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