NeuroImage: Clinical 4 (2014) 232–239

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Ventral striatum gray matter density reduction in patients with schizophrenia and psychotic emotional dysregulation ☆

Katharina Stegmayer [a,*], Helge Horn [a], Andrea Federspiel [a], Nadja Razavi [a], Tobias Bracht [a], Karin Laimböck [a], Werner Strik [a], Thomas Dierks [a], Roland Wiest [b], Thomas J. Müller [a], Sebastian Walther [a]

[a] University Hospital of Psychiatry, Bern, Switzerland
[b] Support Center of Advanced Neuroimaging (SCAN), University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern, Switzerland

ARTICLE INFO

Article history:
Received 17 October 2013
Received in revised form 9 December 2013
Accepted 17 December 2013
Available online 27 December 2013

Keywords:
Dimensions
Emotional dysregulation
Limbic system
Brain circuits
Psychopathology

ABSTRACT

Introduction: Substantial heterogeneity remains across studies investigating changes in gray matter in schizophrenia. Differences in methodology, heterogeneous symptom patterns and symptom trajectories may contribute to inconsistent findings. To address this problem, we recently proposed to group patients by symptom dimensions, which map on the language, the limbic and the motor systems. The aim of the present study was to investigate whether patients with prevalent symptoms of emotional dysregulation would show structural neuronal abnormalities in the limbic system.
Method: 43 right-handed medicated patients with schizophrenia were assessed with the Bern Psychopathology Scale (BPS). The patients and a control group of 34 healthy individuals underwent structural imaging at a 3T MRI scanner. Whole brain voxel-based morphometry (VBM) was compared between patient subgroups with different severity of emotional dysregulation. Group comparisons (comparison between patients with severe emotional dysregulation, patients with mild emotional dysregulation, patients with no emotional dysregulation and healthy controls) were performed using a one way ANOVA and ANCOVA respectively.
Results: Patients with severe emotional dysregulation had significantly decreased gray matter density in a large cluster including the right ventral striatum and the head of the caudate compared to patients without emotional dysregulation. Comparing patients with severe emotional dysregulation and healthy controls, several clusters of significant decreased GM density were detected in patients, including the right ventral striatum, head of the caudate, left hippocampus, bilateral thalamus, dorsolateral prefrontal and orbitofrontal cortex. The significant effect in the ventral striatum was lost when patients with and without emotional dysregulation were pooled and compared with controls.
Discussion: Decreased gray matter density in a large cluster including the right ventral striatum was associated with severe symptoms of emotional dysregulation in patients with schizophrenia. The ventral striatum is an important part of the limbic system, and was indicated to be involved in the generation of incentive salience and psychotic symptoms. Only patients with severe emotional dysregulation had decreased gray matter in several brain structures associated with emotion and reward processing compared to healthy controls. The results support the hypothesis that grouping patients according to specific clinical symptoms matched to the limbic system allows identifying patient subgroups with structural abnormalities in the limbic network.

1. Introduction

Structural alterations in cerebral gray matter have been repeatedly reported in schizophrenia, particularly in the prefrontal cortex, the superior temporal gyrus, the limbic system (medial temporal lobe, hippocampus, entorhinal cortex, amygdala) as well as in the insula, the thalamus and the cerebellum (Bora et al., 2011; Ellison-Wright et al., 2008; Glahn et al., 2008; Horn et al., 2009). Considerable heterogeneity of results across studies on structural anatomy has been noted, however (Haijma et al., 2012; Honea et al., 2008). In addition to differences in methodology and population demographics, heterogeneous symptom patterns and symptom trajectories may critically contribute to the inconsistent findings. Furthermore, the distribution of anatomical alterations does not yield unique hints to understand the pathophysiology of the different symptoms associated with schizophrenia. Linking dimensional assessment of behavioral domains and mental states to brain circuitry may be necessary to progress in schizophrenia research (Heckers, 2011).

* Corresponding author at: University Hospital of Psychiatry, Bolligenstrasse 111, 3060 Bern, Switzerland. Tel.: +41 31 930 9757; fax: +41 31 930 9404.
E-mail address: stegmayer@puk.unibe.ch (K. Stegmayer).

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http://dx.doi.org/10.1016/j.nicl.2013.12.007

Investigations of more homogeneous patient groups aimed to overcome this issue. In addition to the classical consideration of positive and negative symptoms, there is growing evidence that investigating core symptoms may lead to meaningful results, as demonstrated for formal thought disorder (Horn et al., 2010; McCarley et al., 1993; Shenton et al., 1992), hallucinations (Barta et al., 1990; Gaser et al., 2004; Nestor et al., 2007) and delusions (Pankow et al., 2012; Spencer et al., 2007). In addition, factor analysis to psychopathology as rated with the scales for assessment of positive and negative symptoms has been applied to reduce symptom variance in a large patient group; this resulted in distinct associations with structural alterations, e.g. between the paranoid/hallucinatory subsyndrome and the superior temporal cortex (Nenadic et al., 2010).

If psychopathology in schizophrenia spectrum disorders is the result of a functional imbalance of higher order brain systems, it should be possible to match specific psychotic symptoms on the respective brain functions and systems. Based on this assumption, we have developed the Bern Psychopathology Scale (BPS) as a research instrument to group psychotic symptoms into three biologically relevant dimensions referring to the language, limbic and motor systems (Strik et al., 2010).

Dysfunction in the limbic system in schizophrenia is a growing area of interest. Particularly, abnormalities in emotion processing and regulation are cardinal features in psychiatric disorders (Taylor and Liberzon, 2007). They may be pivotal to produce abnormal salience (Kapur, 2003) and threat beliefs, possibly underlying specific psychotic symptoms such as persecutory delusions (Freeman and Garety, 2003). Biased emotion processing may cause aggression, suspiciousness and poor social performance of patients with schizophrenia (Kee et al., 2003; Phillips et al., 2003), and was associated with positive psychotic symptoms (Abi-Dargham et al., 2000; Pankow et al., 2012). In addition, patients with schizophrenia show aberrant functional brain activation in neuronal regions implicated in emotion and reward processing e.g. the amygdala, insula, anterior cingulate, orbitofrontal cortex and ventral striatum (Aleman and Kahn, 2005; Brunet-Gouet and Decety, 2006; Kirsch et al., 2007; Pankow et al., 2013; Schlagenhauf et al., 2008; Walter et al., 2009).

In the light of these findings from functional brain imaging, we expected changes in limbic structures to be associated with emotional dysregulation and delusions of threat, covered in the BPS by the affectivity dimension. Particularly, we hypothesized that gray matter volumes in the limbic system would differ between patients presenting with severe emotional dysregulation and patients without emotional dysregulation. In addition, the structural alterations in patients presenting with severe emotional dysregulation would also differ from controls.

2. Methods

2.1. Subjects and clinical assessment

In total, 43 patients (16 women and 27 men) of the University Hospital, Bern, Switzerland, meeting DSM IV (American Psychiatric Association 1994) criteria for schizophrenia were included. Diagnoses were given following thorough clinical interviews and review of all records available, however the structured clinical interview for DSM IV (SCID) was not applied. 40 patients were treated with atypical or typical antipsychotics. Three patients were drug free at the time of the study. Five patients received typical antipsychotics (four typical and atypical and one only typical). A control group of 34 healthy individuals was included (18 women and 16 men). All subjects were right handed. Groups did not differ in age or gender distribution (see Table 1). However, controls had longer duration of education ($t = -3.4$, $df = 75$, $p = 0.001$).

Participants provided written informed consent. The protocol was approved by the local ethics committee.

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) as well as the Bern Psychopathology Scale. The BPS was explicitly developed as a research instrument to attribute psychotic symptoms to behavioral dimensions and the suspected underlying brain systems, namely the language, the motor and the limbic systems. It is neither intended as a diagnostic tool in terms of the ICD-10 or DSM-IV categories, nor attempted to cover every phenomenon associated with psychoses.

The affectivity dimension includes symptoms of emotional dysregulation, attributed to the limbic system (http://www.puk.unibe.ch/BPS) e.g. delusions of threat or supernatural power, tension, psychotic anxiety, suspiciousness, aggressiveness or social avoidance and unpleasant body sensations. Global severity of symptoms is rated on 7 point Likert scales ranging from −3 (e.g. most severe psychotic anxiety) to +3 (e.g. most severe psychotic grandiosity), whereas 0 refers to normal behavior; (Strik et al., 2010). The global rating does not represent a sum score of the single items but instead refers to a global clinical impression after assessing the presence and severity of all items. One or two very severe impairing signs therefore may drive the global impression, whereas multiple mild signs may not sum up to high global severity ratings. The major differences of the BPS compared to other psychopathological scales (e.g. the PANSS) are first the possibility to attribute psychotic symptoms to behavioral domains and second the dual rating system that focuses on both single signs and the global impression. The latter allows weighting the impact of single signs with prominent severity.

We chose a prototypical approach to data analysis, assuming that severe emotional dysregulation was reliably related to psychosis, while the mildest forms (+1 and −1 on the global BPS scale) may overlap with normal or reactive emotional dysregulation. Based on this consideration and lacking precedents to provide a rationale for the cut-offs, we defined three patient subgroups according to the severity of emotional dysregulation, regardless of the direction (+ or −) on the global rating. The first group consisted of patients with evident and severe emotional dysregulation (sED; $n = 14$; 7 women and 7 men) defined by high ratings in the global affectivity scale (≤ -2 or $\geq +2$); the second group of patients with less evident and mild emotional dysregulation (mED; $n = 22$; 5 women and 17 men; BPS global affectivity −1 or +1); the third group of patients with normal affectivity (no symptom of emotional dysregulation, nED; $n = 7$; 4 women and 3 men; BPS global affectivity = 0). Patient subgroups did not differ in duration of illness, number of episodes, chlorpromazine equivalent dosage, PANSS scores (negative, positive and total scores), duration of education, age or gender distribution and total gray matter volume (see Table A, Supplementary data).

2.2. Structural MRI acquisition and data processing

Imaging was performed on a 3T MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) with a standard head coil. 3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) images for each subject have been obtained (Deichmann et al., 2004), providing 176 sagittal slices with 256 × 224 matrix points with a non-cubic field of view (FOV) of 256 × 224, yielding a nominal isotopic resolution of 1 mm^3 (i.e. 1 mm × 1 mm × 1 mm). Further scan parameters were 7.92 ms repetition time (TR), 2.48 ms echo time (TE) and a flip angle of 16° (FA).

Structural images were processed using SPM8 (Wellcome Trust Center for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm). All preprocessing steps were conducted using standard procedures as implemented in SPM8 (Matlab version 7, release 2008a; The MathWorks, Inc., Natick, MA, USA), in particular the voxel-based morphometry (VBM) toolbox. The images have been normalized, modulated and smoothed with 8 mm full-width at half maximum (FWHM) kernel.

2.3. Statistical analyses

Statistical tests were performed using SPM routines and SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Independent two-sample t tests, one way