Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Specific cerebral perfusion patterns in three schizophrenia symptom dimensions

Katharina Stegmayer [a,*], Werner Strik [a], Andrea Federspiel [a], Roland Wiest [b], Stephan Bohlhalter [c], Sebastian Walther [a]

[a] Translational Research Center, University Hospital of Psychiatry, Bern, Switzerland
[b] Support Center of Advanced Neuroimaging (SCAN), University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern, Switzerland
[c] Neurology and Neurorehabilitation Center, Kantonsspital Luzern, Lucerne, Switzerland

ARTICLE INFO

Article history:
Received 19 August 2016
Received in revised form 2 March 2017
Accepted 5 March 2017
Available online xxxx

Keywords:
Paranoia
Formal thought disorder
Movement disorder
Symptom domains
Bern Psychopathology scale
Threat

ABSTRACT

Dimensional concepts such as the Research Domain Criteria initiative have been proposed to disentangle the heterogeneity of schizophrenia. One model introduced three neurobiologically informed behavioral dimensions: language, affectivity and motor behavior. To study the brain-behavior associations of these three dimensions, we investigated whether current behavioral alterations were linked to resting state perfusion in distinct brain circuits in schizophrenia.

In total, 47 patients with schizophrenia spectrum disorders and 44 healthy controls were included. Psychopathology was assessed with the Positive And Negative Syndrome Scale and the Bern Psychopathology scale (BPS). The BPS provides severity ratings of three behavioral dimensions (language, affectivity and motor). Patients were classified according to the severity of alterations (severe, mild, no) in each dimension. Whole brain resting state cerebral blood flow (CBF) was compared between patient subgroups and controls.

Two symptom dimensions were associated with distinct CBF changes. Behavioral alterations in the language dimension were linked to increased CBF in Heschl's gyrus. Altered affectivity was related to increased CBF in amygdala. The ratings of motor behavior instead were not specifically associated with CBF.

Investigating behavioral alterations in three schizophrenia symptom dimensions identified distinct regional CBF changes in the language and limbic brain circuits. The results demonstrate a hitherto unknown segregation of pathophysiological pathways underlying a limited number of specific symptom dimensions in schizophrenia.

1. Introduction

Heterogeneity in symptom presentation and course of schizophrenia has hampered the search for pathobiological substrates of the disorder. Most neuroimaging studies, which applied a categorical approach failed to explain why the reported brain alterations would lead to the plethora of different symptoms seen in schizophrenia. It was the assumption to investigate a homogenous group of patients that probably posed the problem. Recent efforts include dimensional approaches to psychopathology (e.g. the Research Domain Criteria (RDoC) initiative of the NIMH) (Goghari et al., 2010; Insel et al., 2010). Linking these dimensional assessments to brain circuitry may be crucial for advances in schizophrenia research (Heckers, 2011).

Dimensions derived from factor analyses of standard rating scales were associated with widespread structural brain alterations (Koutsouleris et al., 2008; Nenadic et al., 2010). Likewise, one early example of perfusion data (resting state cerebral blood flow: CBF) related three factors to distinct CBF patterns in schizophrenia (Liddle et al., 1992). However, in general these dimensions were not linked to particular brain circuits; except for severity of symptoms of the factor reality distortion (hallucinations and delusions) which was related to reduced volume in key regions of the salience network (Palaniyappan et al., 2011). Until now, only single symptom approaches successfully identified abnormalities in brain circuits with distinct functional neuroanatomy. For instance, patients with auditory verbal hallucinations or formal thought disorders present functional and structural changes of the auditory and language system (e.g. the superior temporal gyrus, the inferior frontal gyrus, and the arcuate fascicle) (Horn et al., 2010; Hubl et al., 2004; Kircher et al., 2001; Nagels et al., 2016; Viher et al., 2016). Instead, paranoid experience of threat as well as delusions of reference were linked to abnormalities of the limbic system (e.g. ventral striatum, head of caudate nucleus and amygdala) (Pinkham et al., 2015; Stegmayer et al., 2014b). Finally, disturbed motor behavior was related to the cerebral motor system (e.g. the basal ganglia, and premotor

* Corresponding author at: University Hospital of Psychiatry, Bolligenstrasse 111, 3060 Bern, Switzerland.
E-mail address: stegmayer@puk.unibe.ch (K. Stegmayer).

http://dx.doi.org/10.1016/j.schres.2017.03.018

Please cite this article as: Stegmayer, K., et al., Specific cerebral perfusion patterns in three schizophrenia symptom dimensions, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2017.03.018

cortices) (Walther, 2015; Walther et al., 2011a, b; Walther et al., in press; Walther and Strik, 2012). However, the situation is less clear when moving the focus from single symptoms to more complex behavioral dimensions, such as those derived from factor analyses (Liddle et al., 1992; Nenadic et al., 2010; Schroder et al., 1996).

To address this problem, we introduced a neurobiologically informed rating scale (the Bern Psychopathology scale; BPS), organizing schizophrenia symptoms in three behavioral dimensions. Thus we approach psychopathology in the context of hypothesized neural circuits and behavioral dimensions, which has been proposed by the RDoC initiative (Carpenter, 2016). The BPS dimensions are operationally defined based on language, affectivity and motor behavior (Strik et al., 2010). In particular, the language dimension includes formal thought disorders such as incoherence, perplexity or alogia, while the affectivity dimension comprises signs of paranoid experiences of threat or power, such as delusions of persecution or grandiosity. Finally, the motor dimension includes altered motor behavior such as hyperkinesia or reduced motor activity (Strik et al., 2010). In fact, BPS ratings were linked to distinct gray matter (GM) changes: aberrant motor behavior with GM of the supplementary motor area (SMA) (Stegmayer et al., 2014a) and abnormal emotional valence with the limbic system (Stegmayer et al., 2014b). However, a comprehensive investigation of the brain behavior associations of the BPS dimensions with a state marker such as cerebral blood flow (CBF) is missing.

In the present study we therefore tested whether current behavioral abnormalities in neurobiologically informed dimensions of psychopathology would be linked to resting state CBF alterations in distinct brain circuits. Particularly, we expected language alterations to be linked to changes of the cerebral language circuit, affectivity alterations to be related to functional changes in limbic structures and altered motor behavior linked to changes of the cerebral motor system (Walther, 2015). Our hypotheses would be rejected if the three behavioral dimensions demonstrated common cerebral correlates.

2. Materials and methods

2.1. Subjects

In total, 47 patients with schizophrenia spectrum disorders according to DSM-5 and 44 healthy controls were included. General exclusion criteria for both groups were substance abuse or dependence other than nicotine, current severe medical or neurological condition, history of head trauma with concurrent loss of consciousness and specific exclusion criteria for MRI scans. All study participants were of middle European decent, native German speakers and right handed. Additional exclusion criteria for healthy controls were history of any psychotic disorder and first-degree relatives with schizophrenia spectrum disorders. All subjects provided written informed consent. The study protocol adhered to the declaration of Helsinki and was approved by the local Ethics Committee.

Forty-three patients were treated with atypical or typical antipsychotics. Four patients were drug free at the time of the study. Patients and controls did not differ in age, education and gender distribution as well as mean global cerebral blood flow and head movements (Table 1).

2.2. Procedure

The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) for axis-I disorders and the structured clinical interview for DSM IV (SCID II) for axis-II disorders were conducted by a trained clinician (trained by experts; $K > 0.80$) in all participants. Antipsychotic dosages were calculated as chlorpromazine equivalent doses (CPZ) (Woods, 2003).

Table 1
Sample demographic variables.

	All patients	Healthy controls	T/χ^2	Df	p
Age	38.8 ± 13.6	38.2 ± 11.4	−0.230	89	0.819
Gender (% men)	61.7%	59.1%	0.065	1	0.833
Education (years)	13.4 ± 3.1	14.1 ± 2.7	−1.190	89	0.820
Global CBF	54.0 ± 9.2	53.3 ± 5.8	0.431	89	0.668
Mean motion x (mm)	−0.0151 ± 0.2431	0.0012 ± 0.1164	−0.406	89	0.686
Mean motion y (mm)	0.0953 ± 0.1932	0.0312 ± 0.2021	1.539	89	0.127
Mean motion z (mm)	−0.0278 ± 0.3774	−0.0853 ± 0.4715	0.639	89	0.524
Mean motion α (degrees)	0.0006 ± 0.0066	0.0066 ± 0.0062	−0.042	89	0.967
Mean motion β (degrees)	−0.0003 ± 0.0030	0.0001 ± 0.0014	−0.747	89	0.457
Mean motion γ (degrees)	0.0007 ± 0.0046	0.0002 ± 0.0029	0.615	89	0.540
Duration of illness (years)	12.3 ± 12.3	–	–	–	–
Number of episodes	6.4 ± 7.2	–	–	–	–
First episode patients (%)	25.5	–	–	–	–
Schizophrenia (n)	36	–	–	–	–
Schizophreniform disorder (n)	9	–	–	–	–
Schizoaffective disorder (n)	2	–	–	–	–
PANSS pos	18.2 ± 6.4	–	–	–	–
PANSS neg	18.4 ± 5.1	–	–	–	–
PANSS tot	72.6 ± 17.1	–	–	–	–
CPZ 5 years	221.1 ± 283.1	–	–	–	–
CPZ	400.2 ± 344.2	–	–	–	–

CBF = cerebral blood flow: n = number; PANSS = Positive And Negative Syndrome Scale; pos = positive symptom scores; neg = negative symptom scores, tot = total scores; CPZ = chlorpromazine equivalent doses.

2.3. Psychopathology assessment

Psychopathology was assessed using the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) as well as the Bern Psychopathology scale (BPS) at the day of the MRI scan. The BPS is a research instrument to assess psychotic symptoms of three behavioral dimensions: language, affectivity and motor dimension (https://www.puk.unibe.ch/BPS). Global severity of impairment for each dimension is rated on a 7 point Likert scale ranging from −3 (e.g. most severe psychotic anxiety) to +3 (e.g. most severe psychotic grandiosity), whereas 0 represents normal behavior. The BPS comprises no sum score or global score across the three dimensions; detailed information is given in the original publication (Strik et al., 2010). Good internal consistency and external validity of the BPS has been shown (Bracht et al., 2012; Lang et al., 2016; Lang et al., 2015a; Lang et al., 2015b; Schoretsanitis et al., 2016; Stegmayer et al., 2014a, b; Steinau et al., 2017; Strik et al., 2010).

In line with previous studies (Lang et al., 2015b; Stegmayer et al., 2014a, b) we chose a prototypical approach to data analysis: we defined three patient subgroups according to the severity of alteration (severe, mild and no alteration) for each dimension, regardless of the direction (+ or −) on the global rating. This approach enhances feasibility, as dimensional analysis across all seven BPS global score levels would require much larger samples to account for the rare cases at both extreme ends of the scale. Patient subgroups of all three dimensions did not differ in clinical and demographic variables, mean global CBF and motion parameters. However patient subgroups differed in PANSS scores (Supplementary material: Table S1).

2.4. Structural and functional MRI acquisition and data processing

Imaging was performed on a 3T MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany) with a 12-

Please cite this article as: Stegmayer, K., et al., Specific cerebral perfusion patterns in three schizophrenia symptom dimensions, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2017.03.018