Specific cerebral perfusion patterns in three schizophrenia symptom dimensions

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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

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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-

channel radio frequency headcoil for signal reception. 3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) images for each subject have been obtained, providing 176 sagittal slices with 256×256 matrix points with a non-cubic field of view (FOV) of 256 mm, yielding a nominal isotropic resolution of 1 mm³ (i.e. 1 mm $\times$ 1 mm $\times$ 1 mm). Further scan parameters for the anatomical data were 7.92 ms repetition time (TR), 2.48 ms echo time (TE) and a flip angle of 16° (FA). In addition we obtained 110 functional images [pseudo Continuous Arterial Spin Labeling (pCASL) sequence], providing 20 slices with 64×64 matrix points with a non-cubic FOV of 230 mm, yielding a nominal isotropic resolution of 4.27 mm³ (i.e. 3.6 mm $\times$ 3.6 mm $\times$ 6 mm). Further scan parameters for the functional images were TR of 4000 ms, TE of 18 ms and a FA of 25°.

Structural and perfusion images were processed using SPM8 (Wellcome Trust Center for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm).

Preprocessing of the perfusion images was conducted with an in-house written MATLAB program toolbox (Walther et al., 2011b). In detail, ASL images were co-registered to the T1 weighted images, normalized, realigned, re-sliced and smoothed with 8 mm full-width at half maximum (FWHM) kernel. From the time series of the ASL signal, the mean regional resting state cerebral blood flow (CBF) was calculated voxelwise.

2.5. Statistical analyses

Statistical tests were performed using SPM routines and SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Two-sample t-tests, one way ANOVAs and chi-square tests (χ^2) were used to test group differences in continuous and categorical variables. Effects of psychopathological dimensions on CBF were investigated using one way ANCOVAs, multiple regression analyses and two sample t-tests respectively.

First, we explored CBF differences between controls and all patients independent of symptomatology using a two-sample ANCOVAS with head motion parameters as covariates of no interest. Second, we tested the effect of behavioral dimensions on CBF. Therefore, we calculated one multiple regression analysis including severity ratings of all three symptom dimensions as well as CPZ equivalents and individual motion parameters in patients. This approach was applied to disentangle the effects of one dimension from the other two. Effects for each dimension were calculated within the multiple regression analysis.

We applied a threshold of $p < 0.05$ Family Wise Error (FWE) to correct for multiple comparisons. For illustration purposes, we extracted the data from significant clusters of the whole brain analyses for each subject with the SPM toolbox MarsBaR (Brett et al., 2002). In addition, we performed an exploratory analysis comparing Z-transformed mean perfusion values between patient groups using univariate analysis and post hoc t-tests corrected for multiple comparisons (Sidak). Likewise we explored transformed mean perfusion values between patient groups accounting for the direction ($+$ or $-$) on the global severity rating, and healthy controls (Supplementary material, Fig. S2). Images were produced using MRIcron (Rorden et al., 2007).

3. Results

3.1. Decreased cerebral blood flow in schizophrenia in general

Patients had decreased CBF in the temporal and parietal lobe compared to controls (Table 2, Supplementary material: Fig. S1). Patients had no areas with increased CBF. Patients had no perfusion alterations compared to controls within the frontal lobe at the $p_{(FWE)} < 0.05$ threshold.

Table 2
Decreased CBF in schizophrenia patients.

Brain regions	MNI coordinates			Peak		Cluster
Controls > patients	x	y	z	T(83)	p(FWE-corr)	Voxels
Left inferior parietal lobe (IPL)	−58	−36	16	4.974	0.005	6
Left superior temporal gyrus/Heschls' gyrus	−44	−30	16	4.447	0.032	5

CBF = cerebral blood flow; no clusters for patients > controls. Covariates: mean motion parameters.

3.2. Altered cerebral blood flow in Heschl's gyrus and the amygdala linked to behavioral dimensions

Two dimensions were associated with distinct perfusion patterns at rest. The language dimension was linked to CBF in the right Heschl's gyrus (MNI coordinates: x = 58, y = −12, z = 4; $T_{(1,36)} = 6.24$; $p_{(FWE-corr)} = 0.005$; cluster size = 17 voxels; see Fig. 1A). Post hoc test detected highest perfusion values in controls and patients with severe language alterations. Patients with mild or no alterations had lower CBF than healthy controls and lower CBF than patients with severe language alterations (Fig. 1, Supplementary material: Fig. S2). The behavioral direction (language inhibition or disinhibition) did not distinguish the CBF values in the cluster within right Heschl's gyrus. Thus perfusion differed according to severity of the behavioral alteration but not according to direction of alteration (Fig. S2).

The affectivity dimension was linked to CBF changes in the left amygdala (MNI coordinates: x = −28, y = 4, z = −18; $T_{(1,36)} = 6.01$; $p_{(FWE-corr)} = 0.009$; cluster size = 14 voxel; see Fig. 1B; Supplementary material: Table S3). Again, highest perfusion values were found in controls and patients with severe alterations of affectivity, while patients with mild or no alterations had lower CBF than patients with severe alterations of affectivity. Patients without alterations had lower CBF than those with severe alterations and controls (Fig. 1, Supplementary material: Fig. S2).

We found no significant cluster in the motor dimension linked to CBF. This held also true for less conservative statistical thresholds.

Exploratory tests of the effect of behavioral dimensions on CBF with a less conservative threshold are provided in the supplement (Supplementary material, Table S3).

4. Discussion

We investigated dimensions of psychopathology in schizophrenia in the context of hypothesized neural circuits. We demonstrated resting state CBF changes in distinct brain circuits for two out of three dimensions of current schizophrenia psychopathology. Therefore, the null hypothesis of a common cerebral correlate associated with all three dimensions (language, affectivity and motor behavior) was rejected in this study. Particularly, behavioral alterations in the language dimension were linked to changes in cerebral blood flow (CBF) within the cerebral language system, i.e. right Heschl's gyrus. Behavioral alterations in the affectivity dimension were associated with changes of CBF in the left amygdala. However, we failed to detect CBF changes linked to altered motor behavior. The results for the language and affectivity dimensions were specific, as we covaried for symptom severity of the other two dimensions and for CPZ. These findings argue for distinct pathobiological pathways contributing to a limited number of symptom dimensions in schizophrenia.

In contrast, in line with the literature group comparisons between patients and controls demonstrated hypoperfusion in the STG and IPL (Allen et al., 2016; Kindler et al., 2015; Liu et al., 2012; Ota et al., 2014; Pinkham et al., 2011; Walther et al., 2011b; Walther et al., in press). Most of these CBF group differences share unspecific topography, i.e.
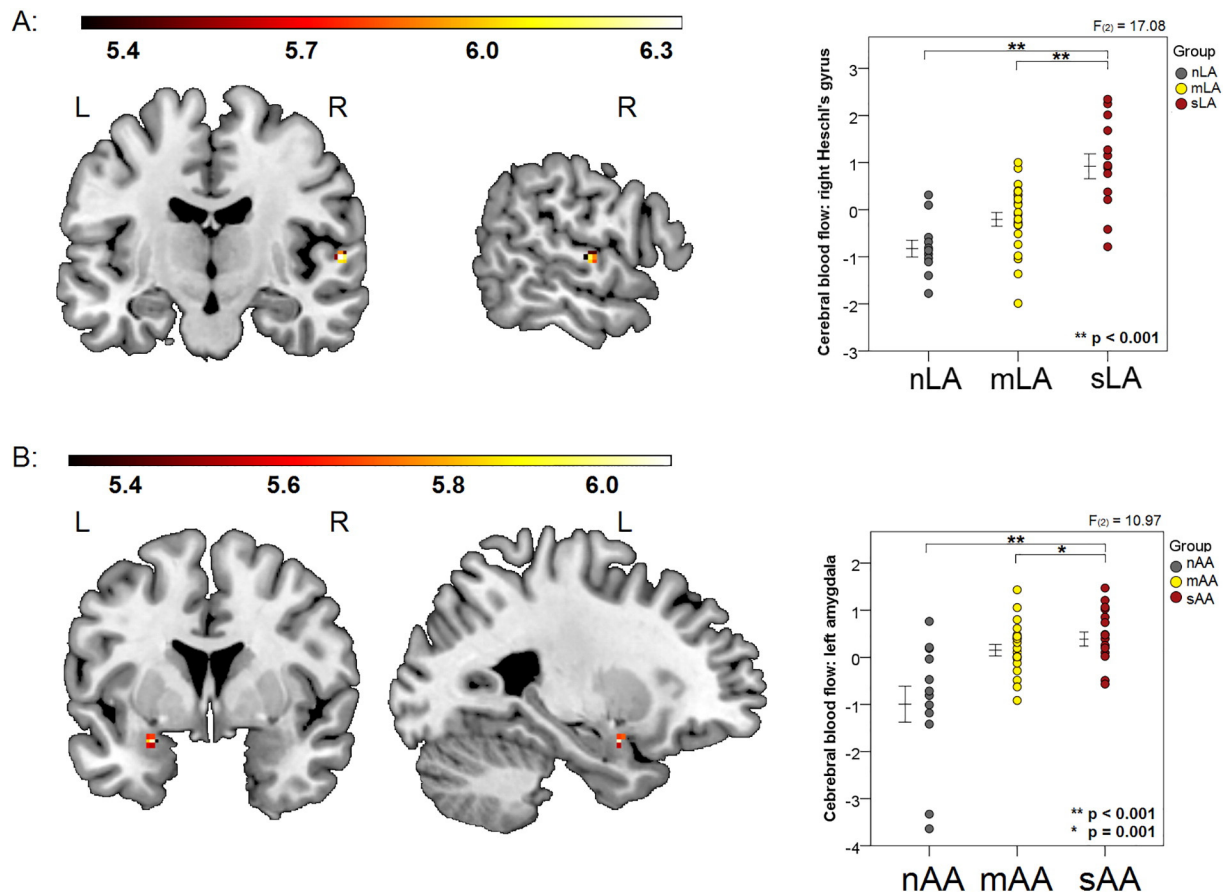
Fig. 1. A: CBF in the right Heschl's gyrus associated with language alterations. B: CBF in the left amygdala associated with altered affectivity. Correlation map of volumes with CBF (*t*-test) were statistically thresholded at $p < 0.05$, FWE-corrected and displayed on the section of the standard MNI-template. Exploratory analysis: Z-transformed mean perfusion values (CBF-values) in the cluster. sLA: severe language alteration, mLA: mild language alteration. nLA: no language alteration. sAA: severely altered affectivity, mAA: mild altered affectivity. nAA: no altered affectivity. Covariates: A: mean motion parameters, CPZ equivalents, severity ratings of the affectivity and motor dimensions (BPS global motor and BPS global affectivity); B: mean motion parameters, CPZ equivalents, severity ratings of the language and motor dimensions (BPS global motor and BPS global affectivity).

hardly translate into core schizophrenia symptoms. Instead, investigating distinct behavioral dimensions with the BPS identified cerebral changes in different brain circuits. Common to the findings in these symptom dimensions was the fact that both states of behavioral inhibition and disinhibition were associated with increased perfusion, indicating increased neural activity. Thus, clinical symptom dimensions quantified with refined assessment including multiple symptoms may inform on system-specific changes of functional neuroanatomy and may therefore complement single symptom approaches (Mathalon and Ford, 2012). This could be a relevant extension of the proposed RDoC domains (Insel et al., 2010).

4.1. Language dimension - altered CBF in the language system

Behavioral alterations of the language dimension including loose associations, auditory verbal hallucinations or thought block were associated with increased CBF in the right Heschl's gyrus. Thus, in line with the literature alterations in the language dimension were associated with changes in the language network (Horn et al., 2012; Kindler et al., 2015; Nagels et al., 2016; Viher et al., 2016), including formal thought disorders (Horn et al., 2010; Horn et al., 2009; Horn et al., 2012; Kircher et al., 2001) and auditory verbal hallucinations (Homan et al., 2013; Hubl et al., 2004).

Interestingly increased CBF of the Heschl's gyrus was right lateralized. While left hemisphere dominance in language function has been reported there are indications of bilateral language processing (Scott and McGettigan, 2013). In general, studies in schizophrenia reported hypoperfusion within the temporal cortex. Likewise, we

detected hypoperfusion of the STG in patients, particularly in those without behavioral language abnormalities. Thus, we may speculate that disturbances of the language dimension lead to increased resting state CBF in a cortical area that is usually hypoperfused in schizophrenia. Indeed, the relative hyperperfusion in the right Heschl's gyrus argues for a localized neural dysfunction specifically in patients with behavioral alterations in the language dimension leading to either inhibitory or excitatory effects in the language network.

4.2. Affectivity dimension - altered CBF in the limbic system

Behavioral alterations in the affectivity dimension such as delusions of threat, suspiciousness, or unpleasant body sensations were linked to CBF changes in the left amygdala. The amygdala is critical for initiating a rapid response to threat and processing salience (Ramirez et al., 2015). Our finding of amygdala hyperperfusion in subjects with severe alterations in the affectivity dimension parallels those of a recent report (Pinkham et al., 2015). Thus, increased neural activity in the amygdala may well reflect the neural responses to the paranoid experience of threat. In line with this, we demonstrated previously an association between severe alterations in the BPS affectivity dimension and reduced ventral striatal volume (Stegmayer et al., 2014b). Furthermore, paranoid threat increased structural connectivity between nucleus accumbens (NAcc) and amygdala (Bracht et al., 2014), which was attributed to avoidance behavior in rodents (Ramirez et al., 2015). Avoidance is one of the safety seeking behaviors used by patients with persecutory delusions (Freeman et al., 2007; Schoretsanitis et al., 2016), which co-occur with high levels of anxiety (Ben-Zeev et al., 2012). In contrast,

Zhu et al. detected perfusion of the anterior cingulate cortex to be associated with delusion severity according to the PANSS single item delusions. However, in their study patients with severer delusions also showed generally increased symptom severity which may explain differences between studies. The dimensional approach of the BPS allowed identifying cerebral changes related to a dimension of altered behavior in key regions of the limbic circuit, i.e. amygdala perfusion and ventral striatum volume (Stegmayer et al., 2014b). It extends previous reports of neural correlates of single symptoms, such as delusions (Menon et al., 2011) or threat (Wolf et al., 2015) and thus provides evidence for the hypothesized association between limbic dysfunction and clinical presentation of paranoid threat and persecutory delusions (Heinz and Schlagenhauf, 2010; Winton-Brown et al., 2014).

4.3. Motor dimension – no altered CBF in the motor system

In contrast to the other two BPS dimensions we failed to detect behavioral alterations in the motor dimension linked to CBF. Previously, perfusion of premotor areas correlated with actigraphically recorded amount of movement in schizophrenia (Walther et al., 2011b), a marker that also correlated with ratings of the BPS motor dimension (Bracht et al., 2012). In addition we reported structural GM volume in the SMA to be linked to BPS motor ratings (Stegmayer et al., 2014a) and SMA resting state hyperperfusion is a marker of state catatonia in schizophrenia (Walther et al., in press) Still, covarying for language and affectivity, we failed to detect a specific perfusion pattern associated with motor ratings. This contrast to previous findings could be due to reduced specificity of a global motor rating or to covariance issues.

4.4. Limitations

This study was not designed to examine a possible effect of current and past antipsychotic treatment, which may affect brain perfusion. Antipsychotic dosage at the time of scanning differed in the motor dimension with higher dosage in patients with severe motor alterations. However, all but four patients were on a stable antipsychotic medication and CPZ were entered as covariate in our analysis.

Moreover we applied a prototypical approach investigating severity of behavioral alterations in the respective dimensions. Thus, we did not account for the direction (+ or −) on the BPS global rating in the whole brain analysis. Our study is likely to be underpowered to analyze the direction of BPS global ratings. However, post-hoc tests of CBF values including direction of BPS global ratings argue for plausibility of the analysis of the BPS severity ratings. In fact, we detected a U-shaped, quadratic distribution of CBF-values in the selected regions of interest. Future studies with much larger samples need to address whether this U-shaped distribution holds true when analyzing the whole dimensional spectrum of the BPS ratings.

4.5. Conclusion

In conclusion, behavioral abnormalities in the language and affectivity dimension of schizophrenia were linked to distinct patterns of cerebral perfusion. The results argue for specific localized behavior-brain associations in these psychopathological dimensions on top of general cerebral alterations in schizophrenia. Therefore, distinct pathophysiological pathways may contribute to a limited number of specific symptom dimensions in schizophrenia.

Contributors

All authors contributed to and have approved the final manuscript. SW designed the study, wrote the protocol and acquired funding. KS recruited participants and performed measurements. KS and SW analyzed the data, interpreted the results, and wrote the first draft of the manuscript. AF and RW helped with data analysis. SB and WS contributed to data interpretation and manuscript writing.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.03.018.

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