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Brain structural correlates of schizotypy and psychosis proneness in a non-clinical healthy volunteer sample

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ABSTRACT

Schizotypal traits are phenotypic risk factors for schizophrenia, associated with biological changes across a putative schizophrenia spectrum. In this study, we tested the hypothesis that brain structural changes in key brain areas relevant to this spectrum (esp. medial and lateral prefrontal cortex) would vary across different degrees of schizotypal trait expression and/or phenotypic markers of psychosis proneness in healthy non-clinical volunteers. We analysed high-resolution 3 Tesla magnetic resonance images (MRI) of 59 healthy volunteers using voxel-based morphometry (VBM), correlating grey matter values to the positive and negative symptom factors of the schizotypal personality questionnaire (SPQ, German version) and a measure of psychosis proneness (community assessment of psychic experiences, CAPE). We found positive correlations between positive SPQ dimension and bilateral inferior and right superior frontal cortices, and positive CAPE dimension and left inferior frontal cortex, as well as CAPE negative dimension and right supplementary motor area (SMA) and left inferior parietal cortex. However, only the positive correlation of the right precuneus with negative schizotypy scores was significant after FWE correction for multiple comparisons. Our findings confirm an effect of schizotypal traits and psychosis proneness on brain structure in healthy subjects, providing further support to a biological continuum model.

1. Introduction

Early intervention and detection of people at risk of developing psychosis have become a major focus of clinical research on schizophrenia. Schizotypal traits are a putative phenotypic marker of elevated risk for schizophrenia, and evidence has accumulated that there might be a schizotypy–schizophrenia spectrum not only with regards to symptoms and clinical signs, but also common underlying biological factors (Raine, 2006; Hazlett et al., 2012; Nelson et al., 2013; Ettinger et al., 2014). Persons with high schizotypy show subtle deficits in range of cognitive and motor domains reminiscent of those seen (though more pronounced) in schizophrenia (Ettinger et al., 2015). Non-clinical samples with high expression of schizotypy, or even schizotypal personality disorder, in fact show some brain functional alterations: This includes, among others, cognitive deficits in basic visual processing such as visual backward masking (Cappe et al., 2012), as well as attention (Schmidt-Hansen and Honey, 2014), and working memory (Chun et al., 2013; Smith and Lenzenweger, 2013). Functional imaging studies also corroborate this spectrum model, showing activation changes in high schizotypy (non-clinical) subjects in tasks sensitive to dopaminergic modulation (Aichert et al., 2012; Ettinger et al., 2013), as well as a direct link between the disorganisation dimension of schizotypy and striatal dopamine D2/D3 receptors (Chen et al., 2012).

Schizotypal traits might also be related to variation in brain structure, a major putative biological marker of schizophrenia and common liability for psychosis. Beside an older study, which used a semi-quantitative morphometric method in 17 healthy subjects (Raine et al., 1992), there are two recent studies which have explored potential brain structural correlates of psychometric schizotypy or psychosis proneness in healthy subjects using voxel-based morphometry (VBM) methods. Ettinger et al. assessed schizotypy using the Rust Inventory of Schizotypal Cognitions (RISC) in 55 healthy volunteers applying a dimensional design, in which schizotypy scores were correlated with grey matter volume in a voxel-wise fashion (Ettinger et al., 2012); they found a negative correlation with RISC schizotypy scores in two clusters comprising the medial prefrontal/anterior cingulate/orbitofrontal cortices, and the left insula/middle and superior

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temporal cortices, but no positive correlations. In contrast, Modinos and colleagues used the CAPE questionnaire (Community Assessment of Psychic Experiences (Brenner et al., 2007; Konings et al., 2006; Verdoux et al., 2003)) to compare two groups with high vs. low attenuated positive psychotic experiences (Modinos et al., 2010). Rather than using a categorical design, they initially screened 600 students using the CAPE questionnaire before selecting the high vs. low scoring groups as extremes along the continuum in their screening sample; in their analysis, they found the high scoring positive symptoms group to have higher grey matter volume in posterior cingulate cortex and precuneus areas. An additional analysis found a positive correlation with CAPE positive factor scores in both regions. Hence, these two studies using current VBM methodology, identified medial and lateral prefrontal and anterior cingulate, as well as posterior cingulate and precuneus areas showing a relation to measures of attenuated positive symptoms. In addition, two most recent studies have identified brain structural effects in grey matter with reduced grey matter density in high schizotypy individuals (based on the SPQ) in the dorsolateral prefrontal and insular cortices (Wang et al., 2015), as well as reduced middle frontal grey and white matter, reduced inferior fronto-occipital fasciculus anisotropy, and greater fasciculus uncinatus asymmetry in high schizotypy (using SPQ) individuals (DeRosse et al., 2015).

In this study, we aimed to test hypotheses with a two-fold rationale: first to replicate previous findings, and secondly to expand on them by comparing results across two different inventories assessing schizotypy and psychosis proneness, respectively. More specifically, we tested the hypothesis that medial and lateral prefrontal areas, as well as posterior cingulate and precuneus regions show correlations with SPQ (Schizotypal Personality Questionnaire) and CAPE (Community Assessment of Psychic Experiences). These two inventories tap overlapping, but not identical phenotypic features that are present across a spectrum, including healthy non-clinical subjects, healthy subjects at risk, as well as schizotypal high-risk, schizotypal personality disorder, and schizophrenia patients. While the SPQ is one of the most widely used psychometric self-report measures of schizotypy (based on initial DSM-III-R criteria (Raine, 1991)), the CAPE is increasingly used also in screening of individuals at high-risk for developing psychosis, and thus a potentially useful tool for early detection of schizophrenia (Boonstra et al., 2009; Mossaheb et al., 2012). In order to assess similar positive and negative symptom dimensions (mirroring the dichotomy of symptoms in schizotypal personality disorder and schizophrenia), we focused on the positive and negative symptom factors, resp., derived from each of the two psychometric measures.

2. Methods

2.1. Subjects

We included 59 healthy subjects (29 female, 30 male; mean age 30.8 yrs, SD 10.0) in this study, who were recruited from the community and gave written informed consent to a study protocol approved by the local Ethics Committee of Jena University Medical School, and in accordance with the Declaration of Helsinki. We had excluded, for this analysis, four left-handed subjects, given that differing handedness might introduce additional variation in brain structure, and that this small subgroup did not permit subgroup analysis to fully address the issue of handedness.

All subjects were screened for absence of current or previous psychiatric disorders (including substance abuse or dependence), psychiatric or psychotherapeutic treatment, or a first-degree family history of psychotic disorders using a semi-structured interview. Further exclusion criteria for the study were: neurological conditions, major internal medical conditions, a history of traumatic brain injury/loss of consciousness, and intellectual disability/learning impairment (IQ < 80, as estimated by the MWT-B (Antretter et al., 2013; Lehrl, 2005), a German language inventory applied to estimate IQ, similar to the NART). The screening process included a semi-structured pre-screening, and after study inclusion, all subjects underwent a careful screening that included questions on personal psychiatric and general medical history, as well as the history of use of alcohol and illicit substances. Following the screening, subjects were scanned. We thus report only on healthy volunteers selected from the general population assessed for inclusion and exclusion criteria.

Subjects completed two inventories: first, the Schizotypal Personality Questionnaire—German version (SPQ-G), a validated German translation (Klein et al., 1997) of Raine's original inventory, originally based on DSM-III-R criteria for schizotypal personality (Raine, 1991); secondly, the Community Assessment of Psychic Experiences (CAPE), a self-report questionnaire assessing schizotypal traits and psychosis proneness (Konings et al., 2006). Both questionnaires, which the subjects completed around the time of scanning, deliver scales for positive and negative symptom dimensions. In the case of the SPQ-G, we chose to group the single items to positive vs. negative schizotypy scores, following the evaluation of the German version of the SPQ (Klein et al., 1997), and chose this over the initial three-factor solution proposed by Raine, because of conceptual comparability to the CAPE positive and negative symptom dimensions, and the similarity of the positive vs. negative dichotomy to the symptom structure in schizotypal personality disorder and schizophrenia. Thus, for analysis of SPQ-G data, we used the two-factor solution (positive vs. negative; or cognitive-perceptual vs. interpersonal) as derived from the SPQ-G validation studies (Klein et al., 1997, 2001), while for CAPE analysis, we used only the positive and negative symptom dimensions (but not the depressive symptom dimension, which has no similar match in the SPQ-G structure).

Subject scores for the SPQ-G positive schizotypy factor were: mean 6.90 (SD 4.551, range 0–21, kurtosis 0.931, skewness 1.058), for negative schizotypy factor: mean 3.80 (SD 3.934, range 1–22, kurtosis 7.156, skewness 2.264). For the CAPE, subjects scored on the positive dimension score with a mean of 24.53 (SD 3.505, range 20–36, kurtosis 1.468, skewness 1.199), and negative dimension score mean 23.98 (SD 6.216, range 15–44, kurtosis 0.731, skewness 0.902).

2.2. MRI acquisition and voxel-based morphometry (VBM) analysis

For all subjects, we obtained high-resolution T1-weighted MRI scans on a 3 Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) using a standard quadrature head coil and a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, a 9°, 192 contiguous sagittal slices, in-plane field of view 256 mm, voxel resolution 1 × 1 × 1 mm; acquisition time 5:21 min).

For voxel-based morphometry (VBM) analysis, we used the VBM8 protocol (Structural Brain Mapping group, Jena University Hospital, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm/vbm8) implemented as a toolbox in SPM8 (Statistical Parametric Mapping, Institute of Neurology, London, UK). This included an automated quality insurance protocol, which all scans (in addition to being checked visually for artefacts) passed.

All T1-weighted images were corrected for bias-field inhomogeneities, then spatially normalised and segmented into grey (GM), white matter (WM), and cerebrospinal fluid (CSF) within the same generative model (Ashburner and Friston, 2005). As described previously (Gaser, 2009), the segmentation procedure was further extended by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997), and using a hidden Markov Random Field model (Cuadra et al., 2005). For exclusion of artefacts on the grey–white-matter border (i.e. incorrect voxel classification), we applied an internal grey matter threshold of 0.2, which is more conservative than the usually applied 0.1 threshold.

For statistical comparison, we applied the general linear model (GLM) approach implemented in SPM8. We performed four analyses, using separate GLMs for each of the four parameters (SPQ-G positive and negative schizotypy score, respectively, and CAPE positive

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