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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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dimension and negative dimension scores, respectively), and included age and gender as nuisance variables in each of the four GLMs in order to remove variance related to these variables. Given the anatomical hypotheses for the precuneus and lateral and medial prefrontal cortex, as derived from the previous studies (including those on RISC, CAPE, and SPG-Q (Ettinger et al., 2012; Kuhn et al., 2012; Modinos et al., 2010)), we first performed all whole-brain analyses at a threshold of $p < 0.001$ (uncorr.), and then differentiated between areas included in the hypothesis and those outside of these areas (which would be reported as results on an exploratory basis).

3. Results

3.1. Brain structure and SPQ-G

For the positive schizotypy score derived from SPQ-G, we found significant positive correlations ($p < 0.001$, uncorr.) with grey matter in the left anterior cingulate cortex and a smaller right supplementary motor area (SMA) cluster, but no negative correlations (apart from a small three-voxel cluster outside the grey matter mask).

For the negative schizotypy score from the SPQ-G, we identified significant positive correlations with grey matter in the precuneus (right > left), left inferior parietal cortex, right superior frontal gyrus, right inferior frontal gyrus, right inferior temporal gyrus, and left inferior frontal cortex. Again, there was no significant negative correlation (apart from a small five-voxel cluster outside the grey matter mask). Of note, part of the right precuneus cluster (maximum intensity voxel 14;−75;37; $k = 14$) also remained significant after family-wise error (FWE) correction for multiple comparisons, both at cluster-level ($p = 0.033$) and peak-level ($p = 0.037$).

3.2. Brain structure and CAPE

There was a positive correlation of CAPE positive symptom dimension and grey matter in the left inferior frontal cortex, and a smaller cluster in the left inferior parietal cortex, but no negative correlations.

For CAPE negative symptom dimension, there was a significant positive correlation with grey matter in the left inferior parietal cortex, right SMA, left precuneus, and right inferior temporal gyrus.

Overviews of all findings are given for SPQ-G in Fig. 1, and CAPE in Fig. 2, respectively, as well as in Table 1.

4. Discussion

In this study, we tested the hypothesis that different degrees of trait schizotypy and psychosis proneness in a non-clinical cohort would be related to variation of brain grey matter. Our findings corroborate and extend previous studies, which have implicated medial and lateral prefrontal cortices, as well as the precuneus, and in particular with different contributions of positive vs. negative dimensions of schizotypy. Unlike cohorts used in high-risk research, our sample was a non-clinical community-based sample, and our approach was aimed at testing the hypothesis of correlations in the general population. Three aspects of our study deserve particular attention.

First, we link two previous studies on schizotypy and psychosis proneness (Modinos et al., 2010; Ettinger et al., 2012) providing—in one sample—a direct comparison of two different measures, which are derived from schizotypal personality criteria (SPQ) and early psychosis research (CAPE), respectively. In our analyses, the precuneus emerges as a finding significant for both questionnaires, and in both cases showing a positive correlation with the negative symptom (schizotypy) dimensions. For the SPQ analysis, the precuneus finding also survives conservative family-wise error (FWE) correction for multiple comparisons. A similar positive correlation of psychosis proneness with precuneus volume was also shown in one previous VBM study using CAPE (Modinos et al., 2010), while the other VBM study did not explicitly address negative schizotypy (applying the RISC questionnaire total score (Ettinger et al., 2012)), hence the precuneus association might be specifically linked to this particular aspect of negative (as opposed to positive or overall) schizotypy. It is unclear whether the lack of overlap between the positive SPQ and positive CAPE dimensions is due to differences captured by these inventories. The CAPE has also been developed to assess proneness to psychosis in the community, and has been applied also in early intervention settings for prodromal psychosis or high risk populations (Mossaheb et al., 2012). The inclusion of features indicative of psychosis-like traits or symptoms has been a matter of recent debate (Nelson et al., 2013). From our findings, it appears that differentiating positive from negative schizotypy might not only be important for conceptual or taxonomic reasons, but that

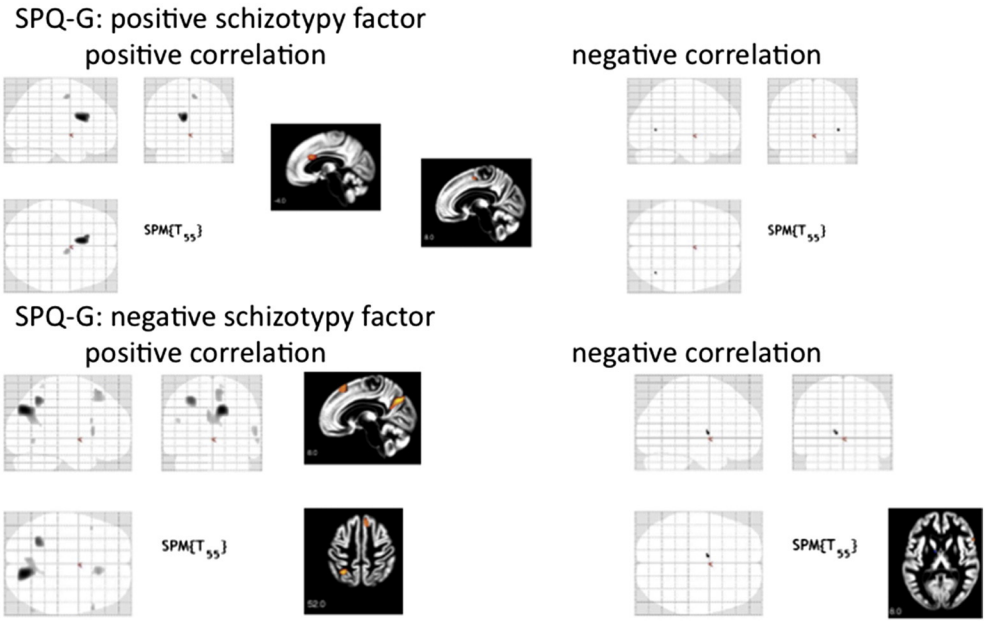

Fig. 1. VBM analysis of correlation between SPG-Q positive schizotypy scores (1a), and negative schizotypy scores (1b), with positive correlations on the left side, negative correlations on the right (all $p < 0.001$ uncorr.).

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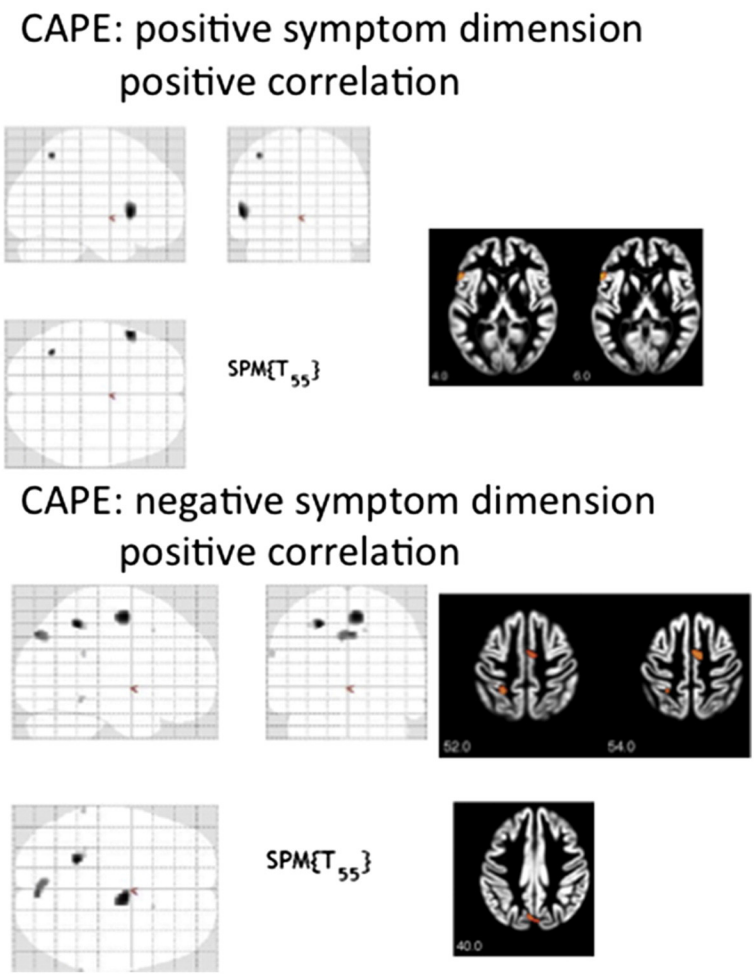

Fig. 2. VBM analysis of correlation between CAPE positive dimension scores (1a), and negative dimension scores (1b), with positive correlations on the left side, negative correlations on the right (all $p < 0.001$ uncorr.).

these two aspects of schizotypy are actually linked to different biological features. Correlation with total schizotypy might thus be at risk of failing to identify associations.

The role of the precuneus in schizophrenia has only recently become a focus of research, and it is yet unclear how this brain structure might link to negative symptoms. Brain structural imaging studies have shown an increase of precuneus grey matter in unaffected biological relatives of schizophrenia patients, who are at elevated risk of developing psychosis (Xiao et al., 2013). High-risk groups for schizophrenia also show altered precuneus activation during a working memory task, which is associated with the expression of negative symptoms (Falkenberg et al., 2015). In schizophrenia, aberrant precuneus activation has been shown during resting state (Mingoia et al., 2012; Guo et al., 2014; Wang et al., 2014). Yet, it is still far from being clear how altered precuneus structure or function relates to the pathophysiology of negative symptom dimensions.

The second major aspect of our study is the association of schizotypy with prefrontal regions. The lateral and prefrontal cortices have been of particular interest because of their role in schizophrenia, and associated morphometric changes (Xiao et al., 2013). Although in our study, both SPQ and CAPE positive dimensions showed some associations with prefrontal structures, these did not overlap anatomically, i.e. left anterior cingulate cortex vs. left inferior prefrontal cortex. Several factors, including lack of power to detect more subtle associations, might have contributed to this. A recent study on cortical thickness and schizotypy found a positive correlation of right dorsolateral prefrontal cortical thickness with higher loading on the positive factor of SPQ-G (Kuhn et al., 2012); the authors used the same German translation as we did in this study, yet cortical thickness does not always correlate well with grey matter density or volume detected in VBM studies (Hutton et al., 2009; Kong et al., 2015), so a direct comparison is difficult. Indeed, there seems to be more evidence for prefrontal changes in subclinical cohorts: a recent study on offspring of schizophrenia patients with high schizotypal features (a putative ultra-high risk group) actually did show an association of schizotypal traits with prefrontal brain structure (Diwadkar et al., 2006). It remains unclear whether other factors, such as genetic liability unrelated to schizotypy, might have mediated this association, thus making it specific to this study population. Overall, while our findings are within the anatomical hypothesis for the prefrontal cortex, they do not indicate an unequivocally strong effect, such as seen for the precuneus and negative schizotypy, hence calling for further replication.

Third, the direction of associations was a remarkably consistent feature within our study. All of our significant correlations, apart from a few very minor clusters, were observed when testing positive, but not negative correlations. This was consistent across both SPQ and CAPE measures, and both positive and negative symptom dimensions. In the two previous VBM studies mentioned, this appeared to be less consistent: in the study using CAPE, all categorical effects were found in the high > low schizotypy comparisons (but no higher grey matter values in low vs. high schizotypy subjects (Modinos et al., 2010)), whereas the study using RISC found negative correlations in the anterior cingulate/orbitofrontal regions (Ettinger et al., 2012).

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Table 1
Overview of co-ordinates and anatomical labels for correlation analysis of grey matter VBM ($p < 0.001$, uncorr.) with SPQ-G positive and negative schizotypy scores, and CAPE positive and negative symptom dimensions, respectively (only clusters with voxels $k > 10$ are mentioned).

Co-ordinates of maximum voxel	Anatomical region	k (number of voxels)
A) SPQ-G: positive correlations with positive schizotypy score		
−8; 18; 24	Left anterior cingulate cortex	463
9; −4; 54	Right supplementary motor area (SMA)	56
B) SPQ-G: positive correlations with negative schizotypy score		
14; −75; 37	Right precuneus [a]/cuneus	1195
−28; −55; 49	Left inferior parietal/superior parietal cortex	328
9; 27; 61	Right medial superior frontal gyrus/SMA	314
60; 20; 7	Right inferior lateral frontal cortex	69
62; −61; −3	Right inferior temporal gyrus	12
−46; 17; 24	Left inferior lateral frontal cortex	19
C) CAPE: positive correlations with positive symptom dimension		
−56; 20; 4	Left inferior lateral prefrontal cortex	216
−39; −55; 57	Left inferior parietal cortex	21
D) CAPE: positive correlations with negative symptom dimension		
−22; −46; 51	Left inferior parietal cortex	79
8; −7; 57	Right supplementary motor area (SMA)	264
3; −79; 42	Left precuneus	117
69; −42; −11	Right inferior temporal cortex	14

[a] Parts of this cluster (right cuneus) was also significant at $p < 0.05$, FWE correction (both peak-level and cluster-level).

Intuitively, this pattern might seem at odds with the continuum model of schizotypy and schizophrenia. Brain structural effects in schizophrenia are almost exclusively regional loss of volume, but not increase. In a linear association model, one would therefore rather expect negative correlations, with structural deficits in schizophrenia representing the extreme end of the distribution. However, the basic assumption of this model, a simple linear relationship, might be too simplicistic. There are at least two interpretations to reconcile these seemingly disparate associations. A first explanation is that the nature of correlations/associations as approached in our and similar other studies does not differentiate variations that are related to a (quasi-linear) continuum from "protective" variations, i.e. changes that might be present to a higher degree in low-schizotypy subjects. There is, however, little data on such brain structural variation mediating resilience to mental illness. However, a similar case has been made in imaging findings in schizotypal personality disorder where higher regional brain activity has been interpreted as a protective or compensatory change within the schizophrenia spectrum (Buchsbaum et al., 2002). A second, and possibly often neglected, reason might be that the relationship of the variables is not simply linear. With the emergence of clinical psychopathology (e.g. in schizotypal personality disorder or frank psychosis), additional factors might affect brain structural variation in a particular region. Also, the schizotypy factor per se (positive or negative), when studied across the entire continuum, might show non-linear relations, for example an inverted U shape. Hence, across a phenotypic continuum, which spans from healthy controls with little schizotypal features, over those with high schizotypal features, to patients with schizotypal personality disorder, and finally those with schizophrenia, the relationship/associations in the first two might be linear, but when shifting to the two latter groups, the volumes of a given structure might get smaller again with increasing/additional disease burden. For example, disease-related factors in clinical populations might interact with the factor described by increasing loading of schizotypy. Hence, assessing associations only within a part of the spectrum (i.e. healthy subjects with varying degrees of schizotypy) might only capture the rising flank of the characteristic 'inverted U curve' and thus show significant linear correlations, but this might not hold for a study including clinical samples. The model of an inverted U shape function has previously been proposed to explain non-linear effects, for example related to dopaminergic effects in schizotypy (Mohr et al., 2004).

Both models (compensatory changes and inverted U shape association) would be consistent with a recent meta-analysis of morphometry studies of unaffected relatives of schizophrenia patients, i.e. subjects whose increased genetic liability is often accompanied with attenuated symptoms (incl. increased schizotypy): this meta-analysis found unaffected relatives of schizophrenia (as compared to a healthy control group) to show larger right precuneus volume, while the schizophrenia patients (compared to healthy controls) show smaller right precuneus volume (Xiao et al., 2013); however, the overall overlap between unaffected relatives and patients was rather small, indicating that only few of the regional changes in schizophrenia might show (linear) spectrum characteristics.

There are now several studies at the other end of this putative spectrum, i.e. in clinical populations including schizotypal personality disorder (SzPD) and schizophrenia. Taken together, these studies also suggest that different cortical areas might follow different patterns of abnormalities, including "severity-abnormalities" (i.e. higher structural effects in schizophrenia than schizotypal personality disorder than healthy controls, resembling a linear model), as well as "compensation-abnormalities", where schizotypal personality disorder patients show higher volumes that controls or schizophrenia patients, resembling protective or compensatory factors (Hazlett et al., 2012). However, most findings of abnormalities obtained in schizotypal personality disorder are seen in prefrontal and superior temporal cortical regions (Hazlett et al., 2008, 2014), and little is known about structural effects in the precuneus or adjacent parietal regions (Zhou et al., 2007). There are, to the best of our knowledge, no studies comparing the continuum of schizotypal traits in healthy volunteers with schizotypal personality disorder patients, which would enable direct testing of this part of the continuum hypothesis.

Another aspect to be considered in our study, as well as the other imaging studies on schizotypal traits, is the use of different factor solutions. As outlined above, we grouped SPQ-G items according to a two-factor solution derived from validation studies in several non-clinical samples (Klein et al., 1997, 2001). While this mirrors some of the earlier studies by Raine and colleagues (Raine, 1992), there have also been studies in favour of a three factor solution, separating cognitive-perceptual, interpersonal, and disorganised aspects of schizotypal personality (Raine et al., 1994). While the CAPE also captures schizotypal traits, it is not derived from the initial delineation of schizotypal personality disorder criteria as the SPQ (or SPQ-G, resp.); yet, the parallel use of

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positive vs. negative feature delineation allows similar analyses in our study, even though the single items of the SPQ-G vs. CAPE diverge and thus do not capture identical constructs. The latter aspect might also be a major reason for the difference in VBM results between these two questionnaires.

We need to consider several limitations of this study. First, our sample size, although similar to previous studies, might have been too moderate in size to capture more subtle associations. This might be particularly the case for prefrontal areas. Although we used two different inventories, these both rely on self-rating and thus might not capture important aspects of schizotypy such as abnormalities in affect or language, which are better detected by a rater or clinician. Also, our exclusion of subjects with a first-degree family history of psychosis might have limited the sample to a subset of healthy subjects; yet one might argue that this approach is less prone to mixing phenotypic characterisation with putative genetic risk. Finally, it is unclear whether the associations between schizotypy and brain structure might change over time. Although most of these traits might be stable as phenotypes, it is not known whether age-related changes might obscure (or facilitate) detection of brain-phenotype correlations.

In conclusion, our findings confirm a positive correlation between negative schizotypy and the (right) precuneus in healthy, non-clinical subjects. Positive schizotypy might be associated with prefrontal areas in the anterior cingulate and inferior lateral prefrontal cortex, although the anatomical divergence across the two inventories used remains unclear. Overall, our findings are consistent with a continuum model of schizotypy and psychosis and its underlying brain structural variation.

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The authors declare that the funding institutions had no influence on the analyses carried out and presented here.

Contributors

I.N. and C.G. designed the study.

I.N., K.L., M.D., St.S., and H.S. contributed to patient recruitment and scanning.

I.N., C.L., K.L., M.D., N.S., St.S., and C.G contributed to data collection, processing, and pre-processing.

I.N., C.L., L.F., and C.G. contributed to implementation of the image processing pipeline, imaging data analysis, and interpretation.

I.N. wrote the first drafts of the manuscript and all authors commented on/approved the final version.

Conflicts of interest

The authors declare no conflicts of interest other than the funding received for carrying out this research.

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