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Research report

Identifying grey matter changes in schizotypy using partial least squares correlation

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ABSTRACT

Neuroimaging research into the brain structure of schizophrenia patients has shown consistent reductions in grey matter volume relative to healthy controls. Examining structural differences in individuals with high levels of schizotypy may help elucidate the course of disorder progression, and provide further support for the schizotypy-schizophrenia continuum. Thus far, the few studies investigating grey matter differences in schizotypy have produced inconsistent results. In the current study, we used a multivariate partial least squares (PLS) approach to clarify the relationship between psychometric schizotypy (measured by the Oxford-Liverpool Inventory of Feelings and Experiences) and grey matter volume in 49 healthy adults. We found a negative association between all schizotypy dimensions and grey matter volume in the frontal and temporal lobes, as well as the insula. We also found a positive association between all schizotypy dimensions and grey matter volume in the parietal and temporal lobes, and in subcortical regions. Further correlational analyses revealed that positive and disorganised schizotypy were strongly associated with key regions (left superior temporal gyrus and insula) most consistently reported to be affected in schizophrenia and schizotypy. We also compared PLS with the typically used General Linear Model (GLM) and demonstrate that PLS can be reliably used as an extension to voxel-based morphometry (VBM) data. This may be particularly valuable for schizotypy research due to PLS' ability to detect small, but reliable effects.

Together, the findings indicate that healthy schizotypal individuals exhibit structural changes in regions associated with schizophrenia. This adds to the evidence of an overlap of phenotypic expression between schizotypy and schizophrenia, and may help establish biological endophenotypes for the disorder.

Abbreviations: GM, grey matter; O-LIFE, Oxford-Liverpool Inventory of Feelings and Experiences; UnEx, Unusual Experiences; CogDis, Cognitive Disorganisation; IntAn, Introvertive Anhedonia; ImpNon, Impulsive Nonconformity; SPQ, Schizotypal Personality Questionnaire; VBM, voxel-based morphometry; GLM, general linear model; PLS, partial least squares; BSR, bootstrap ratio; LV, latent variable.

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1. Introduction

Schizophrenia is a psychiatric disorder characterised by disturbances in cognition such as memory deficits, hallucinations, bizarre beliefs and behaviours, and impaired executive function (e.g., Danion, Rizzo, & Bruant, 1999; Engh et al., 2010; Hoffman, Rapaport, Mazure, & Quinlan, 1999, for a review see; Barch & Ceaser, 2012). Such behavioural symptoms may be broadly categorised into three factors: positive, which includes delusional thoughts and unusual perceptual experiences; negative, which describes social and physical anhedonia and introversion; and disorganised, which may lead to decreased sensory-motor functions and inappropriate affect (Basso, Nasrallah, Olson, & Bornstein, 1998; Cuesta, Ugarte, Goicoa, Eraso, & Peralta, 2007). Studies suggest that these symptoms may partly be linked to subtle differences in brain structure (Chua & McKenna, 1995; Gaser, Nenadic, Volz, Büchel, & Sauer, 2004; Salgado-Pineda et al., 2011). These structural alterations occur in both first-episode and chronic schizophrenia patients (e.g., Kubicki et al., 2002; Olabi et al., 2011; Wright et al., 1999) and include reduced whole brain volume, reduced total grey matter volume, and local GM volume reductions mainly in frontal lobe gyri, cingulate cortex, insula, thalamus, postcentral gyrus, and medial temporal areas (Shepherd, Laurens, Matheson, Carr, & Green, 2012). There also seems to be a relationship between the degree of GM structural changes and illness duration, with chronic patients mostly showing a more widespread and severe pattern of reductions compared to first-episode patients (Whitford et al., 2006; for a review see; Hulshoff Pol & Kahn, 2008). However, this association is not strictly linear due to the confounding effects of pharmacological treatment, where antipsychotic medication may have either attenuating (Van Haren et al., 2007) or exacerbating (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011) effects that contribute to GM reductions within schizophrenia patients.

Interestingly, volumetric alterations have also been found in schizotypy, a cluster of personality traits that are thought to represent non-clinical, schizophrenia-like traits on a continuum in the general population, with psychosis and clinical illness at the extreme end (Claridge, 1997). This suggests that the cortical abnormalities observed in schizophrenia exist on a dimensional continuum across the schizophrenia spectrum, and may already be present prior to the onset of psychopathology (Ettinger et al., 2012). Schizotypy is usually measured by using self-reported psychometric tests such as the Schizotypal Personality Questionnaire (SPQ: Raine, 1991) and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE: Mason, Claridge, & Jackson, 1995), and is generally organised into a three- or four-factor structure (positive, negative, disorganised, and impulsive) similar to schizophrenia (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). Behavioural, electrophysiological, and functional imaging studies have examined the role of schizotypy in cognition, perception, and motor control, with the majority finding subtle, yet significant, deficits in individuals with high levels of schizotypy compared to those who score low on the measures (e.g., Aichert, Williams, Möller, Kumari, & Ettinger, 2011; Kumari, Antonova, & Geyer, 2008; for a review see; Ettinger et al., 2014).

Although these psychologically healthy individuals present an opportunity to investigate the aetiology of schizophrenia and other related disorders, there are currently only a small number of studies examining the neuroanatomical correlates of schizotypy (for reviews see Modenato & Draganski, 2015; Nelson, Seal, Pantelis, & Phillips, 2013). These include an early study by Raine, Sheard, Reynolds, and Lencz (1992), who found a negative correlation between schizotypy scores and left prefrontal structures, leading the authors to suggest that schizotypal personality is associated with structural deficits that are already evident in nonclinical populations. More recent studies are in line with this, with highly schizotypal individuals showing a decrease in total and local GM volumes in the frontal and temporal lobes, local volume decreases in the insula, and volume increases in the parietal lobe and the cerebellum (DeRosse et al., 2014; Ettinger et al., 2012; Kühn, Schubert, & Gallinat, 2012; Modinos et al., 2009; Nenadic et al., 2015; Wang et al., 2014). An overview of these studies is provided in Table 1.

Despite these recent findings of an association between GM volume and schizotypy, there is considerable variability regarding both the directionality of volume changes and which brain structures are affected. Possible reasons for such differences include: the usage of different schizotypy scales (where some are specifically designed to assess clinical characteristics, such as the SPQ, while others measure general personality traits, such as the RISC and the O-LIFE); dichotomisation of schizotypy into high- and low-scoring groups, which may distort the results by ignoring potentially interesting contributions of medium schizotypy scores (MacCallum, Zhang, Preacher, & Rucker, 2002); and focusing on different schizotypy dimensions (e.g., positive *vs* negative). For instance, the only differences reported by more than one study so far are volume decreases in the left insula (Ettinger et al., 2012; Wang et al., 2014) and volume increases in the right precuneus (Modinos et al., 2009; Nenadic et al., 2015); however, these volume changes have been associated with different dimensions of schizotypy in the different studies. This leaves open the question whether the different schizotypy dimensions have distinct profiles of GM volume changes – similar to symptoms of schizophrenia, where positive symptoms, for instance, have been associated with specific structural changes in language and auditory perception regions (Hirayasu et al., 1998; Steinmann, Leicht, & Mulert, 2014).

In summary, there seems to be an association between brain structure and schizotypy; however, this evidence is not yet conclusive. As such, the main objective of this study was to clarify the effect of nonclinical schizotypy on GM structure in young, healthy individuals, paying particular attention to the different schizotypy dimensions, and to further contribute to the evidence for a continuous relationship regarding brain structures in schizotypy and schizophrenia.

To this end, we extended voxel-based morphometry (VBM) processing with a partial least squares (PLS) correlational approach. This is in contrast to the previous studies examining brain structure in schizotypy that have mostly employed the mass-univariate general linear model (GLM) that is typically used as second-level statistical approach in VBM analyses. Aside from the assumptions that have to be met, mass-univariate tests increase the probability of false positive