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Review article

Neuroimaging findings in schizotypal personality disorder: A systematic review

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ABSTRACT

Background: Schizotypal personality disorder is the prototypical schizophrenia-spectrum condition, sharing similar phenomenological, cognitive, genetic, physiological, neurochemical, neuroanatomical and neurofunctional abnormalities with schizophrenia. Investigations into SPD circumvent many confounds inherent to schizophrenia such as medication and institutionalization. Hence, SPD offers a unique vantage point from which to study schizophrenia-spectrum conditions.
Methods: We systematically reviewed the neuroimaging literature in SPD to establish: (1) whether there are concordant findings in SPD and schizophrenia, possibly reflective of core pathology between the two conditions and (2) whether there are discordant findings in SPD and schizophrenia, possibly reflecting protective factors in the former. The findings are synthesized across structural and functional neuroimaging domains.
Results: A total of 54 studies were identified. Medial temporal lobe structures seem to be compromised in both SPD and schizophrenia. In schizophrenia prefrontal structures are further compromised, whereas in SPD these seem to be larger-than-normal, possibly reflecting a compensatory mechanism. Additional pathology is discussed, including evidence of aberrant subcortical dopaminergic functioning.
Conclusions: SPD is a schizophrenia-spectrum condition that shares pathology with schizophrenia, but is distinct in showing unique neural findings. Future studies are needed to confirm and localize regions of common and disparate pathology between SPD and schizophrenia.

Contents

1. Introduction

In studying the biological relatives of schizophrenia, one often finds a high rate of schizophrenia-spectrum disorders, including schizotypal personality disorder (SPD) (Kendler et al., 1981; Kety et al., 1968). SPD is conceptualized as a "milder" form of chronic schizophrenia, carrying similar phenomenological, cognitive, genetic, physiological, neurochemical, neuroanatomical and neurofunctional abnormalities, albeit to a lesser extent, than that seen in schizophrenia per se (Siever

Abbreviations: CT, Computer Tomography; DSM, Diagnostic and Statistical Manual for Mental Disorders; DTI, Diffusion Tensor Imaging; fMRI, functional Magnetic Resonance Imaging; ICD, International Classification of Diseases; IBZM, [^{123}I]iodobenzamide; MRI, Magnetic Resonance Imaging; MRS, Magnetic Resonance Spectroscopy; MTL, Medial Temporal Lobe; PET, Positron Emission Tomography; ROI, Region-of-interest; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SPD, Schizotypal Personality Disorder; SPECT, Single Photon Emission Computed Tomography.

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and Davis, 2004). The study of SPD offers a unique vantage point to studying the core processes of schizophrenia without the common confounds that are inherent to schizophrenia, such as medication use, institutionalization, poor psychosocial functioning, as well as factors secondary to frank psychosis. Furthermore, given the phenomenological overlap between SPD and schizophrenia and the lack of psychosis in the former, studying SPD may uncover neuroprotective factors (Siever and Davis, 2004).

Previous reviews of neuroimaging findings in SPD have either focused only on structural morphometric findings (Dickey et al., 2002a; Hazlett et al., 2012), or were published over six years ago (Raine, 2006; Siever and Davis, 2004) and the number of studies have doubled since then. Hence, we set out to systematically review the cross-sectional neuroimaging findings in SPD. We set out to establish whether: (a) there is evidence for a core abnormality in SPD and schizophrenia as revealed by similar anomalous neuroimaging findings and (b) neuroprotective factors, as revealed by dissimilar findings with schizophrenia, can be identified in SPD through the lens of neuroimaging.

2. Methods

2.1. Study selection

A systematic computerized literature search of PubMed was conducted in March 2012. The following search strategy was used: ((schizotyp* OR Cluster A) AND (neuroimaging OR CT OR computed tomography OR magnetic resonance OR mri OR fmri OR PET OR positron emission tomography OR SPECT OR single photon computed emission tomography OR single photon emission tomography OR MRS OR magnetic resonance spectroscopy OR DTI OR diffusion tensor imaging)). No time span was specified for date of publication. Furthermore, the bibliographies of the identified studies and previous reviews (Dickey et al., 2002a; Hazlett et al., 2012; Raine, 2006; Siever and Davis, 2004) were manually searched for additional studies not identified in the computerized search.

2.2. Selection criteria

Studies were included according to the following criteria: (a) published in a peer-reviewed journal, (b) written in English, (c) enrolled subjects with diagnosed SPD as per the Diagnostic and Statistical Manual for Mental Disorders (DSM) or the International Classification of Diseases (ICD) as well as a matched healthy comparison group not meeting criteria for a major mental disorder, (d) data reported specifically for the SPD group versus control group. Studies published only as abstracts were not included. It should be noted that ICD does not contain a diagnostic category of SPD, rather it includes schizotypal disorder. Schizotypal disorder, as per ICD criterion, differs from DSM-based SPD, such that ICD allows for schizotypal disorder to include transient quasi-psychotic episodes. However, the schizotypal disorder diagnostic category includes SPD and thus will be included as such in this review.

2.3. Statistical analysis and reporting

Although a meta-analysis of all neuroimaging findings, stratified by imaging modality, was planned, the employment of different region-of-interest (ROI) analyses across studies rather than voxel-wise analyses precluded such quantitative analysis. Hence, we present a qualitative synthesis of findings stratified by imaging modality and make suggestions for future research. Furthermore, we focus on reporting positive findings, or trends toward statistical significance, between diagnostic groups. We deemphasized negative findings, as these may reflect analyses that simply lacked statistical power and indeed, no study reported power calculations for negative results. To enhance the quality of reporting in the present systematic review, we followed standardized guidelines (Moher et al., 2009).

3. Results

3.1. Identified studies

A total of 54 studies described in 49 publications (2 included both MRI/fMRI (Dickey et al., 2008, 2010) and 3 included both MRI/PET (Hazlett et al., 1999; Haznedar et al., 2004; Shihabuddin et al., 2001)) met inclusion criteria. The studies include a total non-independent sample of 1181 SPD and 21,055 healthy control subjects. It should be noted that there is substantial overlap of SPD samples across studies and a conservative estimate of the number of independent SPD subjects studied may be in the range of 300–400. A flowchart illustrating the study selection strategy is detailed in Fig. 1. In reviewing the neuroimaging studies, an attempt was made to focus on frontal, temporal and striatal regions, as these regions are most robustly affected in schizophrenia.

3.2. Structural neuroimaging

The first neuroimaging study in schizophrenia employed computerized tomography (CT) and showed enlarged ventricles in the schizophrenia sample relative to the healthy comparison group (Johnstone et al., 1976). The CT findings in SPD have been mixed, with conflicting findings regarding ventricle volume and ratio with the whole brain (summarized in Table 1). These preliminary studies suggested there may be a signal for some brain-based structural abnormality in SPD, but the resolution of CT did not permit quantification of cortical or subcortical structures. The advent of magnetic resonance imaging (MRI) truly revolutionized the field of structural neuroimaging, and has made inroads in elucidating neural abnormalities in SPD.

Meta-analyses of MRI studies in schizophrenia proper show a widespread reduction in gray matter volume across frontotemporal and subcortical regions (Ellison-Wright et al., 2008; Glahn et al., 2008). MRI studies in SPD are summarized in Table 2. These studies have

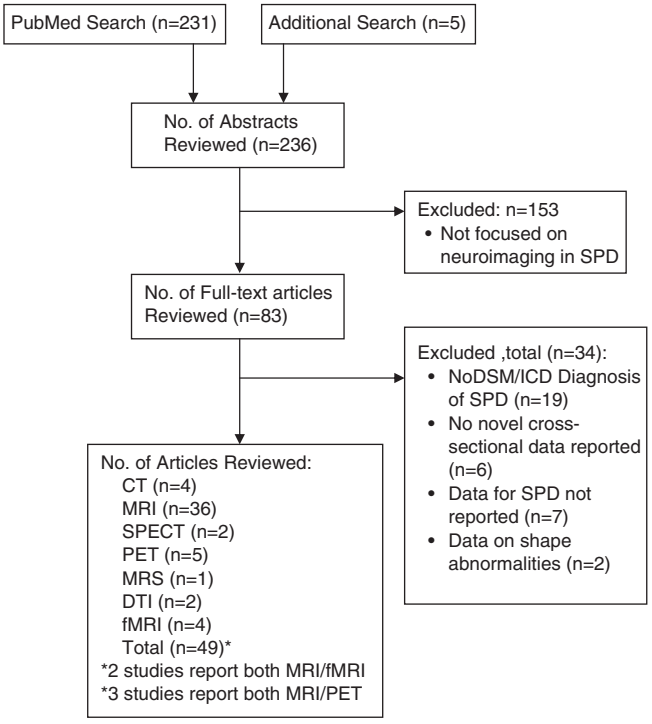

Fig. 1. Flowchart illustrating the literature search and exclusion process (PRISMA diagram).