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Short communication

# Neural substrates of a schizotypal spectrum in typically-developing children: Further evidence of a normal-pathological continuum

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## HIGHLIGHTS

- 28 health children were administered a 3T MRI scan, and parents completed a new measure of the psychosis spectrum/schizotypy (The PSI-C).
- Similar neural structures implicated in psychotic disorders were associated with psychosis-spectrum behavior in healthy children.
- Caudate, amygdala, hippocampal, and middle temporal gyrus volumes were associated with all subscales of the PSI-C.
- Results indicated a sexually-dimorphic pattern of brain-behavior links that are consistent with findings from the schizophrenia literature.

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## ABSTRACT

Schizophrenia represents the extreme end of a distribution of traits that extends well into the general population. Using a recently developed measure of psychotic-like traits in children, we examined the neural substrates of psychotic (and other psychiatric) symptoms using structural magnetic resonance imaging (MRI). Twenty-eight typically-developing children (14 males) between the ages of 6–17 years underwent a 3 T MRI scan. Parents completed the Psychiatric and Schizotypal Inventory for Children. Results revealed that caudate, amygdala, hippocampal and middle temporal gyrus volumes were associated with quantitative dimensions of psychiatric traits. Furthermore, results suggest a differential a sexually-dimorphic pattern of brain-schizotypy associations. These findings highlight brain-behavior continuities between clinical conditions such as schizophrenia and normal trait variation in typical development.



## 1. Introduction

Schizophrenia is a severe neuropsychiatric condition characterized by unusual sensory/perceptual experiences (hallucinations, delusions), cognitive and linguistic disorganization, odd behavior, social withdrawal, and mood disturbance (DSM-5; [2]). Recent advances in psychiatry recognize that neurodevelopmental (NDD) and neuropsychiatric disorders (NPD) reflect quantitative, dimensional traits that are distributed throughout the general population [7]. Indeed, it has been demonstrated that the schizophrenia phenotype may be represented along a normal-pathological continuum [20,33]. Even severe symptoms such as hallucinations and delusions are relatively common in the general population [20] with prevalence rates of hallucinations ranging from 10% [53] to over 70% [40,56]. Forty-three percent of respondents who were not under psychiatric care reported at least some auditory hallucinations [44]. The presence of many key symptoms of schizophrenia, therefore, do not always indicate psychiatric morbidity, but rather, reflect the broad spectrum of human experiences [20,27].

Schizotypy refers to multiple personality dimensions that represents an endophenotype along the psychosis continuum. Schizotypy is found in the general population [27], and includes unusual sensory/perceptual experiences, magical thinking, cognitive disorganization, social anxiety, and withdrawal [43]. Along the

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schizotypal personality dimension, those at the higher end are at increased risk of schizophrenia [4].

The psychosis continuum may extend beyond the behavioral manifestations of the phenotype; common neural substrates appear to underlie severe, prodromal, and mild symptom expression [33]. For example, similar neural structural and functional variations have been observed in unaffected family members of clinically-affected probands with psychotic disorders [9]. Establishing brain-behavior links in both clinically-significant behaviors and those that occur as part of typical development is a particularly important step in understanding the continuities and discontinuities that exist between normal and pathological behavior.

A range of brain atypicalities, including enlarged ventricle volumes [10] and compromised white matter structure [23], have been noted in schizophrenia. However, findings of grey matter (GM) abnormalities are reported most consistently in the schizophrenia literature. A recent meta-review has implicated GM abnormalities in schizophrenia with remarkable reliability [48]. Findings from 32 systematic reviews confirm high consistency across studies, pointing to GM reductions of the anterior cingulate cortex, middle and superior temporal gyri, various frontal regions, amygdala, hippocampus, thalamus, and insula [29].

Some of these GM abnormalities are independent of severity, chronicity, and medication status, and may constitute an endophenotype for schizophrenia [41,54]. Indeed, several recent meta-analytic and empirical studies have confirmed that individuals who are at risk, or exhibit only mild, sub-clinical psychotic-like behavior show similar GM volume reductions as do patients with schizophrenia. These findings were observed in siblings of individuals with schizophrenia [5,8,32,38]; "at-risk" individuals who show subthreshold psychotic symptoms [39,57]; and individuals with schizotypal personality disorder [13,18].

Although findings confirm that GM abnormalities are detectable before the onset of schizophrenia, the functional significance of these GM abnormalities is not well characterized. In individuals with schizophrenia, reduced GM volume in the temporal lobes has been linked to positive symptoms such as hallucinations and delusions [35–37,50], whereas GM reduction in the frontal regions has been associated with negative symptoms (e.g., withdrawal) [37,45,58]. Overall, schizotypal symptoms have been linked to similar GM abnormalities (for a comprehensive overview please see [15], and [30]).

To date, only four neuroimaging studies have examined schizotypal and other psychosis-spectrum symptoms in healthy individuals, and these have yielded inconsistent results. One study [12] reports that adults who scored high (above the median) on the Schizotypal Personality Questionnaire (SPQ; [42]) had less GM volume and cortical thickness in the frontal lobes (rostral middle frontal gyrus) and less GM and cortical thickness in the temporal lobes, relative to those scoring low (below the median) in schizotypy. Similarly, Ettinger et al. [14] report that adults' scores on the Rust Inventory of Schizotypal Cognitions [46] were negatively associated with GM volume in the medial prefrontal area including the superior and orbital medial frontal gyri, the anterior cingulum, and the insula, middle and superior temporal cortex. In contrast, others [31,34] report positive associations between psychotic and schizotypal symptoms and GM volume. For example, when comparing the highest (N = 38) and lowest (N = 38) subjects on a measure of positive psychotic symptoms, that the high-scoring group had greater GM volumes in the medial posterior cingulate cortex and the precuneus. These psychotic symptoms were linearly (positively) correlated with GM in the cingulum and precuneus. Nenadic et al. [34] reported positive correlations between dimensions of the schizotypal and psychotic symptoms (using Schizotypal Personality Questionnaire and the Community Assessment of Psychic Experiences) and GM volumes, in the inferior frontal cortices (bilateral), right superior frontal, right supplementary motor area (SMA), and the left inferior parietal cortex. After correcting for multiple comparisons, however, the only positive association remaining was between the negative schizotypy symptoms and the right precuneus.

In summary, previous work has identified a behavioral continuum of psychotic and schizotypal traits that span from typically functioning healthy individuals, to those exhibiting prodromal psychotic states, up to fully-developed schizophrenia. Recent work suggests this continuum may extend to the neuroanatomic level, as manifested in GM abnormalities. However, the directionality of the associations between psychotic and schizotypal dimensions and GM volumes in healthy individuals have thus far been inconsistent, with some [14,12] reporting negative associations between GM volumes and schizotypy scores in healthy adults, while others [31,34] report positive associations. Two of these previous studies have dichotomized the construct, by examining the median split or extreme groups of the schizotypal continuum. Furthermore, these studies have been limited to adults and have combined male and female participants, despite known age and sex differences in brain morphology and psychosis risk. Finally, although schizotypy is a multidimensional construct [27], previous studies have treated it largely as unitary construct, focusing only on the overall scores, thereby potentially obscuring differential patterns of relationships between different trait dimensions and particular brain substrates. The aim of our study was to examine the relationship between dimensions of psychotic and schizotypal behavior and brain structures in typically developing children. Indeed, this is the first study of its kind to examine brain-behavior links in the psychosis/schizotypy continuum in healthy children using a dimensional measure designed for children.

Here we examine normal variations in GM content in a cohort of typically-developing children. We focus on structures that have been consistently implicated in fully developed schizophrenia and studies that have explored relationship between schizotypy in healthy and at risk individuals. We relate the volumetric indices of these structures to a continuously distributed measure of cognitive, sensory-perceptual, emotional, social, and behaviour functioning in typical children, using a recently developed measure of the schizotypy/psychosis continuum normed on a nationally-representative sample. We also explore gender-specific patterns of these brain-behaviour links.

## 2. Methods

### 2.1. Subjects

Twenty-eight children (14 males, 14 females) ranging in age from 6 to 17 years, participated in this study. Families were recruited from a rural, demographically stable community in central Pennsylvania. All families were screened for the presence of psychological and psychiatric illnesses in first-degree relatives. Children were within the normal range of intellectual functioning (See Table 1).

### 2.2. Measures

The Psychiatric and Schizotypal Inventory for Children (PSI-C; [16] Evans et al. under review) is a 43-item parent-report measure that assesses a wide range of psychotic traits as they manifest in typical children. This measure was adapted from the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; [27]), widely-used measure of schizotypal and psychotic features as they manifest in typical adults and adolescents. The PSI-C was normed on a demographically representative United States sample