



## Subcortical surface shape in youth at familial high risk for schizophrenia



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### A B S T R A C T

Abnormalities in the subcortical brain regions that support cognitive functions have been reported in schizophrenia. Relatives of those with schizophrenia often present with psychosis-like traits (schizotypy) and similar cognition as those with schizophrenia. To evaluate the relationships between subcortical structure, schizotypy, and cognitive function, we assessed shape and volume of the hippocampus, amygdala and thalamus in untreated youth at familial high risk for schizophrenia (HRSZ). The sample consisted of 66 HRSZ and 69 age-matched healthy controls (HC). Subjects' cognitive functions and schizotypy were assessed, and T1-weighted brain MRI were analyzed using the FSL software FIRST. The right hippocampus and right amygdala showed significantly increased concavity (inward displacement) in HRSZ compared to HC. While regional subcortical shape displacements were significantly correlated with sustained attention and executive function scores in HC, fewer correlations were seen in HRSZ. This suggests a possible alteration of the local structure-function relationship in subcortical brain regions of HRSZ for these cognitive domains, which could be related to anomalous plasticity.

### 1. Introduction

Schizophrenia is an incapacitating disorder: the effects of cognitive deficits (e.g. impaired attention, memory), positive symptoms (e.g. delusions, hallucinations), and negative symptoms (e.g. social withdrawal) (Keshavan et al., 2011) may lead to severe functional disability. First-degree relatives of individuals with schizophrenia, including offspring, dizygotic twins and full siblings, are at familial high risk for developing schizophrenia (HRSZ) and have about a 10% chance of developing the disorder (Gottesman, 1991). Schizotypy refers to traits, such as magical ideation and perceptual aberration, which may reflect psychosis proneness and may be present in HRSZ. We (Tandon et al., 2012a) and others (Kwapil et al., 2008) have shown that schizotypal features may be a good predictor of transition to psychosis. High schizotypy potentially identifies clinical high risk within the HRSZ group, as suggested by an association between schizotypy and working memory deficits and higher perseverative errors (Diwadkar et al., 2006). Additionally, it has been shown that HRSZ are impaired in

cognitive functions such as sustained attention, executive functioning and verbal memory (Diwadkar et al., 2011; Keshavan et al., 2010; Seidman et al., 2006; Sitskoorn et al., 2004; Snitz et al., 2006).

It is of importance to investigate the neurobiology of HRSZ, because detailed knowledge of neural abnormalities can help guide more efficient preventative care (Correll et al., 2010; Tandon et al., 2012b). Studying HRSZ during youth is opportune for analyzing aspects of premorbidty given that the peak age of schizophrenia conversion is in late adolescence and early adulthood. In the brain of youth, regional synaptic underdevelopment or excessive pruning due to genetic, epigenetic or environmental factors, or pathophysiological factors such as inflammation, may result in regional structural deficits. Brain structures are not uniform, and specific structural alterations in individual subregions within the hippocampus, amygdala and thalamus may lead to deficits in brain networks that support specific cognitive function. Several groups have investigated structural anomalies in subcortical regions known to support cognition (Buchmann et al., 2014; Mathew et al., 2014; Rahm et al., 2015).

**Abbreviations:** HRSZ, familial high risk for schizophrenia; HC, healthy controls; FIRST, FMRIB's Integrated Registration and Segmentation Tool; CHR, clinical high risk for schizophrenia; SCID, Structured Clinical Interview for DSM-IV Disorders; SD, standard deviation; CPT, Continuous Performance Test; CPT-IP, Continuous Performance Test – identical pairs version; WCST, Wisconsin Card Sort Task; CVLT, California Verbal Learning Test; SPGR, spoiled gradient recall acquisition; MNI, Montreal Neurological Institute; ICV, intracranial volume; CA, Cornu Ammonis; DS-CPT, Degraded Stimulus CPT

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The hippocampus, amygdala and thalamus have been shown to be both structurally and functionally abnormal in patients with schizophrenia as well as in non-psychotic relatives (Bois et al., 2014; Buchmann et al., 2014). Several studies have shown that HRSZ have cognitive impairments related to the hippocampus, such as sustained attention, verbal memory and executive functioning (Keshavan et al., 2010). It has been reported that patients with schizophrenia show bilateral hippocampal volume reductions associated with deficits in cognitive function and verbal declarative memory (Mathew et al., 2014). An association of bilateral hippocampal volume reductions with decreased verbal memory scores has been shown in HRSZ as well (Francis et al., 2013). Reduced amygdala volumes were found in schizophrenia patients and their relatives (Li et al., 2015; van Erp et al., 2016; Seidman et al., 1999). In schizophrenia, stereotyped thinking was associated with right amygdala volume reduction (Rahm et al., 2015). Additionally, subregions of the amygdala support facial emotion processing, which has been shown to be deficient in HRSZ and those with schizophrenia. (Liu et al., 2014; Allott et al., 2015; Leszczyńska, 2015). Reduced bilateral thalamic volumes have been shown in schizophrenia probands (Li et al., 2015; van Erp et al., 2016) and their relatives (Seidman et al., 1999). Magnetic resonance spectroscopy findings in the thalamus of HRSZ suggest metabolic as well as structural/functional anomalies that are potentially related to altered synaptic plasticity (Tandon et al., 2013). HRSZ have been shown to have deficits in attention, memory and emotion processing in addition to experiencing magic ideation and perceptual aberrations, abnormalities that can be traced to subcortical structure differences. It is important to study the hippocampus, thalamus and amygdala together given that the functional impairments faced by HRSZ and probands are not usually experienced in isolation. By studying subcortical structures that support these aberrant functions, more insight into the coordinated structure/function relationship in HRSZ can be gained.

Subcortical shape analysis has been used in recent years for determining alterations within sub-regions of the hippocampus, thalamus and amygdala (Johnson et al., 2013; Danivas et al., 2013; Qiu et al., 2013). While anterior hippocampus is involved in emotion processing and associative memory, the posterior hippocampus is involved in spatial learning and memory (Bannerman et al., 2004). Likewise, the thalamus is also highly specialized, with its different sub-regions serving as nodes for different thalamocortical loops (Cronenwett and Csernansky, 2010). Abnormalities in thalamocortical loop circuitry have been linked to deficits in sleep spindles, which are associated with increased schizotypy presentation (Buchmann et al., 2014). Findings of inward displacement in surface shape provide information about where the abnormal structure occurs (Scanlon et al., 2014). In turn, this regional information could contribute insight into disruptions in cognitive function that the subcortical structures support (Amad et al., 2014).

To date, we are aware of only one other investigation analyzing the relationship between subcortical brain region shape and symptomology in youth at risk for schizophrenia, although the sample examined those at clinical high risk for schizophrenia (CHR), rather than familial high risk. Dean et al. (2016) showed inward displacement (concavity) in the left ventral posterior hippocampus, which positively correlated with symptom severity in the 38 CHR subjects (Dean et al., 2016). Other regions associated with cognition, including the thalamus and amygdala, have not previously been investigated by shape analysis in a youth population to our knowledge.

In the present study, we compared the shape and volumes of the left and right hippocampus, thalamus and amygdala of HRSZ youth to those of age-matched healthy control subjects (HC) and analyzed structural anomalies in relation to cognition and schizotypy. We hypothesized that there would be more inward displacement in these regions in HRSZ compared to HC and that displacement would relate to increased symptomology of schizotypy and cognitive deficits among HRSZ.

**Table 1**  
Subject demographics.

	HC	HRSZ	Test statistic, <i>p</i> -value
N	69	66	
Mean age ± SD (years)	17.1 ± 4.3	16.4 ± 3.5	<i>t</i> = 1.00, <i>p</i> -value = 0.319
Age range (years)	8.6–25.4	10.1–24.7	
Gender			
Male	30	33	Chi-square statistic = 0.576, <i>p</i> -value = 0.448
Female	39	33	
First-degree relatives			
Offspring	–	54	–
Siblings	–	12	–
Ethnicity			
Caucasian	56	29	*Chi-square statistic = 20.04, <i>p</i> < 0.001
African-American	13	37	

## 2. Methods

### 2.1. Subjects

Participants were 66 non-psychotic first-degree relatives (54 offspring and 12 siblings) of patients diagnosed with schizophrenia or schizoaffective disorder and 69 healthy controls. There was no significant between-group difference in age or gender. See Table 1. Subjects were Caucasian and African Americans, defined by self-report; the group difference of proportions of Caucasians and African Americans between HRSZ and HC was significant ( $p < 0.001$ ), (see Table 1), thus ethnicity was used as a covariate in all analyses. Data were collected at Western Psychiatric Institute and Clinic, Pittsburgh. First-degree relatives of patients with schizophrenia were recruited by community advertisement and communication through the treating physicians of the patients. The Structured Clinical Interview for DSM-IV Disorders (SCID) (Spitzer et al., 1992) was used to confirm schizophrenia diagnoses of the participants' proband relatives. All participants received a complete explanation of the experiment and signed consent. Participants younger than 18 years gave informed assent, and the parent or guardian signed consent. The study was approved by the University of Pittsburgh Institutional Review Board.

Individuals with a diagnosis of a psychotic disorder at baseline were excluded from the HRSZ sample. None of the participants met DSM criteria for mental retardation. None had any significant neurological or medical illness, and none had received any antipsychotic medications.

### 2.2. Cognitive and psychopathological measures

The Continuous Performance Test (CPT) – identical pairs version section was administered and the *d* prime scores were used to evaluate sustained attention (CPT-IP) (Cornblatt et al., 1989). The Wisconsin Card Sort Task (WCST, Grant and Berg, 1948) was administered and the perseverative error measure was used to index executive functioning (Lavoie and Everett, 2001; Rüscher et al., 2008). The California Verbal Learning Test (CVLT) was administered and the word list memory delayed recall correct measure was used to assess verbal memory (Delis et al., 2000).

The Chapman Schizotypy Scales (Chapman et al., 1978; Eckblad and Chapman, 1983) were administered to both HRSZ and HC. The scores from the Magical Ideation and Perceptual Aberration Scale were combined into one score indexing schizotypy, referred to here as a Chapman score.

Group differences between HRSZ and HC in CPT-IP, perseverative error, Chapman score and CVLT were determined by ANCOVA using the CRAN R package version 3.2.3 s. Ethnicity was used as a covariate. ANCOVAs were adjusted for multiple comparisons by Bonferroni correction. Chapman, CPT-IP, perseverative error and CVLT scores were

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