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Subcortical surface shape in youth at familial high risk for schizophrenia

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ABSTRACT

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 premorbidity 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, *p*-value
N	69	66	
Mean age ± SD (years)	17.1 ± 4.3	16.4 ± 3.5	$t = 1.00$, p-value = 0.319
Age range (years)	8.6–25.4	10.1–24.7	
Gender			
Male	30	33	Chi-square statistic = 0.576, p-value = 0.448
Female	39	33	
First-degree relatives			
Offspring	–	54	–
Siblings	–	12	–
Ethnicity			
Caucasian	56	29	*Chi-square statistic = 20.04, $p < 0.001$
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; Rüsch 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

Table 2
Cognitive and Psychopathological measures profile and results.

	CPT-IP		CVLT		Perseverative Error		Chapman	
	HC	HRSZ	HC	HRSZ	HC	HRSZ	HC	HRSZ
N	60	61	42	42	67	61	62	66
Score mean ± SD	1.75 ± 1.0	1.25 ± 0.89	13.24 ± 2.15	13.55 ± 2.30	12.04 ± 8.53	13.70 ± 8.24	4.77 ± 4.71	7.92 ± 7.00
Score range	[− 0.26–4.24]	[− 0.57–3.12]	[7–16]	[8–16]	[3–45]	[1–39]	[0–19]	[0–41]
Test statistic, *p*-value between groups	$t = -2.841$, $^*p = 0.021$, corrected		$t = 0.826$, $p = 0.411$		$t = 0.843$, $p = 0.401$		$t = 1.331$, $p = 0.185$	

analyzed for their correlations with regional shape displacements.

For all analyses, significance was considered at $p \leq 0.050$.

2.3. Structural magnetic resonance imaging

Structural brain imaging was performed using a 1.5 T GE SIGNA imaging system (General Electric Healthcare, Marlborough, MA, USA). A three-dimensional spoiled gradient recall acquisition (SPGR) T1-weighted scan was acquired with 124 coronal slices, slice thickness 1.5 mm without interslice gap, matrix 256 × 256 × 192, in-plane field of view 24 cm, repetition time TR = 25 ms, and echo time TE = 5 ms. Subjects with images with strong motion or field inhomogeneity artifacts were excluded from analyses.

Volumes were obtained using the FSL software FIRST (FMRIB's Integrated Registration and Segmentation Tool, fsl.fmrib.ox.ac.uk). Group difference between HRSZ and HC in volumes of left and right hippocampus, amygdala and thalamus were assessed using ANCOVA while covarying for intracranial volume (ICV) and ethnicity. Significance was adjusted for multiple comparisons by Bonferroni correction.

Brains were preprocessed for shape analysis using Free-Surfer software (version 5.1, freesurfer.net) to remove non-brain tissue from the T1 images by first-level autoreconstruction followed by manual editing of non-brain tissue for quality control (Mathew et al., 2014). Preprocessing by Free-Surfer resulted in final 3D brain images with a voxel size of 1 × 1 × 1 mm.

Preprocessed brains then underwent shape analysis via FSL software FIRST. FIRST creates a surface mesh of the assayed structure for each subject in 3D common space based on 336 manually labeled MR images used by FIRST through a Bayesian framework. An average mask is then created from all meshes of the structure from the cohort. Each vertex on the mask represents the average vertex in 3D space across all subjects. The non-parametric 'randomise' statistical process includes one map per subject of the scalar values of the perpendicular vectors between each vertex on the surface of the subject's structure and the corresponding vertex on the average mask. A positive value at a surface vertex represents outward displacement from the average (convexity) and a negative value represents inward displacement (concavity) (Patenaude et al., 2011).

Two types of shape analysis were completed in this investigation: group differences and correlations. Group differences were rendered by performing F-tests at each vertex (Patenaude et al., 2011) using the 'randomise' statistical process. Group difference shape analyses were completed for the right and left hippocampus, amygdala and thalamus: HRSZ vs. HC. Statistical maps of regions of subcortical surface that correlated with schizotypy and cognitive scores were produced by using the score as a voxel dependent explanatory variable in a general linear model analysis. Eight shape analysis correlations were completed for the six subcortical regions: displacement vs. CPT-IP, perseverative error, CVLT and Chapman scores for both HRSZ and HC groups separately. In the F-test and correlational analyses, ethnicity was used as a non-voxel dependent covariate. The 'randomise' algorithm used in the FIRST analyses performs a multiple comparison correction for its 5000 permutations (Dean et al., 2016), thus we did not use any further multiple comparison correction.

Description of regions of statistical significance in the group difference shape analysis were supplemented by labels generated from the Juelich Histological Atlas (Eickhoff et al., 2005, 2006, 2007) by visual inspection, which were overlaid onto the MNI standard space. Regions of significance overlapping ≥ 80% with the region labeled by the atlas were reported.

In structures that presented a region of correlation through the shape analysis, average displacements were calculated across the region of significant correlation using the fslstats tool for each subject. Each subject's average displacement is the mean of all displacement vectors in the region of significance delineated by the statistical map given through the shape analysis. These average displacements were used in a post hoc analysis of correlation with cognitive scores.

3. Results

3.1. Cognitive and psychopathological measures

The CPT-IP d prime score was significantly lower in HRSZ compared to HC. There was no significant difference between groups for Chapman score, perseverative error or CVLT score. See Table 2.

3.2. Volumes

There was no significant difference in volume between HRSZ and HC for any of the subcortical structures.

3.3. Age and shape analysis

There was no significant difference in age between groups. See Table 1. The ages of each group were normally distributed (Shapiro-Wilk normality test for HRSZ: $W = 0.978$, p-value = 0.287 and for HC: $W = 0.970$, p-value = 0.099). Additionally, there was similar distribution of age within the two groups. In order to investigate the dependence of subcortical shape on age, we ran a correlational analysis between subcortical shape and age in HRSZ and HC separately. There was no correlation between age and shape of right and left thalamus or hippocampus in either group. In HC, the left ($R = 0.389$, $p = 0.0002$) and right amygdala ($R = 0.347$, $p = 0.002$), and in HRSZ, the left (trending, $R = 0.290$, $p = 0.083$) and right amygdala ($R = 0.349$, $p = 0.030$) showed more outward displacement with increased age. There was no interaction effect between the slopes of correlations of shape and age for HRSZ compared to HC (p-values of interaction effect: left: $p = 0.835$; right: $p = 0.411$). To further verify potential age effects in the amygdala, the shape analyses were run with and without covarying for age, and the results were not different. Therefore age was not used as a covariate in the shape analyses.

3.4. Shape analysis group difference: HRSZ vs. HC

The ventral posterior right hippocampus showed significant inward displacement in the Cornu Ammonis (CA) region and the subiculum ($p = 0.050$, corrected) in HRSZ compared to HC. The dorsal lateral right amygdala had significant inward displacement in the superficial group and laterobasal group regions ($p = 0.022$, corrected) in HRSZ

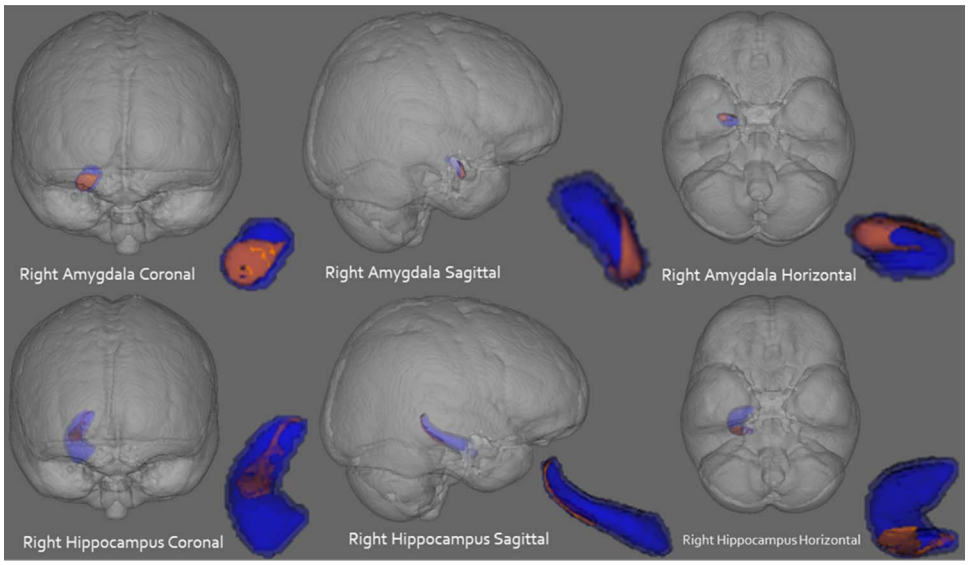

Fig. 1. Regions of statistical difference in shape between HRSZ and HC. Gray: Whole Brain. Blue: Surface mask of hippocampus or amygdala. Orange: Region of significant inward displacement in HRSZ compared to controls ($p \leq 0.05$, corrected); corresponding subcortical subfields according to the Juelich Histological Atlas: Right Amygdala: Superficial Group and Laterobasal Group; Right Hippocampus: Cornu Ammonis and Subiculum.

compared to HC. See Fig. 1. No regions of significant difference between groups were found in the left thalamus ($p = 0.126$, corrected) or right thalamus ($p = 0.219$, corrected), left amygdala ($p = 0.059$, corrected) or left hippocampus ($p = 0.121$, corrected).

3.5. Shape analysis correlations

See Table 3 for locations of shape-score correlation and *p*-values from shape analysis. The *p*- and *R*- values for correlations between scores and average displacement generated through the post-hoc analysis are displayed in Table 4. No region showed a correlation between displacement and CVLT score.

3.5.1. Hippocampus

Right hippocampus shape correlated with CPT-IP d prime scores in HC such that lower scores were associated with inward displacement (Fig. 2). There were no correlations between left hippocampus shape and cognitive or psychopathological measures in either the HC or HRSZ.

3.5.2. Thalamus

Left thalamus shape was correlated with CPT-IP d prime scores in HC such that lower scores were associated with inward displacement (Fig. 3). Right thalamus shape was correlated with CPT-IP d prime scores in HRSZ and HC such that lower scores were associated with inward displacement. Right thalamus shape was correlated with Chapman score in HRSZ such that increased schizotypy was associated with inward displacement (Figs. 4 and 5).

3.5.3. Amygdala

Left amygdala shape was correlated with CPT-IP d prime scores in HC such that lower scores were associated with inward displacement (Fig. 6). Left amygdala shape was correlated with perseverative error in HC such that higher scores were associated with inward displacement (Fig. 7). Left amygdala shape was correlated with Chapman score in HC such that increased schizotypy was associated with inward displacement (Figs. 8 and 9).

Right amygdala shape was correlated with CPT-IP d prime scores in HRSZ and HC such that lower scores were associated with inward displacement.

We found significant shape differences in HRSZ compared to HC in the right hippocampus and right amygdala, and differences in some correlations between shape and psychopathological measures in HRSZ compared to HC.

4. Discussion

This study evaluated the shape of hippocampus, amygdala and thalamus of a youth population at familial high risk for schizophrenia, and thus at genetic risk for developing psychosis, and the relationships between regional surface displacements and cognition in the domains of attention, executive function and verbal memory using FSL FIRST. We studied HRSZ who were antipsychotic free. Sustained attention was shown to be significantly worse in the HRSZ group compared to HC. Our investigation revealed inward surface displacement in HRSZ compared to HC in the right ventral posterior hippocampus, and the right dorsal lateral amygdala, although no volume differences between groups were found in the hippocampus, thalamus or amygdala. Furthermore, correlations between shape displacements and sustained attention and executive function found in healthy controls were absent in HRSZ.

Our study showed significant inward displacement in the right ventral posterior hippocampus. Very few studies have conducted shape analysis on a high-risk group for schizophrenia, and the results have been somewhat inconsistent. Dean et al. reported significant correlation between the left ventral posterior hippocampus concavity and severe positive symptoms at baseline in a smaller ($n = 38$) and somewhat older group of youth with clinical high risk (Dean et al., 2016). Ho and Magnotta reported inward displacement in left and right anterior hippocampi in a smaller sample ($n = 30$) of HRSZ youth (Ho and Magnotta, 2010). Additionally, Li et al. (2015) analyzed the shape of multiple subcortical regions including the hippocampus, thalamus and amygdala in a smaller sample ($n = 21$) of familial high risk subjects of both youth and adults, and did not find any shape difference (Li et al., 2015). Through our analysis, the right CA and subiculum region were identified as focal areas of inward displacement. While literature findings have been located in left and right hemispheres, our group differences were lateralized to the right hemisphere. This further underscores the difficulty of consistent localization of subcortical anomaly before psychosis onset. Abnormalities in these sub-regions have been implicated in schizophrenia symptomology. Indeed, volume differences in the CA and subicular regions have been implicated in memory deficits in schizophrenia and HRSZ (Francis et al., 2013; Mathew et al., 2014). Furthermore, in the subiculum, shape differences have been observed between schizophrenia groups with different forms of hallucinations (Amad et al., 2014).

Our analysis shows structural deficits in the right dorsal lateral amygdala spanning the superficial group and laterobasal group in HRSZ compared to HC. The superficial group of the amygdala responds to

Table 3
Regions of significant correlations between displacement and cognitive scores and schizotypy using correlational shape analysis. *p*-values are those found at the vertex with highest correlational significance within the surface region.

	CPT-IP		Perseverative Error		CVLT		Chapman	
	HC Significance, region	HRSZ Significance, region	HC Significance, region	HRSZ Significance, region	HC Significance, region	HRSZ Significance, region	HC Significance, region	HRSZ Significance, region
Left Hippocampus	$p = 0.623$	$p = 0.151$	$p = 0.836$	$p = 0.817$	$p = 0.799$	$p = 0.973$	$p = 0.263$	$p = 0.855$
Right Hippocampus	$^{*}p = 0.025$, Anterior	$p = 0.068$	$p = 0.657$	$p = 0.582$	$p = 0.621$	$p = 0.193$	$p = 0.538$	$p = 0.749$
Left Thalamus	$^{*}p = 0.006$, Dorsal, Medial, Lateral	$p = 0.383$	$p = 0.677$	$p = 0.254$	$p = 1.000$	$p = 1.000$	$p = 0.815$	$p = 0.173$
Right Thalamus	$^{*}p = 0.016$, Medial, Lateral	$^{*}p = 0.039$, Anterior Dorsal, Ventral Posterior	$p = 0.504$	$p = 0.287$	$p = 1.000$	$p = 1.000$	$p = 0.599$	$^{*}p = 0.023$, Dorsal, Ventral, Medial, Lateral
Left Amygdala	$^{*}p = 0.026$, Anterior, Posterior	$p = 0.100$	$^{*}p = 0.001$, Anterior, Posterior	$p = 1.000$	$p = 0.065$	$p = 0.658$	$^{*}p = 0.027$, Medial, Lateral	$p = 0.765$
Right Amygdala	$^{*}p = 0.007$, Dorsal, Medial, Lateral	$^{*}p = 0.010$, Anterior	$p = 0.163$	$p = 0.342$	$p = 0.500$	$p = 0.614$	$p = 0.090$	$p = 0.751$

$^{*}p \leq 0.050$.

dynamical facial emotion (Liu et al., 2014), a process that has been shown to be impaired in both probands and those at high risk (Allott et al., 2015; Leszczyńska, 2015). The laterobasal group of the amygdala has been associated with processing of facial emotions, body posture and voice intonations (Kim et al., 2010). This region is thought to contribute to comprehension of social context to guide mood and actions (Kim et al., 2010). Our findings of structural deficits in these same regions are consistent with the findings of functional deficits.

The CPT-IP d prime score assays signal/noise discrimination (d') in a perceptual-load vigilance task (the Degraded Stimulus CPT or DS-CPT) that is a measure of sustained attention (Nuechterlein et al., 2015). It has been reported that schizophrenia and relatives of schizophrenia have decreased CPT performance (Diwadkar et al., 2011; Nuechterlein et al., 2015). It has been shown that the ventral hippocampus participates in visuospatial attention and inhibitory control (Chudasama et al., 2012). We have demonstrated that HRSZ shows a deficit in sustained attention and a structural difference in a region that is known to support sustained attention (Fig. 1) compared to HC. Our results suggest that attention deficits occur independently of conversion to psychosis and are not a medication effect, since all our subjects were antipsychotic-naïve.

When investigating the association between sustained attention and regional displacement, HC show correlations in the right hippocampus, left and right thalamus and left and right amygdala, although HRSZ only shows this correlation in right thalamus and right amygdala. It has been shown that the hippocampus, thalamus and amygdala are functionally impaired in HRSZ (Bois et al., 2014; Buchmann et al., 2014). One possible explanation of this lack of correlation is that the structure/function relationship is lost in the right amygdala, left thalamus and left amygdala of HRSZ such that loss of function may not be explained by tissue loss alone. Altered neuroplasticity, neurochemical integrity or connectivity of these structures to other key brain regions should be considered as alternate explanations.

Although there is no published cut-off for clinically relevant symptoms, the predictive value of transition to psychosis of the Chapman score has been evaluated. A Chapman score of 11 or more from Chapman Schizotypy Scales Magical Ideation and Perceptual Aberration Scale has been shown to have sensitivity of 55% and specificity of 70% for transition to psychosis in HRSZ (Tandon et al., 2012a). Although neither HC nor HRSZ had an average score above 11, we found correlations between structure and schizotypy score in both groups. Our investigation revealed a correlation between right thalamus regional shape displacement and schizotypy score in HRSZ only. HRSZ but not HC has been previously shown to have a correlation between increased schizotypy and increases in thalamic glutamate and glutamine, which indicates altered neurotransmission (Tandon et al., 2013). Furthermore, deficits in sleep spindles, which are generated in the thalamus, have been shown to be associated with increased magical ideation (Lustenberger et al., 2015). Additionally, decreased mediodorsal thalamic volume has been correlated with decreased sleep spindle numbers in schizophrenia (Buchmann et al., 2014). We found that increased schizotypy, as measured through Chapman's test for magical ideation and perceptual aberration, is associated with inward displacement in multiple regions of the right thalamus, including the mediodorsal thalamus in HRSZ. Our results provide evidence for a structural deficit that may play a role in schizotypy in HRSZ. A future goal for this investigation could be to analyze sleep data in tandem with thalamic shape data.

Additionally, our investigation revealed a correlation between left amygdala regional shape displacement and schizotypy score in HC only. In an analysis of typically developing HC female children, left amygdala gray matter volume correlated with schizotypy scores such that increased social anxiety and withdrawal was associated with decreased volume (Evans et al., 2016). Furthermore, in a study among adolescents with mild intellectual impairments, those with higher schizotypy scores had more gray matter loss in the left amygdala than those with low

Table 4
p-values and *R*-values for post hoc correlation analysis between average regional displacement per subject and cognitive scores and schizotypy. There were no significant correlations between displacement and verbal memory score. '-' refers to regions in which there were no areas of correlation in the shape analysis, so therefore no average displacement value was rendered to be used in a post hoc correlation.

	CPT-IP				Perseverative error				Chapman			
	HC		HRSZ		HC		HRSZ		HC		HRSZ	
	p	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*
Left Hippocampus	–	–	–	–	–	–	–	–	–	–	–	–
Right Hippocampus	0.012	0.32	–	–	–	–	–	–	–	–	–	–
Left Thalamus	0.014	0.32	–	–	–	–	–	–	–	–	–	–
Right Thalamus	0.017	0.31	0.013	0.32	–	–	–	–	–	–	0.003	−0.37
Left Amygdala	0.012	0.32	–	–	< 0.001	−0.42	–	–	0.010	−0.32	–	–
Right Amygdala	0.006	0.35	< 0.001	0.42	–	–	–	–	–	–	–	–

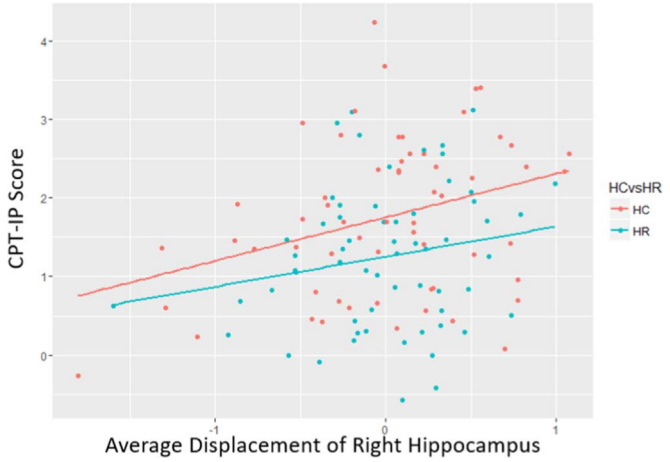

Fig. 2. Plots of CPT-IP score (sustained attention) vs. average regional right hippocampus displacement. Displacement is localized to the anterior region of the right hippocampus. Sustained attention was correlated with displacement in HC (*p*-value = 0.012, *R* = 0.32, corrected) but not in HRSZ (*p*-value = 0.133, *R* = 0.19, corrected). Red circles = HC; Red line = linear fit for HC; Blue circles = HRSZ; Blue line = linear fit for HRSZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

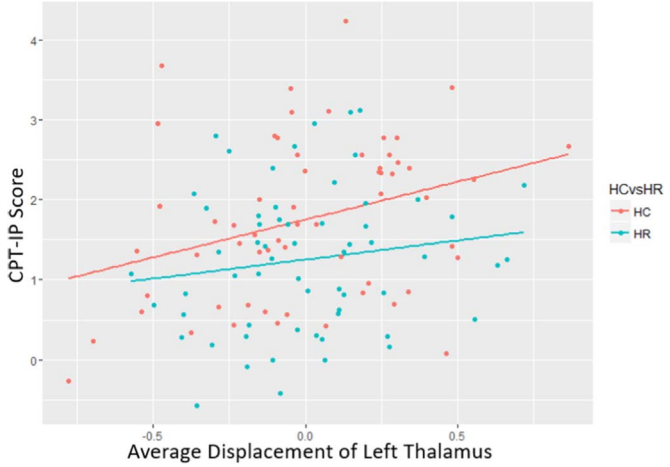

Fig. 3. Plots of CPT-IP score (sustained attention) vs. average regional left thalamus displacement. Displacement is localized to the dorsal, medial, and lateral sides of the left thalamus. Sustained attention was correlated with displacement in HC (*p*-value = 0.014, *R* = 0.32, corrected) but not in HRSZ (*p*-value = 0.245, *R* = 0.15, corrected). Red circles = HC; Red line = linear fit for HC; Blue circles = HRSZ; Blue line = linear fit for HRSZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

schizotypy scores (Moorhead et al., 2009). These results point to the possibility that among those not in a high genetic risk population, the presence of schizotypy may be related to left amygdala structural abnormalities. However, in our study, HRSZ does not exhibit a correlation between schizotypy and the left amygdala shape. A possible explanation for this could be that the structural/functional underpinnings for the phenomenon of schizotypy in HC are different from those in HRSZ and thus subcortical shape is differentially implicated.

Positive correlations between hippocampal volumes and verbal declarative memory scores have been shown in HRSZ (Francis et al., 2013). Our results did not demonstrate a correlation between verbal memory deficit and structure or significant difference between HRSZ and HC groups. This could have been a result of a ceiling effect in the CVLT scores given the at-risk rather than converted status of the HRSZ group. Further investigation is required to determine if verbal memory becomes deficient as this cohort ages.

Our findings of group structural difference between HRSZ and HC in the amygdala and hippocampus are consistent with high risk literature (Ganzola et al., 2014). Additionally, the present study's cognitive and psychopathological measure correlations provide information regarding altered structure/function relationship in the thalamus of HRSZ. These findings are consistent with evidence of decreased thalamo-orbitofrontal connectivity in clinical high risk groups for schizophrenia (Cho et al., 2016). Our results also align with reports of altered structure/function relationship in HRSZ amygdala and hippocampus (Seidman et al., 1999; Dean et al., 2016).

Our sample was larger and younger than that in other analyses (Dean et al., 2016; Li et al., 2015). It has been shown in a first episode sample that antipsychotics may influence hippocampal shape over time (Mamah et al., 2012). A strength of our study is that our sample was antipsychotic-naïve. One limitation of the study was the uneven distribution of African Americans in the HRSZ compared to HC group. This difference was adjusted for by covarying for ethnicity in all of the relevant analyses. Another limitation was the age range of the subjects who show major developmental changes during adolescence. Variation in head size was adjusted for by covarying for ICV and registration of images to standard space during the shape analysis (Patenaude et al., 2011). This study did not show between-group subcortical volumetric differences between HRSZ and HC although other studies have (Li et al., 2015; Mathew et al., 2014; Seidman et al., 1999). This could be explained by differences in age range or sample size.

The next step of this investigation is to analyze these regional shape changes longitudinally. Possible difference in shape between HRSZ at baseline and at a follow up point may provide information about progressive atrophy or a failure of development. Those that convert to psychosis also need to be analyzed. Also, comparing this HRSZ group to a first episode group may provide information about brain changes associated with the emergence of psychosis.

This investigation demonstrates subcortical abnormalities in relation to schizotypy and cognitive symptoms in a young, non-psychotic,

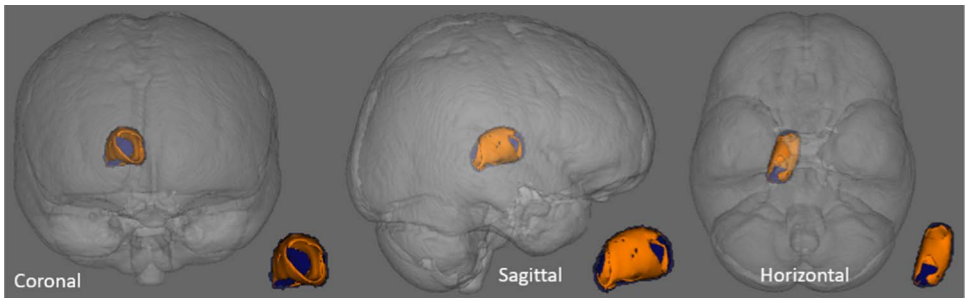

Fig. 4. Regions of significant correlation between Chapman score for schizotypy and right thalamus displacement from mean in HRSZ. Gray: Whole Brain. Blue: Surface mask of thalamus. Orange: Region of correlation of displacement with Chapman score ($p \leq 0.05$, corrected); corresponding subcortical subfields according to the Juelich Histological Atlas: Dorsal, Ventral, Medial and Lateral.

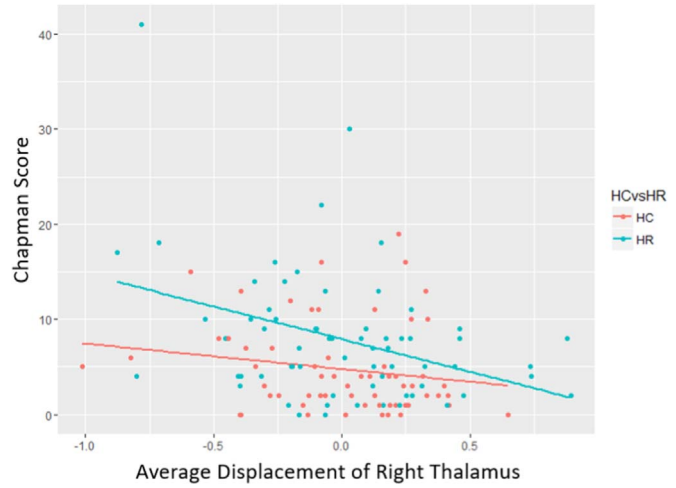

Fig. 5. Plot of Chapman score (schizotypy) vs. average regional right thalamus displacement. Displacement is localized to the dorsal, ventral, medial, lateral thalamus. Schizotypy was correlated with regional displacement in right thalamus in HRSZ (p-value $= 0.003$, $R = -0.37$, corrected), but not in HC (p-value $= 0.169$, $R = -0.18$, corrected). Blue circles = HRSZ; Blue line = linear fit for HRSZ; Red circles = HC; Red line = linear fit for HC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

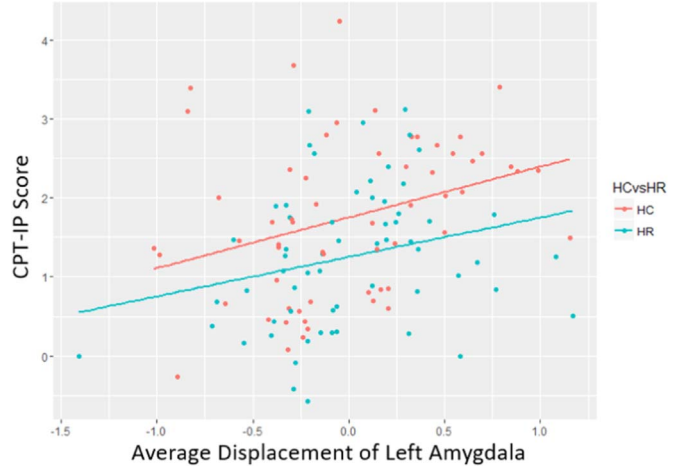

Fig. 6. Plots of CPT-IP score (sustained attention) vs. average regional displacement in the left amygdala. Displacement is localized to the anterior and posterior left amygdala. Sustained attention was correlated with displacement in HC (p-value $= 0.012$, $R = 0.32$, corrected), but not in HRSZ (p-value $= 0.054$, $R = 0.25$, corrected). Red circles = HC; Red line = linear fit for HC; Blue circles = HRSZ; Blue line = linear fit for HRSZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

antipsychotic free, population at high risk for schizophrenia. Right ventral posterior hippocampus and right dorsal lateral amygdala inward surface displacements in HRSZ suggest that the high-risk status may underlie subcortical structural anomalies. Increased schizotypy is

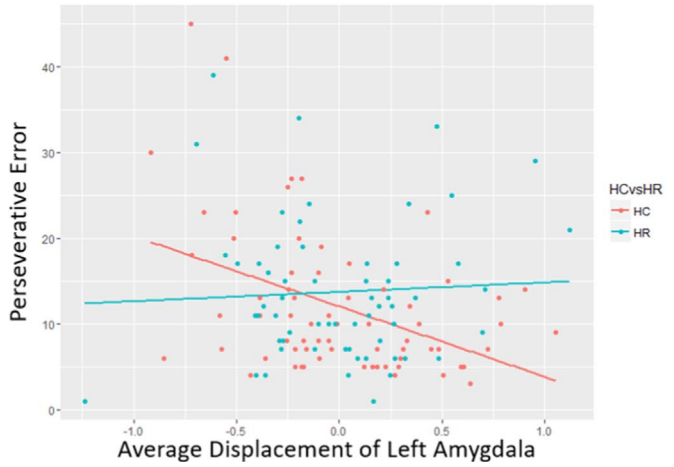

Fig. 7. Plots of Perseverative error score (executive function) vs. average regional left amygdala displacement. Displacement is localized to the anterior and posterior left amygdala. Perseverative error was correlated with displacement in HC (p-value < 0.001, $R = -0.42$, corrected) but not in HRSZ (p-value $= 0.675$, $R = 0.055$, corrected). Red circles = HC; Red line = linear fit for HC; Blue circles = HRSZ; Blue line = linear fit for HRSZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

associated with inward displacement in right thalamus in HRSZ and left amygdala in HC. Furthermore, an absence of correlation between regional hippocampus, thalamus and amygdala surface displacements and both sustained attention and executive function in the HRSZ may indicate dysfunction of these subcortical structures, potentially related to altered neuroplasticity. These structural anomalies have the potential to be biomarkers for increased symptomology in HRSZ.

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Contributors

Kathryn Hill and Nicolas Bolo designed and carried out the experiment and wrote the manuscript.

Suraj Sarvode Mothi designed statistical tests and assisted with experimental design and writing the manuscript.

Paulo Lizano assisted with experimental design and writing the manuscript.

Synthia Guimond assisted with writing the manuscript.

Neeraj Tandon assisted with experimental design and provided technical support.

Elena Molokotos edited MRI images for preprocessing.

Matcheri Keshavan directed all aspects of the study and manuscript writing.

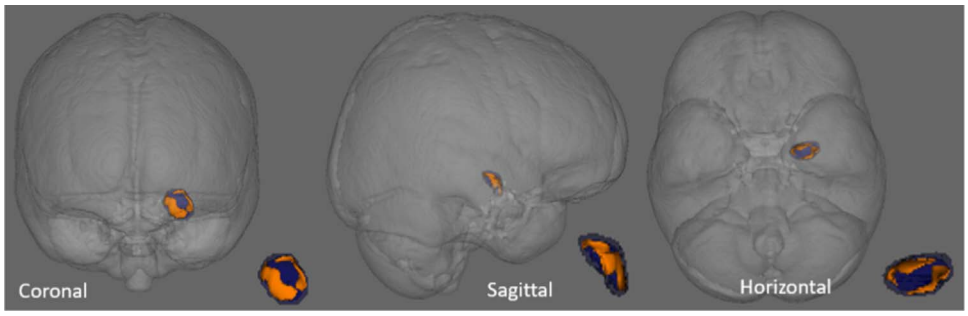

Fig. 8. Regions of significant correlation between Chapman score for schizotypy and left amygdala displacement from mean in HC. Gray: Whole Brain. Blue: Surface mask of amygdala. Orange: Region of significant correlation of displacement with Chapman score ($p \leq 0.05$, corrected); corresponding subcortical subfields according to the Juelich Histological Atlas: Medial, Lateral.

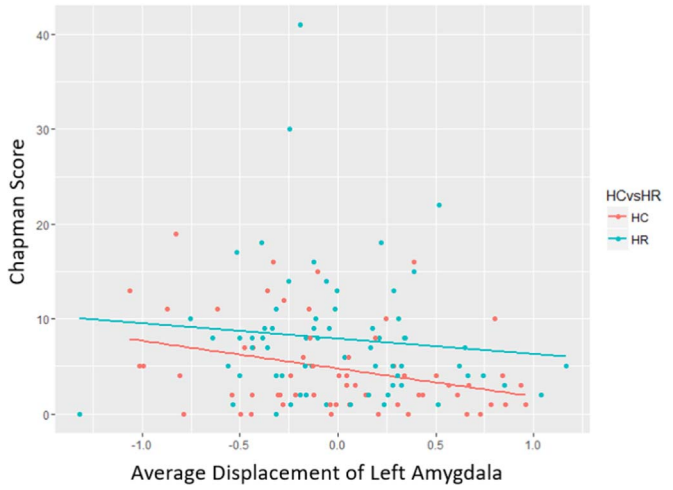

Fig. 9. Plot of Chapman score (schizotypy) vs. average regional right thalamus displacement. Displacement is localized to the medial and lateral regions of the left amygdala. Schizotypy was correlated with displacement in HC (p-value = 0.010, $R = -0.32$, corrected) but not in HRSZ (p-value = 0.414, $R = -0.102$, corrected). Red circles = HC; Red line = linear fit for HC; Blue circles = HRSZ; Blue line = linear fit for HRSZ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Conflict of interest

The authors declare no conflict of interest.

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