Differences in subcortical structures in young adolescents at familial risk for schizophrenia: A preliminary study

Michael K. Dougherty, Hongbin Gu, Joshua Bizzell, Stacy Ramsey, Guido Gerig, Diana O. Perkins, Aysenil Belger

Abstract

Schizophrenia has been associated with reduced volumes of subcortical structures on magnetic resonance imaging (MRI), but the relation of these reductions to familial risk for the disorder is unclear. We investigated the effect of familial risk for schizophrenia on regional subcortical volumes during adolescence, a period marked by steep maturational changes in brain structure and the emergence of psychotic symptoms. A group of 26 non-help-seeking, first-degree relatives of patients with schizophrenia and 43 matched healthy comparisons, between 9 and 18 years of age, underwent MRI scanning and were rated for the presence of prodromal symptoms. Five subcortical regions-of-interest were tested for group differences and group by age interactions, as well as correlations with low-level prodromal symptoms in the familial risk group. Relative to comparisons, familial risk subjects demonstrated greater positive volume–age relationships in hippocampus, putamen, and globus pallidus. These results suggest that relatives of individuals with schizophrenia exhibit structural abnormalities in the sub cortex as early as pre-adolescence, which may reflect altered neurodevelopment of these regions.

Keywords: Hippocampus, Putamen, Basal ganglia, Neurodevelopment, MRI, Volumetric

1. Introduction

Although the pathophysiological mechanisms underlying schizophrenia remain unknown, the disorder has long been associated with alterations in brain structure (Shenton et al., 2001). Volumetric differences from healthy comparisons have been reported as early as the first episode of psychosis (Ellison-Wright et al., 2008; Vita et al., 2006), in adolescents with schizophrenia (Rapoport and Gogtay, 2011), in prodromal individuals, and in unaffected relatives (Boos et al., 2007; Fusar-Poli et al., 2011). Few studies, however, have examined asymptomatic relatives during early adolescence, a stage preceding the period of greatest psychosis risk. Studies of brain maturation in children and adolescents with familial risk for schizophrenia are challenged by the difficulty of controlling for normal developmental effects during a period of rapid cerebral change. It is nevertheless likely that the dynamic functional and structural brain changes that occur during puberty and the early adolescent period represent in and of themselves a factor increasing vulnerability for neuropsychiatric disorders (Paus et al., 2008). Adolescence therefore constitutes a critical period for targeted investigations into the pathogenesis of schizophrenia.

Among the many brain regions that are particularly promising candidates for investigation in the neurodevelopmental hypothesis of schizophrenia are the subcortical regions of the medial temporal lobe (MTL) and the basal ganglia (BG). The hippocampus is an MTL structure that is among the most studied regions in schizophrenia research, and there is now a general consensus that at least some high-risk (HR) subjects experience hippocampal reduction prior to psychosis onset (Boos et al., 2007; Fusar-Poli et al., 2011). The trend during this time period is complex, however, with separate studies supporting environmental (Lawrie et al., 2001; Mattai et al., 2011) and hereditary (Goldman et al., 2008) factors as the dominant force behind pre-psychotic hippocampal reduction. Furthermore, the hippocampus and its MTL counterpart, the amygdala may be variably affected depending on the presence of an affective component of psychosis (Velakoulis et al., 2006), and comparisons across studies of MTL structures are made more difficult by methodological differences, such as the practice in many older studies of examining the amygdala and hippocampus as one complex.

The comparatively fewer studies on the BG in schizophrenia support abnormalities of these regions, with extensive reports of functional differences from controls in caudate, putamen, and globus pallidus.
pallidus (Hazlett et al., 2008; Hoffman et al., 2011; Li et al., 2010; Menon et al., 2001; Morey et al., 2005). Although the BG are difficult to study because they are known to be among the most sensitive regions of the brain to effects of antipsychotics (Brandt and Bonelli, 2008; Ellison-Wright et al., 2008), the functional literature has recognized a significant role of hypermetabolic activity in these regions even in prodromal and unmedicated physiology (Fusar-Poli et al., 2010; Huang et al., 2010; Kegeles et al., 2010; Müller et al., 2002). While there is evidence supporting a correlates of such hypermetabolism with decreased caudate volume (Jayakumar et al., 2006), there is still no consensus on the structural correlates of these pre-psychotic and unmedicated functional differences. Caudate volumes have generally been found to be smaller at disease onset (Brandt and Bonelli, 2008; Ellison-Wright et al., 2008), whereas reductions in the lentiform nuclei have been less frequently reported (Ballmaier et al., 2008). Volumetric studies of unaffected relatives are conflicting, however (Goldman et al., 2008; Lawrie et al., 2001; Rajarethinam et al., 2007), leaving the contribution of genetic risk to BG function and volume uncertain.

By defining how cohorts of familial high risk (FHR) individuals differ from comparable individuals in the general population, especially during an age range that has been relatively understudied and in brain structures whose exact role in pathogenesis is still unclear, the current study aimed to characterize possible pre-symptomatic alterations in neurodevelopment at the level of regional subcortical morphology. Any detected abnormality may or may not prove to be a predictor of conversion on later follow-up. We examined volumetric differences in the regions of the hippocampus, amygdala, putamen, globus pallidus, and caudate nucleus, in non-help-seeking child and adolescent relatives of schizophrenia patients versus healthy comparisons. We further examined whether observed differences were modulated by age, reflecting possible alterations in adolescent neurodevelopment. Finally, we also explored the correlation between regional volumes and the severity of any prodromal psychotic symptoms in the HR group. We hypothesized that FHR adolescents would display volumetric reductions in the subcortical regions, that differences would be greatest in older individuals (presumed closest to possible conversion), and that these regional volumes would negatively correlate with the severity of their subsyndromal clinical symptomatology.

2. Methods

2.1. Subjects

The current study presents the baseline structural MRI data for the first sample recruited in an ongoing multimodal, longitudinal study of children and adolescents with FHR for schizophrenia by the University of North Carolina (UNC) Conte Center. Identification and recruitment of 26 FHR subjects between ages 9 and 18 years was done through the specialized schizophrenia treatment services of UNC hospitals and affiliated clinics, as well as through consumer organizations (North Carolina National Alliance on Mental Illness and Mental Health Association). Healthy comparison (HC) subjects (n=43) were recruited from the same local communities as the FHR subjects, via email advertisements to databases of UNC students and employees as well as county public schools. Subjects were matched for sex, age, and ethnicity. In order to yield a relatively continuous distribution of subjects in each group across the age range, recruitment was structured into three age brackets: 9–11, 12–14 and 15–18 years old. For all subjects, FHR was defined as family history of schizophrenia or schizoaffective disorder in a first-degree relative, and was confirmed with the Family Interview for Genetic Risk (Maxwell, 1998). Diagnosis of the affected relative was confirmed using either the Structured Clinical Interview for DSM IV disorders (adults) or the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (children) (Geller, 1996). All subjects were evaluated with the WASH-U-KSADS. Any Axis I disorder in a healthy comparison subjects or their first-degree relatives resulted in exclusion; FHR subjects meeting criteria for a psychotic disorder or bipolar disorder were excluded. Subjects were also excluded if they had a serious medical or neurological disorder or a history of antipsychotic treatment within 3 months of enrollment. All included subjects underwent a baseline clinical evaluation for the presence and severity of positive, negative, disorganized, and general symptoms, and scores were assigned on each dimension using the Scale of Prodromal Symptoms (SOPS) (Miller et al., 1999). None of the FHR subjects were treatment-seeking at the time of recruitment into the study.

Subjects under 18 years of age gave written assent to participation in the study, while legal guardians of minors and 18-year-old subjects provided written informed consent. The UNC Biomedical Institutional Review Board approved the study.

2.2. Image acquisition and analysis

All subjects were scanned on a 3T General Electric short-bore scanner at the Duke-UNC Brain Imaging Analysis Center. Multi-contrast high resolution MRI pulse sequences were used to allow multi-channel segmentation for optimal fidelity, including T1 weighting (TR prepared 3-D FS MPGR, TR 7.5 ms, TE 3.0 ms, inversion preparation time 450 ms, flip angle 12°, bandwidth/pixel 244 Hz, imaging matrix 256 × 256, FOV 256 × 256 mm, slice thickness 1 mm) and a double-echo dual-contrast FSE sequence (TR 3000 ms, TE 25.1 and 87.7 ms, flip angle 90°, bandwidth/pixel 122.1 Hz, imaging matrix 256 × 192, FOV 256 × 256 mm, slice thickness 2 mm) for optimization of signal-to-noise ratio. Total brain and tissue volumes were obtained with an automatic, expectation-maximization scheme (EMS) brain segmentation tool which used all three MRI contrasts and an atlas prior (Prastawa et al., 2003). A pipeline for automated subcortical segmentation, developed by investigators at the Neuro Image Research and Analysis Laboratories (NIRAL) at UNC and based on an unbiased population atlas embedding probabilistic models of anatomical structures (Gouttard et al., 2007), was used to delineate the subcortical regions-of-interest (ROIs). Each image was visually inspected for gross segmentation errors by two blinded raters, and no such errors were detected. In the interest of preserving the objectivity of the automated method, we elected to neither exclude nor manually correct the frequent but minor errors in boundaries produced by the automated, probabilistic algorithm.

2.3. Statistical analyses

Demographic variables were analyzed with the Fisher Exact Test for categorical variables and the Wilcoxon Two-Sample Rank Test for continuous variables. The categorical variables included sex, race, handedness, and highest level of parental education, which was used as a rough proxy for socioeconomic status and home environment. The continuous variables analyzed were each subject’s age and SOPS scores.

The group and age related differences in total brain tissue volume (TBV=total gray matter [GM] + total white matter [WM]) were first examined in an analysis of covariance (ANCOVA) model with group (FHR, HC), age (9–18 years), and sex (male, female) as between-subject variables and hemisphere (left, right) as a within-subject variable. With no group x hemisphere interactions detected, we combined corresponding left and right subcortical structures and modeled the total volume with ANCOVA models, which include group, sex, and age as well as group by age interaction. Quadratic age trend was tested but dropped from the models due to non-significant findings and limited sample size. The volumetric differences associated with age were estimated by separate age slopes for the FHR and HC groups. Group differences in the volume–age relationship were tested in the interaction between age and group.

Within the high-risk group, Pearson’s r was used to test the association of each SOPS domain (positive, negative, disorganized, general, and total scores) with corrected volume of each subcortical ROI. As a sensitivity analysis to evaluate the potential confounding effect of age, we calculated the partial correlation between SOPS scores and ROI volume while controlling for age.

All tests were two-tailed with a significance level of 0.05. To further safeguard against Type I error, we corrected for multiple comparisons using the false discovery rate (FDR) adjustment.

3. Results

3.1. Demographics

The sociodemographic profile of the sample is shown in Table 1. The familial risk group did not differ significantly from the comparison group in age, sex, ethnicity, handedness, or last grade completed. Parents of the HC group had significantly higher levels of education than those of the FHR group (P<0.01), and HC subjects also differed from FHR by the absence of Axis I diagnoses. Even using the
conservative, non-parametric Wilcoxon test. SOPS scores were significantly higher in the FHR group in all dimensions, although the scores still fell well below a level that could be considered “prodromal” (Miller et al., 1999).

3.2. Volumetric analyses

3.2.1. Total brain volume

The ANCOVA model of TBV (Table 2) demonstrated a nearly significant trend toward larger total volume in the male adolescents than the females, after FDR adjustment. The FHR and HC groups had similar TBV overall and in relation to age, with both study groups showing modest annualized differences of less than 1% in TBV (Fig. 1). In the post hoc analysis of the slope of TBV–age relationship, the increase was significant in the HC group.

3.2.2. Hemisphere asymmetry

MANCOVA models found significant hemispheric asymmetry in all subcortical structures (P < 0.01), but no significant differences between groups (P > 0.50). For both FHR and HC, amygdala and caudate were about 3% larger on the right, while hippocampus, putamen, and globus pallidus were larger on the left by 5%, 2% and 1%, respectively (Supplementary Table 2).

3.2.3. Subcortical structures

With no evidence for group differences in hemispheric asymmetry, data for each ROI were collapsed across both hemispheres to test for group- and age-related differences (Table 2). Effect of sex was not significant in any ROI after FDR correction. Averaging across the age range, the FHR group showed smaller volumes than the HC group in all the subcortical structures. This difference was initially significant in the hippocampus, but did not survive FDR correction. In the analysis of group differences in age effects, however, the groups showed significantly different volume–age relationships in most subcortical structures (P = 0.10 for amygdala, P = 0.06 in caudate, and P < 0.05 for hippocampus, putamen, and globus pallidus with FDR correction; see Table 2 and Fig. 1). Post hoc analysis of each group revealed that the TBV-

| Table 1 |

Demographic characteristics of familial high risk (FHR) and comparison groups.

<table>
<thead>
<tr>
<th></th>
<th>Comparison (n=43)</th>
<th>FHR (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (S.D.)]</td>
<td>14.22 (2.52)</td>
<td>14.49 (2.35)</td>
<td>0.85</td>
</tr>
<tr>
<td>Female [N (%)]</td>
<td>25 (58%)</td>
<td>15 (58%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Caucasian [N (%)]</td>
<td>34 (79%)</td>
<td>19 (73%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Right-handed [N (%)]</td>
<td>32 (76%)</td>
<td>22 (88%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Last grade completed [mean (S.D.)]</td>
<td>7.65 (2.50)</td>
<td>7.42 (2.55)</td>
<td>0.71</td>
</tr>
<tr>
<td>Highest parental education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without high school degree [N (%)]</td>
<td>0 (0%)</td>
<td>4 (15%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High school diploma or GED [N (%)]</td>
<td>4 (9%)</td>
<td>8 (31%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>College degree [N (%)]</td>
<td>11 (26%)</td>
<td>6 (23%)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree [N (%)]</td>
<td>28 (65%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
<tr>
<td>Axis I diagnosis [N (%)]</td>
<td>(0%)</td>
<td>12 (46%)</td>
<td>NA</td>
</tr>
<tr>
<td>SOPS scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive [mean (S.D.)]</td>
<td>1.11 (1.67)</td>
<td>2.34 (2.29)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Negative [mean (S.D.)]</td>
<td>0.91 (1.44)</td>
<td>3.20 (3.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disorganization [mean (S.D.)]</td>
<td>0.51 (0.92)</td>
<td>1.46 (1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>General [mean (S.D.)]</td>
<td>0.63 (1.14)</td>
<td>1.97 (2.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total [mean (S.D.)]</td>
<td>3.15 (3.68)</td>
<td>8.97 (6.70)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NA—not applicable, as Axis I diagnosis in a comparison subject was an exclusion criterion. Bold values are P < 0.05.

* Two subjects were missing handedness data (total n=67), and of the non-right-handed subjects, one was ambidextrous.

| Table 2 |

ANCOVA for subcortical regions-of-interest (ROIs).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male [LSM]</td>
<td>1,249,341</td>
<td>312.5</td>
<td>324.4</td>
<td>487.4</td>
<td>629.0</td>
<td>327.1</td>
</tr>
<tr>
<td>Female [LSM]</td>
<td>1,141,799</td>
<td>306.4</td>
<td>319.7</td>
<td>478.0</td>
<td>623.9</td>
<td>332.1</td>
</tr>
<tr>
<td>Difference [P]</td>
<td>&lt;0.01</td>
<td>0.03</td>
<td>0.14</td>
<td>0.30</td>
<td>0.35</td>
<td>0.08</td>
</tr>
<tr>
<td>Corr. P-value</td>
<td>0.06</td>
<td>0.09</td>
<td>0.21</td>
<td>0.35</td>
<td>0.35</td>
<td>0.16</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy comparison [LSM]</td>
<td>1,199,581</td>
<td>309.6</td>
<td>325.7</td>
<td>483.5</td>
<td>629.9</td>
<td>330.4</td>
</tr>
<tr>
<td>Familial high risk [LSM]</td>
<td>1,191,559</td>
<td>309.2</td>
<td>318.4</td>
<td>482.0</td>
<td>622.9</td>
<td>328.9</td>
</tr>
<tr>
<td>Difference [P]</td>
<td>0.74</td>
<td>0.87</td>
<td>0.02</td>
<td>0.86</td>
<td>0.20</td>
<td>0.61</td>
</tr>
<tr>
<td>Corr. P-value</td>
<td>0.87</td>
<td>0.87</td>
<td>0.12</td>
<td>0.87</td>
<td>0.60</td>
<td>0.87</td>
</tr>
<tr>
<td>Group × Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy comparison [Slope, P]</td>
<td>12,490</td>
<td>0.04</td>
<td>0.02</td>
<td>0.98</td>
<td>−0.09</td>
<td>0.91</td>
</tr>
<tr>
<td>Familial high risk [Slope, P]</td>
<td>3846</td>
<td>0.64</td>
<td>2.18</td>
<td>0.03</td>
<td>3.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Difference [P]</td>
<td>0.40</td>
<td>0.08</td>
<td>0.02</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Corr. P-value</td>
<td>0.40</td>
<td>0.10</td>
<td>0.04</td>
<td>0.06</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LSM—Least Square Mean. Corr. P-value—FDR-controlling P-value adjustments. Bold values are corrected P < 0.05.

* Corrected volume = (total ROI volume/total brain volume) × 100,000. Total ROI volume = sum of left and right ROI volume.
corrected volumes were largely stable across adolescence in the HC group, with non-significant ($P > 0.18$) slopes in all ROIs. In contrast, significant positive-sloping volume–age relationships ($P < 0.05$) were observed in all subcortical structures, relative to TBV, for the FHR group (Table 2 and Fig. 1).

### 3.3. Correlations with prodromal symptoms

Table 3 shows Pearson’s $r$ with corresponding correlations between subcortical structures and SOPS symptoms. None of the correlations were significant after FDR adjustment, although the greatest trends were toward a negative correlation between ROI volume and disorganization scores ($r = -0.58$ to $-0.60$, $P = 0.13$ for hippocampus and putamen). The sensitivity analysis controlling for age did not change the significance of any results (see Supplementary Table 3).

### 4. Discussion

We found that relative to healthy comparison subjects, FHR subjects displayed significant group by age interactions such that TBV-corrected subcortical volumes were larger with age. Volumes were smaller for FHR subjects in all ROIs, suggesting a trend of initially decreased volumes which approach normal during adolescence.

This study’s cohort is unique in that subjects span the entire range of adolescence, including early adolescence. Individuals who go on to develop schizophrenia begin to exhibit neuropsychological abnormalities as early as childhood (Jones et al., 1994), and dramatic neurodevelopmental shifts during adolescence may be critical precipitants of a spectrum of psychopathology (Paus et al., 2008). Therefore, in order to characterize biological markers of risk for schizophrenia in an early presymptomatic stage, the current study encompassed the entire range of adolescence in a non-prodromal FHR cohort.

Our data are consistent with well-established hippocampal reductions in FHR individuals (Boos et al., 2007; Fusar-Poli et al., 2011), although the overall group effect did not survive FDR adjustment. It should be noted that while not reaching significance, other subcortical structures all showed reductions in the same direction. The main findings of our study, namely the positive-sloping group × age interactions of the FHR group, were less anticipated. Regarding the hippocampus, the size of this structure has been shown to exhibit little change relative to intracranial volume (ICV) during healthy adolescence (Mattai et al., 2011; Ostby et al., 2009), as was the case in our healthy comparison subjects. Among FHR studies, a recent comparison of healthy subjects and unaffected siblings of childhood-onset schizophrenia (COS) patients failed to find a significant difference in volume–age relationship, in the setting of non-significant, downward-sloping volume–age curves in both groups (Mattai et al., 2011). The trajectories of Mattai and colleagues’ sample could be at least partially consistent with ours, however, in that non-significant differences between groups are greatest at younger ages. The lack of significance may be due to qualitative differences between our cohort and that of Mattai et al., which included only siblings of childhood-onset patients who were also free of any lifetime Axis I disorder (rather than only psychotic disorders). Interestingly, our study replicates the previously isolated report of positive-sloping group × age interactions...
in the hippocampi of slightly older FHR subjects with some incidence of non-psychotic mental illness (Ho and Magnotta, 2010).

Despite this isolated report in the hippocampi, positive volume–age relationships in the subcortex have little precedent in unmedicated subjects. Longitudinal studies of pediatric neurodevelopment at the National Institutes of Mental Health (NIMH) have revealed that in healthy adolescents the caudate nucleus appears to follow an “inverted U” trajectory across adolescence (Lenroot et al., 2007). Our study’s ability to detect second-order age effects was likely limited by sample size, but our HC plots seem compatible with the subtle negative slope of the post-apical portion of the NIMH plots corresponding to our cohort’s age range. Other subcortical trajectories are not so well studied, but the lenticular nuclei may follow a similar, declining trajectory (Giedd et al., 1996; Ostby et al., 2009), while the amygdala, much like the hippocampus, may also normally exhibit a relatively flat growth trajectory (Giedd et al., 1999). Considering the general absence of literature on subcortical structures in early adolescent FHR cohorts, the trajectories found in our study could possibly provide a novel framework for interpreting the FHR literature across larger age ranges. For instance, an adolescent study found smaller caudates in FHR subjects (Rajarethnam et al., 2007), but studies of unaffected adult relatives have more frequently failed to detect such reductions (Goldman et al., 2008; Hannan et al., 2010; Mamah et al., 2008). These results would be consistent with a volumetric convergence of groups with age.

The possible explanations for our age-related findings are several. Due to the cross-sectional nature of our sample, we cannot determine whether the group × age interactions mirror true intra-subject changes. If cerebral change corresponding to our volume–age relationships could be demonstrated in a longitudinal design, it would be the first example in the subcortex of FHR subjects of the principle that trajectories of cerebral development may be unique markers of psychopathology during adolescence (Shaw et al., 2010). This principle has been demonstrated in the striatum of developmental cohorts with autism (Langen et al., 2009) and ADHD (Castellanos et al., 2002), as well as the cortex of early-onset schizophrenia (Rapport and Gogtay, 2011). An increase in corrected subcortical volumes with age could also be a surrogate marker of pathology, considering that TBV-correction allows for the possibility that our group × age interactions reflect more of a diminution in other cerebral structures rather than a disproportionate increase in the studied ROI’s. Alternate compartments that could be exhibiting such a divergence from the HC trajectory would include cortical gray matter or white matter. The cerebellum is a third, underappreciated compartment that seems to exhibit a compatible negative volume–age relationship in FHR adolescents both in post-hoc, informal analyses of our raw data as well as a recent report of a similar cohort (Greenstein et al., 2011). Follow-up data from our study’s cohort may reveal clues as to whether the FHR group’s age-related differences in relative subcortical volumes represent a suboptimal adaptation to a pre-morbid process, serving as a marker for persistently elevated risk, or instead an effective compensation that is protective against psychosis. Considering the established findings of reduced corrected volumes of several of the subcortical ROIs in unmedicated first-episode patients, it seems more likely that our volume–age relationships are modeling some type of compensatory or “normalizing” process for an intrinsic vulnerability phenotype. Only a minority of FHR individuals (6%–21% depending on type) will actually go on to develop psychosis (Kendler et al., 1993). This is consistent with our sample that is characterized by low (within normal limits) SOPS scores, a conversion rate of 1/26, and no greater than 5/26 separate subjects demonstrating potentially “help-seeking” behaviors after 1 to 4 years of follow-up (data available upon request). The concept of volumetric change mirroring clinical outcome has a precedent in other neuroanatomical regions in childhood psychoses, as well as other psychiatric disorders (Shaw et al., 2010). While cerebral plasticity during the adolescent period may provide a setting in vulnerable individuals for the emergence of psychiatric symptoms in response to “triggers” such as psychological stress and substance abuse (Lodge and Grace, 2011; Paus et al., 2008; Rapport and Gogtay, 2008), such plasticity may also allow for restitutive mechanisms in the absence of such triggers. The positive volume–age relationships in this study could theoretically represent such adaptive maturational mechanisms in the subcortex.

As previously alluded to, we must also consider the limitations of a cross-sectional approach in interpretations of group × age interactions. Specifically, cohort effects could produce interactions in our sample which in reality represent inter- rather than intra-subject differences by age. This could occur by chance due to our relatively small sample size, but also could be a product of our study criteria. The natural history of schizophrenia suggests that a certain percentage of young, non-help-seeking FHR individuals will develop symptoms or even convert before age 18, which would result in exclusion from this study. In other words, it is possible that older FHR individuals in our study represent a slightly lower risk group by virtue of having moved later in the risk-age window without becoming symptomatic.

The exploratory correlation analyses initially revealed negative correlations between disorganized symptoms and volumes of amygdala, hippocampus, and putamen. These findings are consistent with previous reports suggesting that the disorganization domain may index many of the cognitive deficits of the schizophrenia spectrum (Demjaha et al., 2012). Such deficits are among the earliest symptomatic manifestations of disease and/or disease risk (Jones et al., 1994) and also associated with diminished subcortical volumes in high-risk samples (Bhojraj et al., 2011;
Hannan et al., 2010; van Erp et al., 2008). Our results did not survive FDR adjustment and thus should be interpreted cautiously, especially in light of the potential non-specificity of disorganization symptoms. Future studies should attempt to explore these trends with larger sample sizes.

Study limitations not already mentioned include the potential for the somewhat broad delineations of ROIs to mask more striking effects at the subregional level, for example in anterior hippocampus or head of the caudate. Evaluation of other relevant ROIs, such as the thalamus and nucleus accumbens, could have provided additional insight into abnormalities of subcortical circuitry in FHR subjects, but software limitations prevented us from reliably examining these structures. Sample size was small for a cross-sectional study looking at brain structure during such a dynamic period of development, which will also be confounded by gender differences and the onset of puberty. Interactions of sex with age and group should be examined in future studies with larger sample sizes, in conjunction with pubertal markers such as Tanner stage or gonadal hormone levels.

Our sample groups were relatively well matched except for a significant difference in maximum degree of parental education. We were unable to disentangle these factors and therefore related to illness vulnerability. This study is a valuable exploratory investigation of a cohort traditionally difficult to analyze, and the first to our knowledge to examine these particular regional trajectories in relatives of patients with schizophrenia during the dynamic period of adolescent development from 9 to 18 years of age. Replication in a longitudinal design as well as correlation with conversion status is necessary to confirm and expand the significance of these findings. This will contribute to an enhanced understanding of the pre-symptomatic period, which may aid in the identification of “triggers” of psychosis and the development of targeted, early interventions.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.04.016.

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