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Regional Prefrontal Cortex Gray Matter Volumes in Youth at Familial Risk for Schizophrenia from the Harvard Adolescent High Risk Study

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Abstract

Background—Regional prefrontal cortex gray matter reductions have been identified in schizophrenia, likely reflecting a combination of genetic vulnerability and disease effects. Few morphometric studies to date have examined regional prefrontal abnormalities in non-psychotic biological relatives who have not passed through the age range of peak risk for onset of psychosis.

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Contributors: Drs. Seidman, Faraone and Tsuang designed the study and wrote the protocol. Drs. Thermenos and Brown collected the neuroimaging data and performed the interviews at the imaging session. Mr. Hodge supervised data management and performed some statistical analyses. Drs. Makris, Caviness, and Kennedy developed the parcellation methods and provided expert neuroanatomical consultation. Dr. Rosso performed the cortical parcellations and statistical analyses, and wrote the first draft of the manuscript. Drs. Rosso and Seidman edited drafts of the manuscript. All authors contributed to the manuscript and approved its final version.

Conflict of Interest
All authors declare that they have no conflict of interest.

We conducted a region-of-interest morphometric study of prefrontal subregions in adolescent and young adult relatives of schizophrenia patients.

Methods—Twenty-seven familial high-risk (FHR) first-degree relatives of schizophrenia patients and forty-eight control subjects without a family history of psychosis (ages 13–28) underwent high-resolution magnetic resonance imaging at 1.5 Tesla. The prefrontal cortex was parcellated into polar, dorsolateral, ventrolateral, ventromedial and orbital subregions. The Chapman scales measured subpsychotic symptoms. General linear models examined associations of prefrontal subregion volumes with familial risk and subpsychotic symptoms.

Results—FHR subjects had significantly reduced bilateral ventromedial prefrontal and frontal pole gray matter volumes compared with controls. Ventromedial volume was significantly negatively correlated with magical ideation and anhedonia scores in FHR subjects.

Conclusions—Selective, regional prefrontal gray matter reductions may differentially mark genetic vulnerability and early symptom processes among non-psychotic young adults at familial risk for schizophrenia.

Keywords

schizophrenia; magnetic resonance imaging; prefrontal cortex; genetic risk; adolescence; young adulthood

1. Introduction

Since schizophrenia was first posited to be a brain disorder a century ago (Bleuler, 1911; Kraepelin, 1919), a wealth of postmortem and neuroimaging evidence has provided robust confirmation (Johnstone et al., 1976; Selemon and Goldman-Rakic, 1999; Shenton et al., 2001). Among many brain regions, the prefrontal cortex (PFC) has been implicated by an impressive variety of empirical research, and figures prominently in theoretical accounts of schizophrenia (Keshavan et al., 1994; Seidman, 1983; Weinberger, 1987). Schizophrenia has been associated with reduced prefrontal cortical thickness (e.g., (Selemon et al., 1995)), and with reduced gray matter (GM) in lateral, medial, and orbital prefrontal areas (Gur et al., 2000; Kuperberg et al., 2003; Yamada et al., 2007), although the particular subregions implicated vary across studies and negative reports exist (Chemerinski et al., 2002).

Genetic predisposition accounts for approximately 80% of liability for schizophrenia, and is thought to alter brain development in ways that affect an individual's probability of developing psychosis (Keshavan and Hogarty, 1999; Tsuang, 2001). Thus, one way of parsing the heterogeneous findings on PFC morphometry is to disambiguate aspects of pathology related to genetic risk for schizophrenia from those associated with the disease process. Studies of patients' nonpsychotic first-degree relatives can identify brain alterations that mark genetic (familial) loading for schizophrenia.

Anatomical MRI studies of PFC subregions in older adult relatives, who have passed through the age of peak risk for schizophrenia (> age 30), have reported deviations in prefrontal GM integrity, although their regional specificity has varied. One voxel-based morphometry (VBM) investigation found bilateral orbitofrontal cortex (OFC) GM deficits in 36 adult siblings of schizophrenia patients compared with 37 control subjects (McDonald et al., 2004), while two similar sized studies of discordant twin pairs reported a left-sided OFC GM deficit in relation to genetic loading (Hulshoff Pol et al., 2006), or no OFC deficit (Cannon et al., 2002). The latter twin study reported liability-associated GM deficits in the frontal pole and dorsolateral PFC (DLPFC). Some subsequent investigations also found that lateral prefrontal GM was reduced in adult relatives [(McDonald et al., 2006; McIntosh et al., 2006), but see (Borgwardt

et al., 2010; McIntosh et al., 2004)], or was inversely correlated with continuous measures of genetic liability (Cannon et al., 2002; McIntosh et al., 2006). However, in the largest VBM study of adult relatives, unaffected siblings showed a trend for increased lateral PFC GM compared with controls, along with significantly decreased medial PFC and frontal pole GM densities (Honea et al., 2008).

The PFC undergoes maturational alterations in gray matter through the third decade of life, and pathological deviations of these processes may occur in association with both inherited risk and emerging psychosis (Cannon, 2005). Yet, there are few morphometric studies of PFC GM abnormalities in relatives younger than 30, who have not passed through the age of peak risk for psychosis onset (Seidman et al., 2006). In the only region-of-interest (ROI) study of the PFC in young relatives, Lawrie and collaborators (2001) found no significant difference in total PFC GM volumes between FHR and control adolescents of the Edinburgh High Risk Project (EHRP); however, within FHR subjects, total PFC volume did correlate with a quantitative estimate of genetic liability. In subsequent VBM studies, medial PFC GM density emerged as significantly lower in FHR adolescents than controls, and significantly higher in FHR adolescents than first-episode schizophrenia patients (Job et al., 2003; Lawrie et al., 2008). In a different cohort, Diwadkar and colleagues (2006) found reduced regional GM densities of the ventral- and dorsal- lateral PFC in FHR adolescents compared with controls; moreover, DLPFC GM deficits were more pronounced among FHR adolescents with subpsychotic symptoms. In combination, these structural MRI studies in young relatives point to a dual association of medial and DLPFC GM with risk and early disease processes.

We report on an ROI morphometry study of PFC subregions in young relatives of schizophrenia patients. Hand-traced ROI-based morphometry, though labor-intensive and time-consuming, is still considered the gold standard for validating the more exploratory findings of automated VBM studies (Giuliani et al., 2005; Honea et al., 2005; Kubicki et al., 2002). This cross-sectional study tested the hypothesis that FHR subjects would show regional reductions in ventromedial and DLPFC GM volumes compared with controls, and that GM volumes of these subregions would be inversely correlated with subpsychotic symptoms in FHR subjects (i.e., smaller volumes, more symptoms).

2. Methods

2.1. Subjects

Subjects were 27 antipsychotic-naïve FHR children and siblings of persons with DSM-IV (APA, 2000) schizophrenia or schizoaffective disorder, depressed type, and 48 children of healthy adults with no family history of psychosis, selected to be comparable on age (13–28 years) and other demographic variables. They were recruited as part of the Harvard Adolescent Genetic Risk Study, previously described in detail (Glatt et al., 2006; Seidman et al., 2006a,b).

Participants were excluded if they had any lifetime history of psychotic illness, substance dependence, neurological disease, head injury or medical illness with demonstrated cognitive sequelae, sensory impairments, current psychotropic medication use, or a full-scale IQ estimate less than 70. Control subjects had an additional exclusion criterion of any first-degree biological relative with lifetime history of psychotic disorder.

Adult patient probands were drawn from respondents to local newspaper advertisements and announcements posted at Boston area hospitals. Adult control probands responded to similar advertisements in the same catchment areas. After probands gave consent, their children and siblings were contacted to determine eligibility and willingness to participate as study subjects. Human research committees of Massachusetts Mental Health Center, Massachusetts General

Hospital, and Harvard University approved the study. Subjects 18 years and older gave written informed consent. Subjects younger than 18 gave assent while their legal guardian provided consent.

2.2. Psychiatric assessment

Adult patient and control probands completed the Diagnostic and Family Interviews for Genetic Studies (Maxwell, 1996; Nurnberger Jr. et al., 1994). Relatives of probands were screened for psychosis, substance use, and mood disturbance using the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (Geller et al., 1996).

2.3. Subpsychotic symptoms

Subjects completed the Chapman psychosis proneness scales. The Revised Physical Anhedonia Scale (RPAS) assesses reduced capacity to experience physical and sensory pleasures (e.g., "I have often felt uncomfortable when friends touch me") (Chapman et al., 1976). The Perceptual Aberration Scale (PAS) (Chapman et al., 1978) taps perceptual distortions that don't reach the severity of hallucinations (e.g., "Normal colors sometimes seem much too bright to me"). The Magical Ideation Scale (MIS) (Eckblad and Chapman, 1983) inquires about ideas of reference and odd beliefs (e.g., "I might cause something to happen just by thinking too much about it"). Subpsychotic symptom data from all study subjects were previously published (Glatt et al., 2006) and those for this sample of subjects with MRI data are presented in Table 2.

2.4. MRI methods

2.4.1. Acquisition—Whole brain MR images were collected on a Siemens 1.5 Tesla scanner at the Massachusetts General Hospital (MGH) Martinos Center (Charlestown, Massachusetts). A coronal T2-weighted sequence ruled out clinical neuropathology. Two sagittal 3D MP-RAGE, T1-weighted, non-selective inversion-prepared spoiled gradient echo pulse sequences were used for morphometric analyses (TR/TE/T1/flip=2.73s/3.39ms/1.0s/7, bandwidth=190 Hz/pixel, sampling matrix=256×192 pixels, FOV=256×256 mm, effective slice thickness=1.33mm on a 170mm slab of 128 partitions). Images were coded for blind image analysis and transferred to the MGH Center for Morphometric Analysis (CMA).

2.4.2. Gray and white matter segmentation—Brain images were positionally normalized to overcome variations in head position by using a standard 3-dimensional coordinate system (Filipek et al., 1994). This procedure uses the midpoints of the decussations of the anterior and posterior commissure lines and the midsagittal plane at the level of the posterior commissure as points of reference for rotation and translation. Images then were segmented using a semi-automated intensity contour algorithm for external border definition and signal intensity histogram distributions for delineation of gray-white borders.

2.4.3. Cortical parcellation—The neocortex was divided into 48 parcellation units (PUs) per hemisphere (Caviness et al., 1996; Rademacher et al., 1992). This parcellation system approximates architectonic and functional subdivisions, and is based on specific anatomical landmarks present in all brains. All morphometric measurements were performed blind to identifying information. The first author (IMR) parcellated 60 of the 75 subjects, after achieving excellent interrater reliability with a previously trained technician who had parcellated the other 15 brains (ICCs $\geq$ .90). Volumes (ml) were calculated by multiplying the area of each PU by slice thickness, and then summing over all slices containing the PU.

PFC ROIs are shown in Figure 1. The *frontal pole* (FP) was bordered posteriorly by a coronal plane set at the rostral end of the anterior horizontal ramus of the sylvian fissure (AHRS). FP bordered all other PFC ROIs anteriorly. The *dorsolateral PFC* (F1+F2) included the superior and middle frontal gyri, with the central sulcus as its posterior border, the inferior frontal sulcus

as its lateral inferior border, and the paracingulate sulcus as its medial inferior border. The *ventrolateral PFC* (F3t+F3o) had as its superior border the inferior frontal sulcus, the AHRS as its lateral inferior border, and the central sulcus as its posterior border. The *ventromedial PFC* (FMC) was bordered laterally by the olfactory sulcus, superiorly by the paracingulate sulcus, and medially by the interhemispheric fissure. The *orbital PFC* (FOC) was bordered posteriorly by the basal forebrain, laterally by the olfactory sulcus, and medially by the AHRS.

2.5. Statistical analyses

All analyses used relative volumes of PFC ROIs (absolute volume/ total cerebral volume *100) to control for scaling effects of brain size. Two sets of hypothesis-driven analyses were conducted: 1) Repeated measures multivariate analysis of covariance (MANCOVA) examined group differences in regional PFC volumes. Prefrontal volumes were the dependent variables using region/ROI (ventromedial, dorsolateral, ventrolateral, orbital, frontal pole) and hemisphere (left, right) as within-subject repeated measures. Familial risk group (FHR, controls) was the independent variable and age was an à priori covariate. Main or interaction effects of group were followed by least square mean contrasts only if they were statistically significant ($p \leq .05$) at the multivariate level, and after collapsing across any non-significant within-subject dimensions, in order to protect overall Type I error rate. Effect sizes were computed using Cohen's *d* (Cohen, 1988). Although sex and its interactions were entered in the initial MANCOVA, they were not included in the final model because their effects were minimal (p's >.90). For PFC ROIs found to differ significantly between groups, mixed effects ANCOVAs evaluated the effect of familiality; since these mixed models did not alter any findings, their results are not detailed. 2) Pearson's *r* examined associations of psychosis proneness with PFC GM within groups, limiting these correlations to ventromedial and dorsolateral subregions as *à priori* hypotheses. All p-values are two-tailed.

3. Results

Demographic data are presented in Table 1. Groups were comparable except for a significantly lower parental SES in the FHR group.

3.1. Repeated measures MANCOVA

The main effect of group was nonsignificant (F= 3.023, df= 1/72, p= .09), while the interaction of group with region was statistically significant (F= 2.62, df= 4/69, p= .04), indicating that FHR and control subjects differed on some prefrontal regions but not others. The interactions of group with hemisphere and region-within-hemisphere were not significant (p's > .20). Age was a significant covariate (F= 20.40, df= 1/72, p<.001) and interacted significantly with region (F= 5.97, df= 4/69, p≤.001), but not with hemisphere or region-within-hemisphere.

Least square mean contrasts for the significant group × region interaction, adjusting for age and collapsing across hemispheres, showed the FHR group had significantly smaller GM volumes than controls for two PFC regions: ventromedial (F= 5.29, df= 1/72, p= .02, *d*= −0.57) and frontal pole (F= 4.09, df= 1/72, p= .05, *d*= −0.50) (Table 3).

Follow-up ANCOVAs examined whether significant group differences were affected by entering as covariates two sociodemographic variables that differed significantly (PSES) or marginally (IQ) between groups. The group difference in ventromedial PFC remained significant (F=5.92, df=1/68, p=.02) when covarying for PSES (F= 0.05, df=1/68, p= .82) and IQ (F= 0.76, df= 1/68, p= .39). Similarly, there remained a significant group difference in frontal pole volume (F= 5.09, df= 1/68, p= .03) after covarying for PSES (F= 0.67, df= 1/68, p= .42) and IQ (F= 1.67, df= 1/68, p= .20).

3.2. Correlations of subpsychotic symptoms

Ventromedial PFC GM volume showed a significant negative correlation with RPAS in FHR subjects (r= −0.44, p = .03) but not in controls (r= .27, p= .07). Ventromedial PFC GM was also significantly negatively associated with MIS scores in FHR subjects (r= −.42, p= .04) but not in controls (r= .04, p= .77). Ventromedial PFC and PAS scores were non-significantly negatively correlated in FHR (r= −0.29, p= .15) and control (r= −.04, p= .77) subjects.

DLPFC GM volume was not significantly associated with RPAS (FHR: r= 0.12, p= .53; controls: r= −.01, p= .94), MIS (FHR: r= 0.13, p= .54; controls: r= −.11, p= .44), or PAS (FHR: r= 0.06, p= .78; controls: r= .03, p= .84) scores.

4. Discussion

We found bilateral reductions of ventromedial and polar PFC GM volumes in adolescent and young adult relatives of schizophrenia patients. Neither deficit was explained by differences in total brain size, SES or IQ. As hypothesized, ventromedial PFC GM was also negatively correlated with subpsychotic symptoms in FHR subjects. Contrary to our expectations, DLPFC GM was not related to familial risk for schizophrenia or subpsychotic symptoms.

Our pattern of findings suggests that ventromedial PFC (BA 11,12) GM reductions are associated with both genetic vulnerability and early disease processes in young relatives of schizophrenia patients. Compared with controls, FHR subjects had less GM volume in a ventromedial PFC area that overlaps with the medial PFC ROI found to be hyperactive in our functional MRI (fMRI) study of a subset of these FHR subjects (Whitfield-Gabrieli et al., 2009), all of whom are included in this report. We therefore have converging anatomical and functional imaging evidence in the same sample that medial PFC abnormalities are associated with familial risk for schizophrenia in young adulthood. Ventromedial PFC volumes also correlated with self-reported anhedonia and magical ideation, subpsychotic symptoms found to predict the emergence of full-blown psychosis in certain high-risk samples (Horan et al., 2008; Meehl, 1962). Thus, we postulate that ventromedial PFC GM deficits may partly mediate the transition to psychosis by becoming more pronounced among FHR adolescents who convert. This would dovetail with VBM findings of the EHRP where adolescents at heightened genetic risk for schizophrenia had a medial PFC GM density intermediate between that of low-risk adolescents and first-episode schizophrenia patients (Job et al., 2003; Lawrie et al., 2008). In addition, Koutsouleris et al. (2009) found more pronounced ventromedial PFC GM loss in the late versus early stage of the schizophrenia prodrome, suggesting this deficit may progress in parallel with emerging disease.

This is the first report of decreased frontal pole (BA 10, 9) GM volume in young biological relatives of schizophrenia patients. Frontal pole deficits have been found in some studies of older biological relatives (Cannon et al., 2002; Honea et al., 2008), including a twin study where GM declined proportionally with degree of genetic loading for schizophrenia (Cannon et al., 2002). Their presence in both young and older adult biological relatives of patients suggests the hypothesis that frontal pole GM deficits may be stable markers of genetic risk for schizophrenia.

The ventromedial PFC and frontal pole mediate an array of behaviors that are compromised in schizophrenia. Both regions have been implicated in socioemotional and self-monitoring functions, including mentalizing (i.e., “theory of mind”) and reality monitoring. The frontal poles are involved in aspects of self/other distinctions, including the ability to distinguish information that is perceived in the environment (other-generated) from information that is imagined (self-generated) (Simons et al., 2006). Deficits in these abilities, in turn, may underlie the genesis of psychotic symptoms (Frith, 1992). Medial PFC involvement is the most

replicated finding of functional imaging studies of mentalizing (Brunet-Gouet and Decety, 2006). Moreover, in the only fMRI study of biological relatives of schizophrenia patients performing a mentalizing task, medial PFC activation was positively associated with both genetic risk and subpsychotic symptoms (Marjoram et al., 2006).

A lack of significant familial risk group differences in lateral PFC and OFC volumes may be consistent with research linking anatomical abnormalities in these areas with transition to full-blown psychosis (Smieskova et al., 2010; Wood et al., 2008). In a study of prodromal youth, Pantelis and colleagues (2003) found that subjects who developed psychosis ("converters") had significantly less baseline right DLPFC GM, and a significant reduction of OFC GM over time compared with non-converters. In similar longitudinal studies, Borgwardt and colleagues (2007, 2008) found more pronounced reductions of lateral and orbital PFC GM in converters relative to non-converters over time, and Sun et al (2009) reported greater contraction of the right DLPFC in association with psychosis onset. Thus, lateral and orbital PFC GM reductions may mark transition to psychotic symptoms, more so than genetic predisposition to schizophrenia in youth. Alternatively, these reductions may appear later in the developmental course of the disorder, since the DLPFC completes maturation later than the frontal pole and ventromedial PFC (Gogtay et al., 2004). Finally, the absence of significant volume differences in lateral and orbital PFC does not preclude functional abnormalities. In fact, abnormal DLPFC activation has been found in two previous fMRI studies of executive functioning in young FHR subjects (Keshavan et al., 2002), including a subsample from the current study (Seidman et al., 2006b).

As with all studies, this investigation has a number of limitations. Due to the labor- and time-intensive nature of ROI methods, our sample size is limited for the detection of small effects. In addition, the FHR subjects have not passed through the age of risk for onset of psychosis, such that information on clinical outcome is not available. The design of the study also precludes separation of genetic effects from shared environmental effects. Nevertheless, our findings encourage further research into PFC GM subregions as markers of risk for schizophrenia, specifically regarding the hypothesis that they may differentially mark inherited vulnerability and early symptom emergence processes in adolescence and young adulthood.

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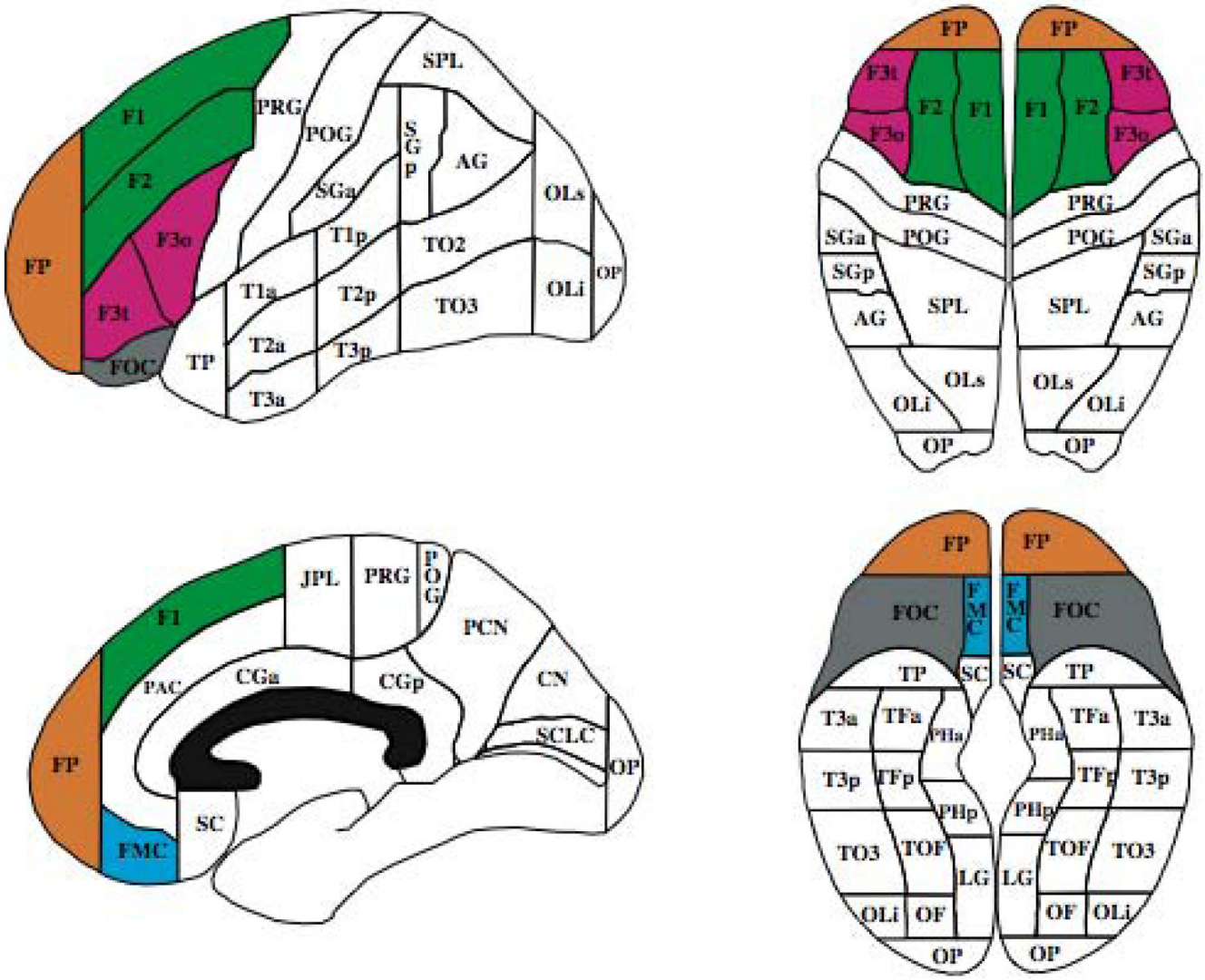

Figure 1.

Parcellation units comprising the prefrontal cortical (PFC) regions of interest: frontal pole (FP; orange), dorsolateral PFC (F1+F2; green), ventrolateral PFC (F3t+F3o; pink), ventromedial PFC (FMC; blue), orbital PFC (FOC; gray).

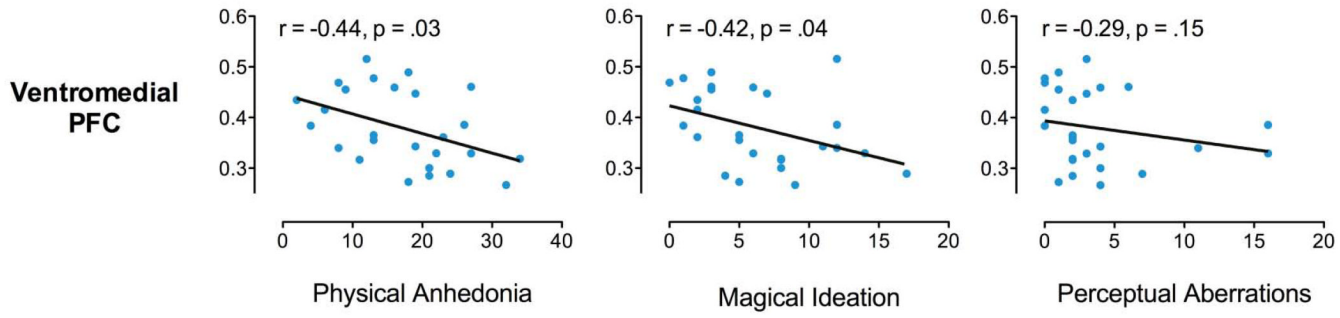

Figure 2.
Relationship of ventromedial prefrontal (VMPFC) GM with scores on three Chapman scales of psychosis proneness in FHR adolescents: A) physical anhedonia; B) magical ideation; C) perceptual aberrations

Table 1

Demographic characteristics [Mean ± SD or N (%)] of youth at familial high-risk (FHR) for schizophrenia and control subjects

	FHR n = 27	Controls n = 48	p
Age (yrs)	19.0 ± 4.2	17.7 ± 3.7	.15
Female	12 (44%)	28 (58%)	.25
Caucasian	14 (52%)	29 (60%)	.15
Right-handed	25 (93%)	42 (89%)	.64
Education (yrs)	10.7 ± 2.7	11.1 ± 3.3	.67
Parental SES [a]	38 ± 26[a]	47 ± 15[a]	.01
Full-Scale IQ [b]	97.4 ± 11.3	103.2 ± 15.4	.10

[a] SES: Socioeconomic status, assessed with the Hollingshead Index

[b] Full-Scale IQ: Prorated from 8 subtests of the Wechsler Intelligence Scale for Children-Third Edition (WISC-III)[56] or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)

Table 2

Scores on Chapman Psychosis Proneness Scales (Mean ± SD) for young adults at familial high-risk (FHR) for schizophrenia and control subjects

	FHR n = 27	Controls n = 48	T-test	p
Psychosis Proneness Scales				
Physical Anhedonia (RPAS)	17.2 ± 8.5	13.0 ± 8.1	2.06	.04
Magical Ideation (MIS)	6.4 ± 4.5	5.9 ± 4.8	0.40	.70
Perceptual Aberrations (PAS)	3.8 ± 4.3	3.2 ± 4.3	0.55	.58

Note: Higher scores indicate more abnormality.

Table 3

Absolute and relative regional prefrontal gray matter volumes in familial high-risk (FHR) and control youth

	Absolute Volumes[a]		Relative Volumes[b]			
	FHR n = 27	**Controls n = 48**	**FHR n = 27**	**Controls n = 48**	**% Difference [c]**	***d*[e]**
Ventromedial, total	4.53 ± 0.18	4.89 ± 0.12	**0.38 ± .01**	**0.42 ± .01** *d*	**−9.22**	**−0.57**
Frontal Pole, total	67.19 ± 2.25	71.07 ± 1.65	**5.72 ± .17**	**6.14 ± .12** *d*	**−6.90**	**−0.50**
Dorsolateral, total	58.75 ± 2.23	59.17 ± 1.15	**4.96 ± .13**	**5.12 ± .09**	**−3.07**	**−0.25**
Ventrolateral, total	16.93 ± 0.51	16.18 ± 0.40	**1.44 ± 0.04**	**1.40 ± 0.03**	**3.22**	**0.23**
Orbitofrontal, total	13.50 ± 0.54	12.57 ± 0.36	**1.15 ± 0.04**	**1.09 ± 0.03**	**5.52**	**0.27**

[a] Absolute volumes in cubic centimeters are given as mean ± standard error;

[b] Significant group × region interaction ($p \leq .04$) in the repeated measures multivariate analysis of covariance predicting left and right relative prefrontal volumes in FHR vs. control subjects, adjusting for total cerebral volume and age;

[c] Percent differences calculated from volumes using five decimal points for accuracy;

[d] Significant difference between groups in follow-up least square mean contrasts, $p \leq .05$;

[e] effect size reported as Cohen's *d*.