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## Alterations in brain structures underlying language function in young adults at high familial risk for schizophrenia

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### Abstract

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1. The authors
2. The families who participated in the research.
3. The research staff.

**Introduction**—Neuroanatomical and cognitive alterations typical of schizophrenia (SZ) patients are observed to a lesser extent in their adolescent and adult first-degree relatives, likely reflecting neurodevelopmental abnormalities associated with genetic risk for the illness. The anatomical pathways for language are hypothesized to be abnormal and to underlie the positive symptoms of schizophrenia. Examining non-psychotic relatives at high familial risk (FHR) for schizophrenia may clarify if these deficits represent trait markers associated with genetic vulnerability, rather than specific markers resulting from the pathological process underlying schizophrenia.

**Methods**—T1 MRI scans from a 3T Siemens scanner of young adult FHR subjects (N=46) and controls with no family history of illness (i.e. at low genetic risk LRC; N=31) were processed using FreeSurfer 5.0. We explored volumetric and lateralization alterations in regions associated with language processing. An extensive neuropsychological battery of language measures was administered.

**Results**—No significant differences were observed between groups on any language measures. Controlling Intracranial volume, significantly smaller center Pars Triangularis (PT) ( $p < 0.01$ ) and right Pars Orbitalis (PO) ( $p < 0.01$ ) volumes and reversal of the L > R Pars Orbitalis ( $p < 0.001$ ) lateralization were observed in FHR subjects. In addition, the L Pars Triangularis and R Pars Orbitalis correlated with performance on tests of linguistic function in the FHR group.

**Conclusions**—Reduced volume and reversed structural asymmetry in language-related regions hypothesized to be altered in SZ are also found in first degree relatives at FHR, despite normal language performance. To clarify if these findings are endophenotypes for Sz, future studies would need to be performed of ill and well family members no longer within the age range of risk for illness to show these deficits segregate with schizophrenia within families. Moreover, measures of complex language need to be studied to determine if FHR individuals manifest impairments in some aspects of language function.

## Introduction

Increasing evidence suggests that brain alterations and subtle neurocognitive abnormalities may predate the manifestations of the clinical features of schizophrenia (SZ) by several years or may reflect the vulnerability for illness that may only be expressed when other risk factors are involved. Investigating such potential precursors is important for distinguishing vulnerability characteristics from those of the illness itself. An important strategy to address this issue is to examine subjects who are at high familial risk (FHR) for the illness by having close family relatives with illness, as well as still being within the age range of risk for the disease. Young relatives of schizophrenia patients are an invaluable group of “at risk” subjects that may shed light on the indicators of vulnerability. The risk for developing schizophrenia or related psychotic disorders is 10–16 % in first-degree relatives as compared with less than 1% among the general population (Gottesman and Shields 1982). Studying these subjects also avoids confounds associated with medications and psychosis invariably associated with studies of patients.

One of the key impairments in SZ is linguistic function and this dimension may also be affected in young FHR individuals (Agnew-Blais & Seidman, in press, 2012). Magnetic Resonance Imaging (MRI) studies have implicated several brain regions underlying language function in the pathophysiology of schizophrenia (reviewed in Shenton et al, 2001; Kubicki et al., 2007; Whitford et al., 2007) and although many of these alterations have been reported in relatives of people with schizophrenia (Boos et al., 2007: meta-analysis), there is a relative paucity of studies investigating the neuroanatomical substrates of language in the illness. In the extant FHR literature (see Table 1), only four publications from two research groups (from Pittsburgh and Edinburgh) have reported on the neural substrates of language in FHR individuals. They report significant decreases in the volumes of the Pars triangularis

(BA 45) (Bhojraj et al, 2009; 2011), prefrontal cortex (McIntosh et al, 2011), supramarginal gyrus, (Bhojraj et al, 2009, 2011), and/or angular gyrus (BA 40) (Bhojraj et al, 2009, 2011b). Of these, the Pittsburgh group(Bhojraj and colleagues) had a broad definition of FHR (needing only 1 relative with SZ, not necessarily first degree). The Edinburgh study (McIntosh et al., 2011) found a relationship of these volume deficits to conversion to psychosis (N=17). The Pittsburgh study (Bhojraj et al, 2009) related structural deficits to a language measure (verbal fluency) underscoring the need for more studies examining these two domains. In this study involving an independent sample of FHR subjects, we addressed more extensive components of language, including phonological awareness.

The anatomy of the language system includes the inferior frontal gyrus (IFG), consisting of the pars triangularis, and orbitalis; inferior parietal cortex (IPC) consisting of the supramarginal and angular gyri; and the superior temporal gyrus (STG) including Heschl's gyrus and Wernicke's area. The IFG is has been shown to mediate the expressive aspects of language (Price 2000; Shalom and Poeppel 2008) of which verbal fluency is one (Hirshorn and Thompson-Schill 2006; Kircher et al., 2009; Lux et al., 2008 Pearlson et al., 1996). The center IFG mediates aspects of language such as phonology, morphology and semantics in addition to syntax (Bookheimer et al, 2002; Hagoort 2005) and it plays a more general role in supporting cognitive functions that are not specific to language (Miller, 2000), but in which language plays a role such as memory retrieval, cognitive control, or processes of selection and/or competition (Thompson-Schill et al., 1999; Moss et al., 2005). The right IFG mediates language prosody (Gandour et al, 2003). The supramarginal gyrus has been shown to be the neural substrate for grammatical processing (Rogalski et al, 2011), and visual word recognition (Stoeckel et al, 2009) while the angular gyrus has been implicated in symbolic processing (Price and Ansari, 2011), and character-to phonological conversion in letter perception (Callan et al, 2005). Finally, the STG, including Heschl's gyrus and Wernicke's area has been implicated in word recognition (Mainy et al, 2008) and auditory language comprehension (Friederici et al, 2010).

Crow et al., (1989, 1990) proposed a theory that schizophrenia arises out of an abnormality in the genetic control for the development of normal cerebral asymmetry that in turn underlies language processing. He further proposed this as the underlying basis for the symptoms of schizophrenia (Crow, 1997; DeLisi, 2001). Some evidence exists from fMRI studies that the processing of language may be abnormal in both people with schizophrenia and their young FHR relatives (Li et al., 2007a,b, 2008; Rajarethinam et al 2011). These studies make a compelling case for further exploration of language related brain anatomy in people at FHR for schizophrenia.

Most family studies of brain structure, with some exceptions (Lawrie et al, 2008; Bhojraj et al 2011a, b; Keshavan et al 2010; Rosso et al., 2010) do not separate out those family members who are in the typical age range for onset of schizophrenia (and thus still at increased risk for illness) from those who are older (e.g., 18–35 for peak risk period versus older). In addition, many of these studies define genetic risk broadly—i.e. as needing only one ill first-degree relative (“simplex”), or even just second degree, to be at risk. By contrast, in families that have multiple affected members (e.g., two or more with psychosis), there is a greater likelihood of transmission of genetic risk across generations. Whereas in simplex families, the possibility exists of non-transmission of a new mutation that has not yet appeared in the germline or an environmental cause. Most studies do not distinguish this characteristic and it is likely to be important. For example, in Seidman et al (2002), in an older group of relatives (mean age 40), nonpsychotic relatives from multiple affected families had more substantial volume reductions in the center hippocampus and had more severe neuropsychological impairments than relatives from simplex families (Faraone et al., 2000). Although, younger relatives 1 within the age of risk for schizophrenia were not

studied to see if this abnormality could predict who later developed schizophrenia, finding hippocampal volume reduction in older well relatives suggests that hippocampal volume reduction may be a familial vulnerability marker that does not necessarily lead to illness.

Deficits in neuropsychological test scores for language functioning have been shown to correlate with reduced brain lateralization in people with schizophrenia (Hoff et al, 1992). Structural MRI studies (O'Donnell et al., 1995; Blackwood et al., 1991; McCarley et al., 2002; Meisenzahl et al., 2004; Lee et al., 2007) have shown lateralization deficits to be associated with language dysfunction in schizophrenia. Recently Oertel et al (2010) found reduced laterality in the planum temporale but not in Heschl's gyrus of FHR subjects. The focus of the present study was to extend the small number of FHR studies to a sample of young people at FHR for schizophrenia who have a high likelihood of inherited vulnerability for illness, and who are studied prior to being considered at ultra-high clinical risk for schizophrenia or in the prodromal stage (Keshavan et al, 2008, Seidman et al 2010, DeLisi et al, 2007), yet while they are still within the peak age of risk for illness. Our specific hypotheses were as follows:

1. Brain regions mediating language would be altered in the FHR subjects in comparison to low familial risk (LRC) subjects. Some of these regions may show altered lateralization
2. Language regions would be correlated with linguistic functions as measured by standardized neurocognitive tests of language.
3. Language functions would be significantly impaired in the FHR group.

## 2. Methods

### 2.1 Participants

Forty six individuals at familial high risk for schizophrenia (FHR) (14 males and 32 females, mean age:  $25 \pm 3.1$  years, range 19–32) with at least 1 first degree family member suffering from schizophrenia or schizoaffective disorder and one second or third degree relative with history of a psychosis, suicide, or psychiatric hospitalization were included in this study (details on demographic characteristics in Table 2). Participants were recruited during 2009–2011 from throughout the Commonwealth of Massachusetts and other New England neighboring regions through brochures and advertisements and by networking through the National Alliance on Mental Illness (NAMI). Thirty one controls (LRC) with no family history of a psychosis in 1<sup>st</sup>, 2<sup>nd</sup> or 3<sup>rd</sup> degree relatives (13 males and 18 females, mean age:  $24 \pm 2.9$  years, range 20–32) were also recruited from the community via advertisements. Participants with a DSM-IV diagnosis of any history of lifetime psychotic disorder were excluded. Additional exclusionary factors were: English not the participant's native language, non-right-handedness, neurological illness, and IQ below 80. The study was approved by the Human Subjects Investigation Committee at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts Institute of Technology, Brigham and Women's Hospital and Veterans Administration Boston Healthcare System, Brockton, Massachusetts. All participants provided written informed consent and the research subjects were paid for their participation.

### 2.2 Procedures

All 77 participants were administered the Diagnostic Interview for Genetic Studies (DIGS). A family pedigree was drawn with information obtained from the participant. All individuals participating in this study received code numbers for processing and storing of data, and no identifying information was obtained about other ill members in the family. All data extracted from interviews including demographic information, psychiatric symptoms,

diagnoses, substance use, and age of onset, were entered into an Excel database by one researcher and data rechecked for accuracy. DSM-IV diagnoses (Axis I for major psychiatric illness and Axis II for personality disorders were made on all participants by a research psychiatrist using all available information collected during the interview). Schizotypal symptoms were measured using the Structured Interview for Schizotypy (SIS; Kendler et al., 1989). Data were acquired on 9 factors from the SIS (magical thinking, ideas of reference, illusions, suspiciousness, psychotic-like symptoms, restricted emotion, social isolation/introversion, schizotypal social anxiety, and anger to slights). A SIS total score was used that summed up all the individual scores into a single composite score.

### 2.3. Neurocognitive Tests

Subjects were administered an extensive battery of 11 verbal neuropsychological tests from several standardized test batteries to test many aspects of linguistic functioning potentially associated with FHR for schizophrenia. The presumed domains and tests included: Semantic knowledge – Vocabulary (Wechsler 1999); Semantic Fluency - Category Fluency, Animal Naming (Benton and Hamsher, 1989); Abstract Reasoning (Delis et al., 2001a), Passage Comprehension (Woodcock Johnson Passage Comprehension Test, Woodcock et al., 2000); Phonological Awareness derived from auditory stimuli (Elision and Blending Words subtests from the Comprehensive Test of Phonological Processing (Wagner et al., 1999); Phonological Awareness derived from visual stimuli including real words (WRAT-4 reading, Wilkinson, 1993), TOWRE Single Word Efficiency - Woodcock-Johnson Letter Word Identification, Woodcock et al., 2000) and non-words (TOWRE Phonemic Decoding Efficiency; Woodcock Johnson Word Attack).

### 2.4 Image Acquisition

All imaging was performed at A.A. Martinos Imaging Center in the McGovern Institute for Brain Research at MIT (Massachusetts Institute of Technology) on a Siemens TRIO TIM 3.0 Tesla research dedicated spectrometer. A 32 channel head coil was used for all participants. The system is equipped with a 40 mT/m gradient set optimized for minimum gradient nonlinearity and eddy currents, particularly important for quantitative diffusion tensor imaging. A certified MRI Technician used a Structured Quality Control Phantom (ACR) to perform quality assurance scans on a weekly basis. These include standard ACR scans as well as additional EPI-based scans. Sequence Descriptions: Localizer: A Fast Low Angle Shot (FLASH) sequence with 3 orthogonal slices in sagittal, coronal, and axial planes was used for orienting the 3D anatomical scan. Acquisition parameters: TR 15 ms, TE 6 ms, flip angle 30 degrees, slice thickness 8 mm, matrix 256×256, FOV 300 mm, acquisition time under 1 min. Images were coded for blind image analysis and transferred to the first author (AF) for morphometric analysis using FreeSurfer 5.0.

Each MRI scan was visually inspected for movement artifacts and radio frequency in homogeneities before image processing using FreeSurfer. Only one scan was deemed unprocessable due to excessive movement artifact. This was excluded from the study. Then each image underwent FreeSurfer image processing. FreeSurfer has three automated stages, each followed by manual image editing by an Image Analyst (AF). The first stage performs skull stripping and motion correction, while the second performs gray-white segmentation (Fischl et al., 2002). The third automatically parcellates the brain using gyral anatomical landmarks and surface area and thickness measurements (Desikan et al., 2006). Each stage has been shown to be valid and reliable with manual tracing and automated methods (Tae et al., 2008). The Image Analyst processing MRI data was blind to any aspect of subject identity and group assignment. Detailed information about the FreeSurfer analysis and processing streams may be found in Francis et al, (2011). We measured the Pars triangularis,



Pars orbitalis, Supramarginal gyrus, Angular gyrus, and STG. However, we did not include the Heschl's gyrus since FreeSurfer did not reliably measure this region.

## 2.5 Statistical analysis

Statistical analyses were performed with the Statistica version 8. Structural measures and age were normally distributed [Shapiro-Wilk's test (W statistic,  $p > 0.1$ )]. The FHR group had smaller intra cranial volumes (ICV) compared with the LRC group [Mean LRC = 1523538 mm<sup>3</sup> SD +/- 253989; Mean FHR = 1414780 mm<sup>3</sup> SD +/- 217666 ( $p = 0.04$ )]. Volumes of language related brain regions were initially compared between study groups using ANCOVA. To control for multiple comparisons, we performed GLM Multivariate analysis of covariance (MANCOVA) with each of the brain language regions as the dependent variables, study group and gender as categorical predictors, and ICV as covariate. Correlations with age were computed using partial correlations with ICV and age at the time of scan as covariates. The correlations were performed only for those regions showing volumetric deficits. Spearman *rho* correlations were used to examine the significant structural abnormalities findings with the SIS scores, since the latter were not normally distributed. All *p*-values were two-tailed. We also examined laterality indices (laterality index = Center volume-right volume / Center volume + right volume) in the 5 language regions. We used a one way ANOVA to examine differences in laterality index. We then used repeated measures ANCOVA with side as the withinsubject factor and study group as between-subject factor to assess group X side interactions, controlling ICV and age. To compare neuropsychological test performance of language function between the groups we used independent samples T tests.

## 3. Results

**Demographic Characteristics:** No statistically significant differences in age, years of education, and sex were found between FHR and LRC subjects, although the FHR group had more female participants than the LRC group. Parental SES was significantly higher in the LRC group than FHR ( $p < 0.03$ ).

**Neuropsychological Characteristics:** None of the language functions were statistically significant between groups at  $p < .05$  uncorrected (See Table 5).

**Language Anatomy Regions of Interest:** Multivariate Analysis of covariance was performed with language regions (Pars Triangularis, Pars Orbitalis, Supramarginal Gyrus, Angular Gyrus and Superior Temporal Gyrus) within each hemisphere as dependent variables, Group and Sex and independent variables with ICV and Age as continuous variables. The MANCOVA analysis for the center hemisphere was significant:  $F(5, 67) = 2.2570$ ,  $p < 0.05$  Wilks lambda = .85585. For the right hemisphere  $F$  was also significant:  $(5, 67) = 3.0165$ ,  $p = 0.016$ ; Wilks lambda = .81625.

Analysis of covariance on all the language regions showed significant gray matter (henceforth GM) decrements in the center pars triangularis ( $p < 0.01$ ) and right pars orbitalis ( $p < 0.01$ ) of the ventrolateral prefrontal cortex (see Table 2).

### Lateralization

We compared the laterality index between the groups in all the language regions. Comparing laterality coefficients using a one way ANOVA showed that the Pars Orbitalis had reversed lateralization ( $p < 0.001$ ). The angular gyrus showed a trend ( $p < 0.06$ ) (see table 3 for all values). The other regions (e.g., Pars triangularis) showed reversed lateralization but this was not significant.

### Group X Side interactions

The repeated measures ANCOVA s showed that there was a significant group X side interaction in the pars triangularis ( $p < 0.02$ ) (see FIG 2), and pars orbitalis ( $p < 0.001$ ) (see FIG 3). No other language regions showed a significant interaction.

### Language anatomy regions and Language functions

Using Pearson's product moment correlations we examined the association of the L Pars Triangularis and R Pars Orbitalis volumes with aspects of linguistic function measured by standardized cognitive tests within the FHR group. The Center PT correlated significantly with the proverbs total achievement score from the DKEFS Proverbs test [ $r = .34$   $p < 0.05$ ] (see table 5). The Right PO correlated significantly with the WJ Letter Word Identification test [ $r = .35$   $p < 0.05$ ], WASI Vocabulary test [ $r = .34$   $p < 0.05$ ], CTOPP Elision standard score [ $r = .35$   $p < 0.05$ ], WRAT-4 Reading standard score [ $r = .32$   $p < 0.05$ ], WJ Passage comprehension standard score [ $r = .34$   $p < 0.05$ ], and Single word efficiency from the TOWRE [ $r = .42$   $p < 0.05$ ], (see table 5). In the control group, the center PT did not correlate with any language task while the right PO correlated only with letter word identification and the Towre test but not others.

## 4. Discussion

The purpose of this study was twofold: 1. To examine whether brain regions mediating language function are altered structurally in FHR subjects and, 2. To determine if language functions associated with these regions were altered in FHR subjects and to examine the brain volume- language associations in the two groups. The results from this study show that FHR subjects have reductions in some brain regions that mediate language, i.e., the center pars triangularis (PT) gray matter (GM) and right pars orbitalis gray matter of the ventrolateral PFC confirming the findings of other studies of FHR youth from independent samples (Bhojraj et al, 2009; 2011). The normal  $L > R$  asymmetry of the Pars Orbitalis was also reversed in the FHR subjects differing from the findings of Bhojraj et al, (2009), Oertel et al, (2010) who showed altered asymmetry, not in the Pars Orbitalis, but rather in the pars triangularis. Nevertheless, this asymmetry occurred within the broader region of interest of Broca's area, a key region for language. Bhojraj et al (2009) had broader criteria for people who were at FHR for schizophrenia. That is, they only needed one ill family member and this member could be a first or second degree relative. Since both the center pars orbitalis and pars triangularis are cognitively linked to linguistic function (Foundas et al, 1996), reduced volume could make one susceptible to abnormalities in language functioning. However, language functions, as measured by an extensive battery of linguistic function tests, were not significantly different in the FHR group compared with the LRC group.

It is interesting that no significant language deficits were observed in the FHR group, although previous studies of some linguistic functions in FHR samples in this age range (mainly  $< 30$  years of age) have shown impairments (Agnew-Blais & Seidman, in press). It is unlikely that this negative result is associated with limited statistical power because this sample was reasonably comparable in size to many studies in the literature that did demonstrate deficits. Moreover, it is unlikely to be a function of a limited selection of measures as many measures tapping different functions were given. However, this set of measures did not tap prosody or more complex linguistic functions tapping into more organizational or executive components of language such as measures of story telling or extended verbal output. Thus, although dysfunctional aspects of phonological processing typical of dyslexia were not observed in this sample, we cannot rule out deficits in more complex language processing associated with executive function. These may be uncovered through fMRI using language paradigms.



Although we did not find significant language deficits in the FHR group by standardized cognitive testing, we did observe putatively atypical associations between language functions and brain volumes. On the whole within subjects, the FHR group showed a stronger association of verbal linguistic measures and brain volumes than was observed within controls (7 significant associations significant compared with 2 in the controls). Second, we found that the pattern of associations in the FHR group was somewhat atypical from expectation as the language measures tended to correlate with right pars orbitalis rather than center. The center PT in the FHR subjects was positively correlated with the proverb interpretation standard score from the DKEFS test. The right Pars Orbitalis was positively correlated with several language tests: the letter word identification test and the passage comprehension standard score of the Woodcock Johnson 3, the Elision standard score of the Comprehensive test of phonological processing, the reading subtest of the WRAT, the vocabulary subtest of the WASI scale, the single word efficiency test of the TOWRE scale.

The pattern we observed raised the question as to whether the language network organization could be altered in the FHR subjects with a stronger association to right then center hemisphere. With the exception of the category fluency test (Animals), most of these tests were significantly inter-correlated in the FHR subjects (results available from first author upon request) suggesting that these could be within the same network of brain regions and possibly localized within the right hemisphere. The category fluency test is known to be localized within the center hemisphere. (Hirshorn and Thompson-Schill 2006; Kircher et al., 2009; Lux et al., 2008; Pearlson et al., 1996).

In addition, previous work with schizophrenia demonstrating reduced or reversed lateralization has been shown to correlate with deficits in language function (Hoff et al., 1992). Moreover, loss of language region asymmetry in schizophrenia (Crow 1997a, 2000a; Hallett et al., 1986) may have a genetic basis (Crow 2000a, b), and may manifest in genetically predisposed subjects. In line with the altered asymmetry finding, several of the language tests were positively correlated with right hemisphere rather than center hemisphere volumes as observed in healthy controls indicating that in ontogeny of the vulnerable brain, several language functions could be lateralized to the right hemisphere instead of the 'normal' center. This could be a trait dependent early indicator of future psychosis. The structural aberrations observed and the correlations with linguistic function indicate that in FHR subjects these may be early premorbid factors that in future longitudinal studies may be shown to predict who among FHR individuals are more vulnerable for developing schizophrenia.

Taken together, our results confirm previous studies in the literature of young people at risk for schizophrenia, (McIntosh et al, 2011,; Bhojraj et al, 2011a, 2011b; Oertel et al., 2010;) and also take them further to show that these findings are specifically present in people who satisfy a more narrow definition for being at genetic high risk, i.e. having likely inheritance of the disorder.

A limitation of this study is that this was not a longitudinal study and thus we do not know whether the abnormalities found are predictive of who later develops illness. In addition, we have not studied the affected individuals within each family to be able to determine whether these abnormalities cluster within families, as one would expect if they have an inherited basis, and further if they segregate with illness within families.

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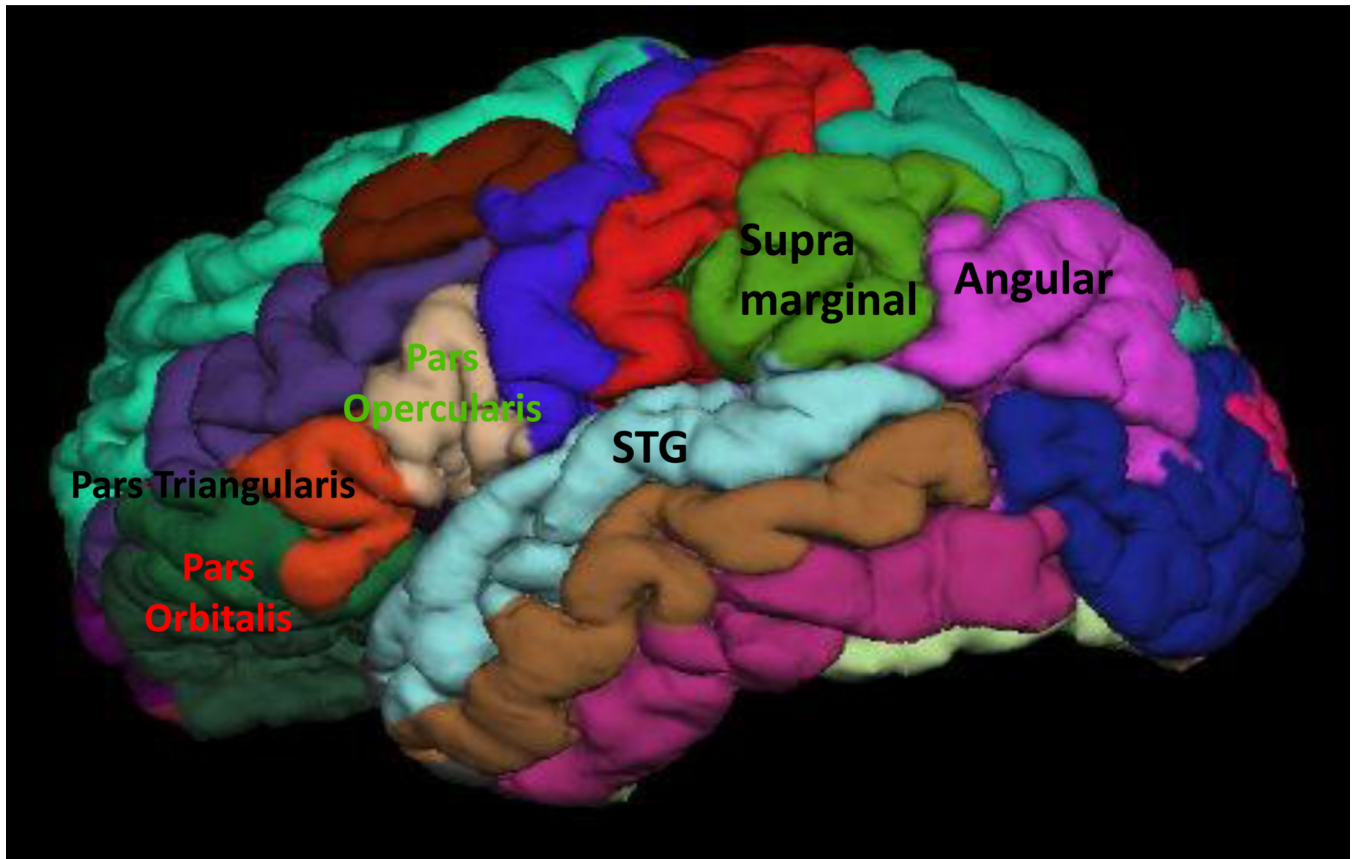
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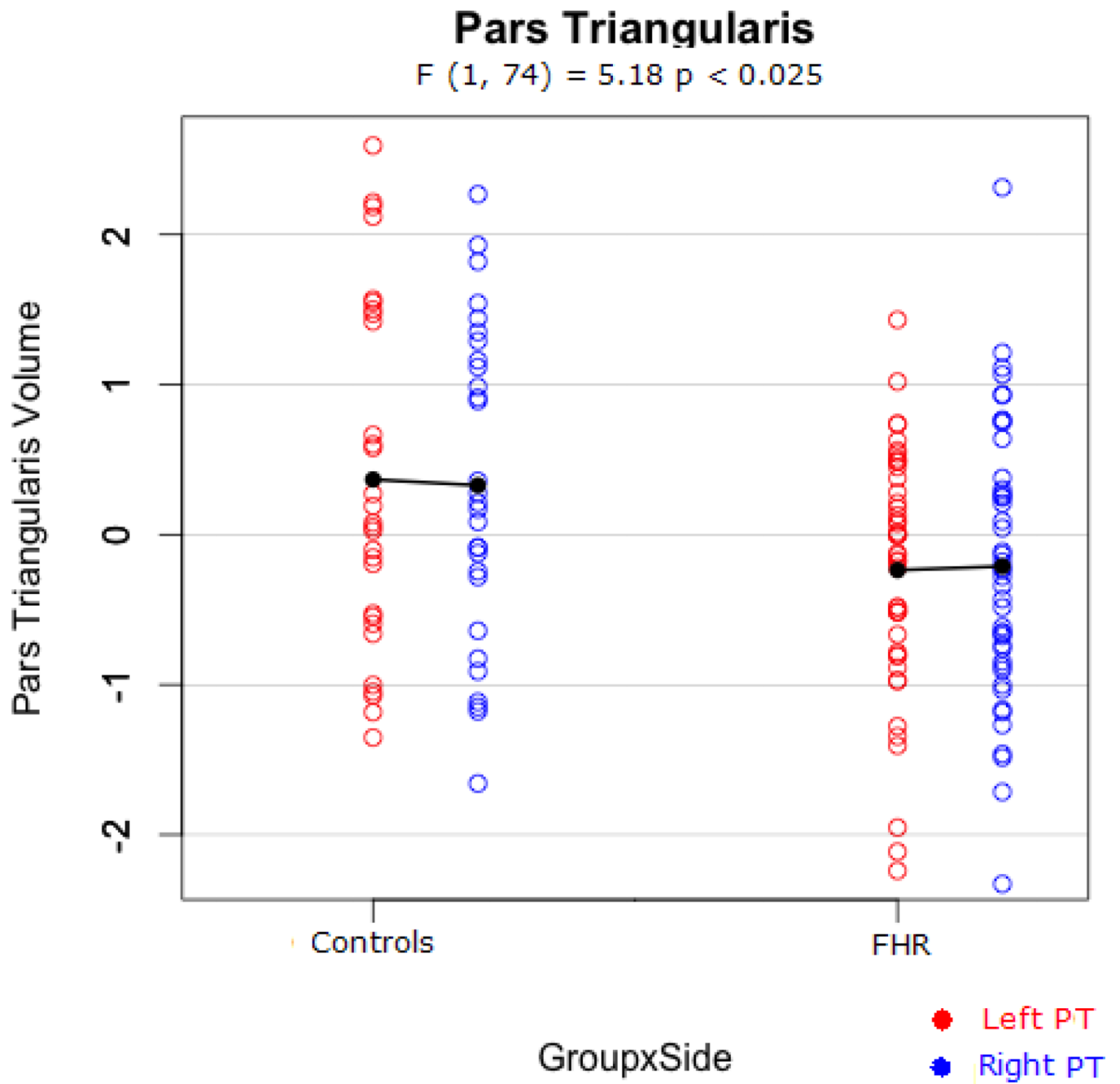
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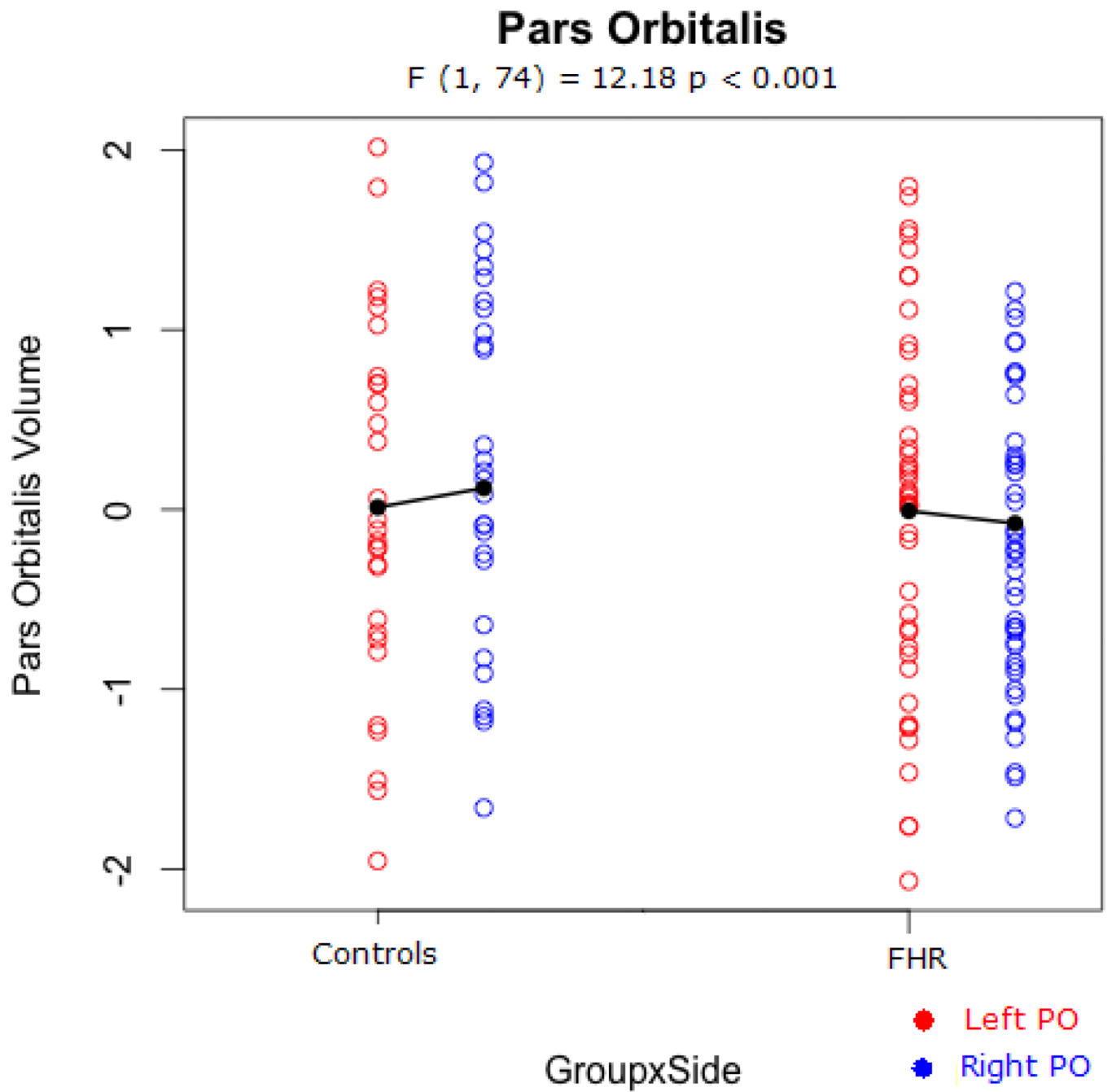




**Figure 1.**  
FreeSurfer parcellation – Language Areas of the brain



**Figure 2.**  
 Comparison of volume of R and L Pars Triangularis across groups.



**Figure 3.**  
Comparison of volume of Right and Center Pars Orbitalis across groups.

**Table 1**

Previous published MRI findings of brain structural alterations in language regions in familial high risk (FHR) subjects. HC=control subjects. ROI=region of interest.

STUDY, Date	Geographic Location	Method	Age Range of subjects	No of Subjects	Main Findings
Bhojraj et al, 2009	Pittsburgh High Risk Study	FreeSurfer	9–25	158 / *	Reduced Pars Triangularis, L Supramarginal, R Angular & R Heschls gyri.
Oertel et al, 2010	Frankfurt	ROI & SPM	26–59	47 <sup>2*</sup>	Reduced Left auditory cortex and L Planum temporal
McIntosh et al, 2011	Edinburgh High Risk Study	Semi-automated ROI	16–25	182 <sup>2**</sup>	Reduced Left inferior Prefrontal gyrus
Bhojraj et al, 2011	Pittsburgh High Risk Study	FreeSurfer	9–25	100 <sup>4*</sup>	Reduced Left & Right Inferior frontal Gyri.

**Inclusion Criteria:**

1. 77 first-degree relatives (66 offspring and 11 siblings) and 17 second-degree relatives. 64 controls.
2. 16 schizophrenia patients, 16 age-matched first-degree relatives, and 15 healthy controls
3. 146 FHR and 36 controls. Longitudinal study. 17 converters.
4. Sixty first and second-degree young relatives of schizophrenia patients. Forty controls.

\* One relative with SZ.

\*\* At least two first or second degree relative with a diagnosis of SZ.

**Table 2**

Demographic characteristics of current subject population: MDD = Major Depressive Disorder; AD=Anxiety Disorder

	<b>FHR (n=46)</b> M±SD / N (%)	<b>LRC (n=30)</b> M±SD / N (%)	<i>p</i> <sup>b</sup>
Age (yrs)	25 ± 3.1	24 ± 2.9	.205
Female	32 (70%)	18 (58%)	.219
Caucasian	38 (79%)	24 (78%)	.500
Education (yrs)	15 ± 2.2	16 ± 1.2	.301
Parental SES <sup>(a)</sup>	2.8±1.4	2.0±1.1	.010
DSM-IV MDD	27 (58.7%)	2 (6.7%)	<.0001
DSM-IV AD	9 (19.6%)	2 (6.7%)	.183
SIS Score >2	33 (71.7%)	11 (36.7%)	.001

<sup>(a)</sup> SES: Socioeconomic status, assessed with the Hollingshead Index.

<sup>(b)</sup> <sup>b</sup> Fisher's exact test or independent *t*-test, two-tailed, for significant differences between high risk subjects and healthy controls.

Table 3

Language Structures: Gray Matter Volumes:

Regional Volumes in mm <sup>3</sup>	Controls N=29		FHR N=45		Effect Size	F (1, 74)	P
	Mean	SD	Mean	SD			
Left Pars Triangularis	2977.4	603.7	2662.4	424.3	0.2889	6.01	0.01*
Left Pars Orbitalis	859.1	162.3	855.8	161.6	0.0101	ns	ns
Left Supra Marginal	7574.1	1516.2	7095.9	989.4	0.1836	ns	ns
Left Angular Gyrus	6641.5	1361.5	6065.5	935.9	0.2393	ns	ns
Left STG	6378.6	928.8	6133.3	616	0.1537	ns	ns
Right Pars Triangularis	2918.3	613.5	2604.2	529.3	0.2644	ns	ns
Right Pars Orbitalis	945.5	306.3	896.9	201.6	0.093	6.96	0.01*
Right Supra Marginal	6876.6	1377.4	6516.6	1182.1	0.1389	ns	ns
Right Angular Gyrus	8230.3	1689.5	7721.5	1218	0.1702	ns	ns
Right STG	5438.8	1164	5252.9	671.3	0.097	ns	Ns

\* Tested for multiple comparisons



**Table 4**

Laterality Indices for Language regions.

Regions	Laterality Coefficients				F (1, 74)	P
	Controls N=29		FHR N=45			
	Mean	SD	Mean	SD		
Pars Triangularis	-6.61	10.33	-5.1	8.04	.508	ns
Pars Orbitalis	-33.24	8.80	-26.82	8.09	10.6	0.001
Supra Marginal	-8.02	8.54	-9.71	6.07	1.01	ns
Angular Gyrus	76.9	3.68	75	4.54	3.49	0.06
STG	-28.0	5.05	-28.2	5.27	.508	ns

Table 5

Language Test Score comparison and Pearson's correlations of Language regions with language measures in FHR and LRC subjects.

Cognitive Test	Language Test Scores Across Groups				Correlations with Brain structure within groups					
	FHR		LRC		FHR		LRC		P	
	Mean	SD	Mean	SD	Left P T	Right P O	Left P T	Right P O	Left P T	Right P O
WASI: Vocabulary (WAVOCSS)	13.57	2.71	13.84	3.24	0.7	.34*	.07	.13	.27	.27
WRAT: Reading Standard Score	110.8	11.7	105	24.52	0.18	.32*	.13	.14	.30	.30
Letter Word Identification (LWISS)	106.2	9.6	104.4	9.1	0.44	.35*	.11	-0.01	.35*	.35*
CTOPP – Elision (ESS)	10.23	1.7	10.18	2.3	0.91	.35*	.21	.13	.11	.11
Passage Comprehension (PCSS)	109.4	9.21	108.2	11.5	0.63	.34*	.18	-.08	.26	.26
TOWRE : Single Word Efficiency (standard score)	100.2	10.78	100.8	11.9	0.81	.42*	.17	-.18	.46*	.46*
DKEFS Proverbs Total Achievement score (SS)	11.37	2.37	10.66	3.44	0.32	.34*	.05	.12	.14	.14
Blending Words Standard Score	11.4	2.16	11.48	2.62	0.89	.14	.14	.05	.19	.19
Phonological Awareness Composite score	103.7	10.69	102.4	16.53	0.68	.11	.11	.21	-.17	-.20
Category Fluency (Animals)	23.1	5.04	23.2	4.3	0.93	.10	.10	.14	-.20	.09
Word Attack Score	105.5	9.92	102.2	10.15	0.19	.09	.09	-.15	.13	.13

\* p< 0.05; PT – Pars Triangularis; PO – Pars Orbitalis