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Fronto-parietal hypo-activation during working memory independent of structural abnormalities: Conjoint fMRI and sMRI analyses in adolescent offspring of schizophrenia patients

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Abstract

Adolescent offspring of schizophrenia patients (HR-S) are an important group in whom to study impaired brain function and structure, particularly of the frontal cortices. Studies of working memory have suggested behavioral deficits and fMRI-measured hypoactivity in fronto-parietal regions in these subjects. Independent structural MRI (sMRI) studies have suggested exaggerated frontal gray matter decline. Therefore the emergent view is that fronto-parietal deficits in function and structure characterize HR-S. However, it is unknown if fronto-parietal sub-regions in which fMRI-measured hypo-activity might be observed are precisely those regions of the cortex in which gray matter deficits are also observed. To investigate this question we conducted conjoint analyses of fronto-parietal function and structure in HR-S (n=19) and controls (n=24) with no family history of psychoses using fMRI data during a continuous working memory task (2 Back), and sMRI collected in the same session. HR-S demonstrated significantly reduced BOLD activation in left dorso-lateral prefrontal cortex (BA 9/46) and bilateral parietal cortex (BA 7/40). Sub-regions of interest were created from the significant fronto-parietal functional clusters. Analyses of gray matter volume from volume-modulated gray matter segments in these clusters did not reveal significant gray matter differences between groups. The results suggest that functional impairments in adolescent HR-S can be independent of impairments in structure, suggesting that the relationship between impaired function and structure is complex. Further studies will be needed to more closely assess whether impairments in function and structure provide independent or interacting pathways of vulnerability in this population.

Keywords

Schizophrenia; Adolescent Offspring; Working Memory; Vulnerability; fMRI; Structural MRI

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Conflicts of Interest. None.

1. Introduction

Adolescent offspring of schizophrenia patients are at increased risk for schizophrenia and psychiatric disorders, and therefore provide an interesting and important group in whom to assess vulnerabilities in developmentally mediated brain dysfunction and structure (Diwadkar et al., 2004). Whereas documented conversion rates to psychosis are relatively low, the incidence of psychopathology (Keshavan et al., 2008), cognitive and affective impairments and *in vivo* imaging related abnormalities (Diwadkar et al., 2006; Keshavan et al., 2002a) is relatively high or significantly different from controls (with no immediate family history of the disorder). The emerging view is that this high risk group (henceforth HR-S) while heterogeneous, nevertheless represents a developmentally vulnerable cohort, characterized by impaired brain function, structure and neurochemistry.

Recent investigations have targeted the understanding of disordered function of prefrontal tasks, in particular working memory (Casey et al., 1995) in HR-S. Working memory is the ability to retain and in the case of specific tasks such as the n-back to manipulate information for brief intervals (Baddeley, 1986; Rypma et al., 1999). In general, load-dependent processing in working memory is generally associated with fronto-parietal activity (Braver et al., 1997; Chafee and Goldman-Rakic, 2000). Primate studies have indicated the presence of single cell units within the superior frontal sulcus that specifically code for the retention of memoranda for brief intervals in time (Fuster, 1989). *In vivo* studies of both spatial and non-spatial working memory suggest that working memory implementation in humans has similarities with primates. For example, both the prefrontal and parietal cortices are sensitive to increases in verbal working memory load (Braver et al., 1997), analogous to increases in phasic activity in prefrontal neurons as a function of memory delay (Funahashi et al., 1989). Further, memory guided saccades in the macaque are implemented in large part by interdependent activity between fronto-parietal units (Chafee and Goldman-Rakic, 2000). Analogously in humans, fronto-parietal connectivity is positively modulated by increases in working memory load (Diwadkar et al., 2000). Though the functional architecture of working memory is not confined to fronto-parietal interactions (Wager and Smith, 2003), the previously cited and other studies (Edin et al., 2007) suggest that fronto-parietal interactions may underlie the development of working memory mechanisms in the brain. Furthermore, working memory deficits have long been thought to lie at the center of cognitive deficits in the schizophrenia diathesis (Goldman-Rakic, 1999) and have been related to independently observed deficits in frontal structure.

1.1 Deficits in HR-S

In HR-S, working memory deficits have been demonstrated when memory maintenance interval increase from brief to longer delays (Diwadkar et al., 2001). Preliminary fMRI studies during working memory tasks suggesting reduced response of the dorsal prefrontal cortex (Keshavan et al., 2002b). Independently of the fMRI results, structural MRI (sMRI) studies have documented fronto-parietal reductions in gray matter (Diwadkar et al., 2006) suggesting an emergent structural impairment related to the ongoing developmental processes of cortical pruning or thinning that are particularly active in fronto-parietal cortex through adolescence (Gogtay et al., 2004). Therefore, in general, it is assumed that impaired fMRI-related fronto-parietal function in HR-S is related to reduced volume or structural integrity of these regions. This has lead to the general notion that, as in the case with the schizophrenia spectrum (Manoach, 2003; Weinberger et al., 2001), HR-S are also characterized by disordered functionality of the frontal lobe. However, it is unknown whether in HR-S, reduced gray matter volume or micro-structure is a necessary condition for the presence of functional alterations in frontal and parietal cortex during working memory. The answer to this question may a) help address the functional relevance of gray

matter deficits in HR-S and b) elucidate the relative contributions of fMRI and sMRI related vulnerabilities in these subjects.

Here we used an established verbal working memory task (Casey et al., 1995; Cohen et al., 1997), the n-back to assess working memory related activation differences in HR-S compared to HC specifically in the frontal and parietal cortices. Then, fMRI-based region of interest masks were created to include clusters with significant differences in activation. Finally, fMRI-based masks were used to extract gray matter volume (based on T1-weighted MRI images) from these functionally defined regions of interest. The noted advantage of this approach is that it allows us to identify working memory related hypo-activity in fronto-parietal cortex in HR-S, and *specifically* assess whether significantly different clusters are characterized by reductions in gray matter. In short, the convergent approach permits an assessment of whether gray matter deficits in HR-S are *necessary* for *differences* in fMRI-measured fronto-parietal function.

2. Methods

2.1 Subjects

Forty three subjects gave informed consent or assent to participate in the fMRI studies. MRI and behavioral protocols were approved by the Human Investigative Committee (HIC) of Wayne State University. Subjects received monetary compensation for their participation. The twenty four controls (HC; age:10–19, mean=14.5 yrs; 8 females) had no family history of psychiatric illness to the 2nd degree. Nineteen HR-S had at least one parent with schizophrenia (HR-S; age:8–19, mean=14.16 yrs; 7 females). Subjects were recruited from the greater Detroit area through advertisements and through out-patient services at the University Psychiatric Center, Wayne State University School of Medicine. Rule outs were achieved through telephone and personal interview, and screening questionnaires, to ascertain if subjects had a history of psychotic illness in first-degree relatives. Diagnoses for parents of HR-S were reached using the Structured Clinical Interview for DSM-IV schizophrenia (First et al., 1997) and consensus meetings chaired by a senior clinician (M.S.K.) discussing all available data. Subjects younger than 15 years were clinically evaluated using the Schedule for Affective Disorders and Schizophrenia -Child Version (K-SADS) (Kaufman et al., 1997); those aged 15 years or above were assessed using the SCID, and all subjects were assessed with the Structured Interview for Prodromal Symptoms (Miller et al., 2003; Miller et al., 2002). Assessments were administered by a trained interviewer (U.R., A.J.). Four HR-S were diagnosed with disorders (which were not exclusionary criteria) including Separation Anxiety

Disorder (n=1), Attention Deficit Hyperactivity Disorder hyperactive type (n=1) and Social phobia (n=1). Table 1 presents the general characteristics of the sample, including the average Global Assessment of Function (GAF) sub-scale of the SIPS. The GAF is an index of the psychological, social, and occupational functioning of individuals providing a measure of the extent of clinically assessed impairment in individuals.

2.2 fMRI and sMRI

MR images were acquired on a Bruker MedSpec 4.0 T full-body scanner with an 8-channel head coil. For fMRI, gradient echo EPI was collected over an 11.5 minute scan time (TR = 2000ms, TE = 30 ms, matrix = 64×64, slices =24, FOV = 240 mm, voxel size = 3.8×3.8×4.0mm). In the same subjects, high resolution sMRI images were axially acquired using a whole brain 3D T1-weighted MPRAGE sequence (TR = 2200ms, TE = 2.56 ms, Flip angle = 13º, FOV = 208×256 mm, voxel size = 1×1×1 mm).

During fMRI, stimuli were projected from a computer onto a screen mounted over the subject's head which they could view through a mirror. An MRI-compatible two-button box was provided to subjects for them to indicate their responses. Foam padding was packed around each subject's head to minimize movement, and subjects were given earplugs to reduce noise. Working Memory Paradigm. Subjects participated in an established verbal n-back paradigm (Casey et al., 1995). Letters were projected in sequence (Presentation Time: 500 ms; ISI: 2500 ms) and subjects signaled if a letter was a target letter (0-back condition) or the same as one shown two letters ago in the sequence (2-back condition). Conditions were blocked (30 s/block) and the paradigm cycled between rest epochs (20 s), 0-back and 2-back conditions.

2.3 fMRI and sMRI Processing

MR images were preprocessed and analyzed using SPM (Statistical Parametric Mapping, Wellcome Department of Imaging and Neuroscience, London, UK). For fMRI, all images were manually oriented to the AC-PC line, realigned to correct for head movement, spatially normalized to the MNI (Montreal Neurological Institute) template brain, resliced (2 mm^3) and smoothed spatially by a Gaussian filter of 8mm full-width half maximum (FWHM). An autoregressive AR(1) model was used to account for serial correlation and regressors modeled as a 30 sec box-car vectors (for each of the task-related conditions) were convolved with a canonical hemodynamic reference wave form, with the six motion parameters included as co-variates of no interest. To isolate *memory related* processing, first level contrasts were computed based on 2Back>0Back contrasts for each subject, and were submitted to second-level random effects analyses of covariance (age and gender as covariates) to identify group differences in memory-related activity.

To identify differences from controls in HR-S, data were spatially thresholded in the dorsal prefrontal cortex (Brodmann Area 9/46) and the superior parietal cortex (BA 7/40) based on structural regions of interest in stereotactic space (Maldjian et al., 2003). Because we wanted to optimize sensitivity to detect clusters with significant voxels (p_u<.05) in order to specifically interrogate fMRI-defined regions of interest, cluster extent thresholds (p_c<.01) were derived based on 10^4 Monte Carlo simulations from voxels across the individual regions of interest (Ward, 2000). The bilateral clusters of peak significance (see Results) within each of the regions were saved as spatial masks (2 mm^3 voxel sizes) in MNI space. sMRI analyses were focused specifically on estimated gray matter underlying these functionally derived masks.

sMRI images were processed using SPM's diffeomorphic image registration algorithm (DARTEL)(Ashburner, 2007). DARTEL optimizes the fidelity of shape-based deformations applied to fit native images in stereotactic space, outperforming all or most competing non-linear deformation algorithms (Klein et al., 2009). It is therefore optimized for assessing structural changes within a stereotactic framework, and is ideally suited for convergent fMRI and sMRI analyses. In brief, following resampling (2 mm^3) and segmentation of MPRAGE images, a rigid gray matter template was created representing the average shape and size of the brains of the 44 subjects included in the study. Subjects' grey matter maps were warped to the coordinate system of the template, with Jacobian modulation used to scale native gray matter volume from native to MNI space. This process of volume-modulation (Good et al., 2001) has been extensively used in voxel-based analyses of gray matter images within the framework of random field methods, and can be used to extract estimated volumes from regions of interest using structural masks. Subsequent sMRI analyses was based on the extraction and summation of voxel-wise volumes across all locations within the functionally defined region of interests.

3. Results

3.1 Behavioral Results

Behavioral results are presented in Table 1. Sensitivity to the task for both groups was compared using *d'* (Macmillan and Creelman, 2005) which accounts for performance characteristics including correct hits and rejections, false alarms and misses. These sensitivity data were submitted to an analysis of covariance with group as single factor and age and gender as covariates. No significant differences in performance were observed (HC:*d'*=3.05, sd=.88; HR-S: *d'*=2.91, sd=.56, $F_{1,39}$<1) suggesting that behavioral measures were equivalent across groups. An analyses of hit rates alone confirmed the sensitivity analyses; HR-S did not differ from HC, $F_{1,39}$<1. By comparison, HR-S responded significantly more quickly, $F_{1,39}$=5.45, p<.023, *MSe*=.043

3.2 fMRI & sMRI Results

Whole Brain Analyses: Main effect of Group—Figure 1 shows clusters under a significant main effect of group with peak loci indicated in Table 2. As seen, four principle regions in the whole brain analyses distinguished HR-S from HC, with the overall peak observed in the left superior parietal cortex. The other regions of significant difference have been implicated in control mechanisms in working memory (dorsal anterior cingulated) (Bakshi et al., In Press), aberrant hyper-activation in the schizophrenia prodrome (superior temporal gyrus)(Crossley et al., 2009), and reduced activation in adult subjects with prodromal symptoms (Fusar-Poli et al., 2010).

Contrast Analyses—Bidirectional contrast analyses (HR-S > HC; HC > HR-S) were conducted to investigate directional differences in activation. No significant clusters were observed for HR-S > HC. For the HC > HR-S contrast, within the parietal cortex, clusters with reduced activity in HR-S relative to HC during working memory were observed bilaterally. Figure 2a depicts bilateral superior parietal hypo-activity in HR-S compared to HC (p_c<.01, extent: 123 voxels) projected to dorsal (a), medial (b) and lateral (c) surfaces of the brain. Significance peaks for the contrasts of interest (HR-S < HC) were observed in left, t_{39}=4.9, x=−26, y=−52, z=60, k_E=346 voxels, and right superior parietal cortex, t_{39}=3.49, x=32, y=−50, z=62, k_E=255 voxels. Figure 2b depicts significant hypo-activity in the left dorsal prefrontal cortex in HR-S relative to HC (p_c<.01, extent: 51 voxels), with significance peak at t_{39}=2.9, p_c<.05, x=−34, y=26, z=42, k_E=137 voxels.

Estimated gray matter (in mm^3) for each of the clusters of maximal significance in the three structural regions of interest was extracted using custom designed scripts written in Matlab (MathWorks, 2007). Extracted volumes were submitted to analyses of covariance with group as single factor and age and gender as covariates. Figure 3 depicts estimated gray matter volume in the functional regions of interest (center) drawn from the fMRI results. Graphs depicting gray matter for each of the hypo-active parietal clusters are depicted in right, $F_{1,39}$=1.28, p>.25, *MSe*=12665, or left parietal cortex $F_{1,39}$=.82, p>.35, *MSe*=18291. Effect sizes (partial η^2)(Cohen, 1988) on the main effect were small (η^2=.03 and η^2=.02 respectively). Similarly, analyses of prefrontal data were also negative, $F_{1,39}$=1.63, p>.2, *MSe*=6211 with a small effect size (η^2=.04) on the main effect of group. The fMRI, sMRI and behavioral results were unaffected when excluding the HR-S (n=4) with non-exclusionary disorders.

4. Discussion

Using a simple working memory task, we studied the response of the frontal and parietal cortices during working memory (2 back) in HR-S relative to controls. Three principal

findings were observed. In general behavioral performance as measured by sensitivity was not compromised in HR-S. fMRI analyses revealed significantly fronto-parietal hypoactivity in HR-S compared to HC suggesting reduced memory-related engagement in offspring compared to controls. The fMRI results confirm previous preliminary fMRI results (Keshavan et al., 2002b). Finally, within clusters of significant fMRI hypo-activity, no significant differences in estimated gray matter volume were observed.

4.1 Activation differences in the schizophrenia diathesis

Early functional studies with PET suggested a pattern of resting as well as task-based "hypo-frontality" that may be related to the pathophysiological effects of the illness on frontal function (Andreasen et al., 1992). However, the fMRI literature on activation differences is characterized by conflicting findings. In general, when performance differences are not accounted for, the engagement of fronto-parietal regions appears to be reduced, leading to a pattern of hypo-activation in schizophrenia and HR-S subjects relative to controls (Broome et al., 2009; Cannon et al., 2005; Keshavan et al., 2002b; Perlstein et al., 2001; Schneider et al., 2007). The direction of activation differences however is affected by considerations of performance. Thus, when fMRI data are compared under conditions of equivalent behavioral performance, schizophrenia is characterized by relative "hyper-frontality" (Jansma et al., 2004; Karlsgodt et al., 2009). These data suggest that working memory implementation in schizophrenia may be characterized by inefficient recruitment, with greater neural resource allocation need to subserve performance levels comparable to controls (Callicott et al., 2003b; Manoach, 2003). A consequent of these results is the suggestion that working memory engagement in the schizophrenia diathesis is not by domain-related, but rather performance-related (Van Snellenberg et al., 2006). The current results accrue from the analyses of block-design data and do not permit the assessment of event-wise changes in activation as a function of performance, though previous event-related analyses have also suggested patterns of hypo-frontality in schizophrenia (Barch et al., 2001).

The literature on individuals with a family relationship to, or clinical risk for, schizophrenia is heterogeneous with studies specifically documenting frontal or parietal dysfunction involving diverse groups and age-ranges. Among these are studies involving adolescent offspring (Diwadkar et al., 2006; Keshavan et al., 2002b), adult siblings (Callicott et al., 2003a; Woodward et al., 2009), and adult or young adult clinically and genetically high risk groups (Crossley et al., 2009; Whalley et al., 2004). In general, the effect sizes of prefrontal impairment based on fMRI studies is moderate to large (Fusar-Poli et al., 2007) and is shared across different vulnerability groups. The specific bases of these differences between groups and controls and the convergence of the results *within* subjects remain unclear. This may also be because the biological bases of these imaging data are quite different.

4.2 Bases of fMRI and sMRI

fMRI activity measured using the Blood Oxygen Level Dependent (BOLD) effect most closely correlates to local field potential activity in the 10–300 Hz (Logothetis, 2002, 2003) or gamma range (Niessing et al., 2005). This relatively low frequency neural signal corresponds most closely to the synaptic inputs to regions reflecting a weighted average of synchronized "dendrosomatic" components of a neuronal population (Juergens et al., 1999). Findings of reduced prefrontal BOLD response in schizophrenia or vulnerability for schizophrenia are consistent with independent investigations showing reduced frontal gamma band power in the illness (Cho et al., 2006). In general reduced functional activity measured with BOLD may relate to reduced synaptic inputs and coherence resulting from altered prefrontal GABA-ergic neurotransmission (Lewis and Gonzalez-Burgos, 2006). This vulnerability trait (evident in our fMRI data) may be inherited by adolescent offspring,

though whether they eventually progress to development or disease may depend on complex processes of development, adaptation or regression (Lewis and Levitt, 2002)

The specific biological correlates of sMRI-related changes in gray matter are less clear. The T_1-weighted signal that is used by most investigations of gray matter is related to the degree of MR-visible water; least visible in white matter, intermediately so in gray matter, and most visible in cerebrospinal fluid (Diwadkar and Keshavan, 2002). Segmentation methods parcel sMRI volumes based primarily (though not entirely) on this single measure of signal intensity (Pommert et al., 2002). However, MRI data have neither the resolution not the specificity to explain the relationship between estimated gray matter volume or density and complex cellular processes including but not restricted to, dendritic remodeling, cell death, synaptic pruning, or plausible encroachment from myelination (Toga et al., 2006). The developmental literature has been most sensitive to these shortcomings in assessing the relevance of MR-based findings. In general, the correspondence between MR-documented developmental changes in gray matter (Thompson et al., 2001), and post-mortem investigations of synaptic density and morphology (Huttenlocher, 1979, 1990) have been consistent in documenting heterochronous cortical development. Nevertheless the neural bases of gray matter estimates and of BOLD appear to be independent. Recent evidence corroborates the non-linear or complex nature of this relationship (Kannurpatti et al.). In assessing BOLD variability and its relationship to estimated gray matter, reductions in BOLD with age during motor and digit symbol tasks *outpaced* reductions in gray matter estimated within the same subjects. Furthermore, correlations between measured BOLD and estimated gray matter volume were sub-linear, with changes in BOLD activation volume being only weakly or unrelated to gray matter. Our results provide a measure of methodological corroboration of these published studies.

4.3 Conclusions

Adolescence remains one of the most neurodevelopmentally active phases in the human lifespan, characterized by both the rapid ascent of cognitive proficiency in multiple domains with an accent on prefrontal development (Case, 1992; Luna et al., 2004), shaping of cortical morphology (Gogtay et al., 2004; Lenroot et al., 2009), and an increase in the connective strength of cortical and sub-cortical regions (Asato et al., 2010). The extended dynamic range of human neurodevelopment is unique across species (Johnson, 2001), providing both opportunities of expansive function and vulnerabilities to disorders when development is derailed (Dahl, 2004). HR-S appear to be characterized by increased *vulnerability* evidenced from data from several domains, including the incidence of psychopathology (Keshavan et al., 2008), cognitive deficits and MRI-based assessments of brain structure and function. Reduced fronto-parietal engagement during working memory may be a direct expression of latent neurodevelopmental vulnerability in a critical sub-circuit that may be lead to manifest expressions of psychopathology later in young adulthood (Lewis and Levitt, 2002). Our results indicate that latent vulnerabilities can be manifestly present in the function but not in the structure within this circuit. The precise meaning of this discordance is elusive. As noted earlier, studies indicate that the relationship between gray matter measures and fMRI-measured function is unclear, and the biological information conveyed by imaging modalities is complementary. Consequently there may be complementary pathways to vulnerability in HR-S which future studies will need to assess using multiple imaging modalities. Finally, a latent vulnerability in function during adolescence is not predictive of eventual pathology, given the brain's enormous reserve of adaptive plasticity and ability to reorganize functional networks, particularly in adolescence (Meunier et al., 2009). However, the relatively high frequency of some form of Axis I psychopathology in HR-S suggests that neuroimaging offers significant potential for

identifying signatures of vulnerability in the adolescent brain, and identifying emergent vulnerability may be essential for prospective identification of disorders in adolescents.

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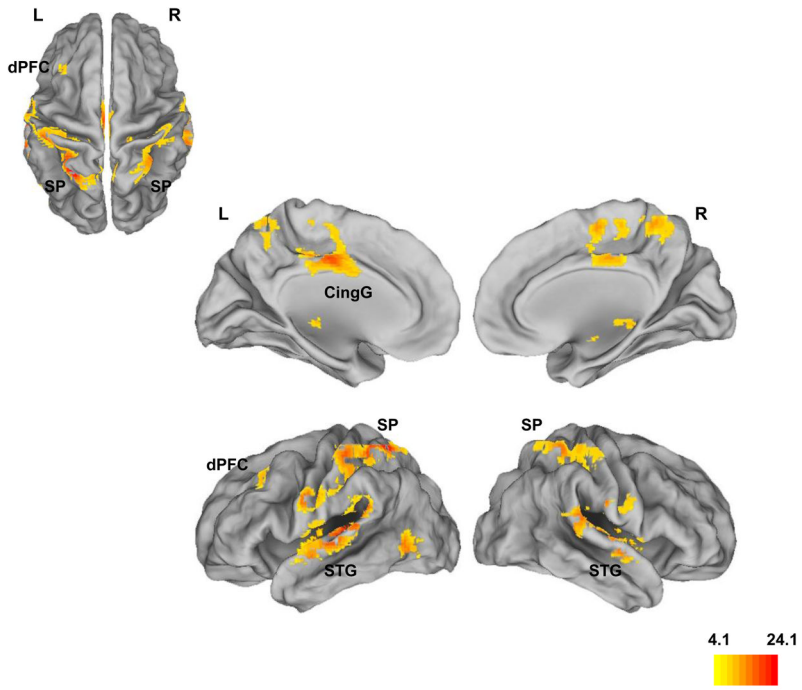

Figure 1. Main effect of group (HR-S, HC)

Whole brain analyses of activation differences between HRS-S and HC depict a main effect of group in the dorsal prefrontal cortex (dPFC), superior parietal cortex (SP), cingulate gyrus (CingG), superior temporal gyrus (STG) and middle temporal gyrus (MTG; See Table 2 for statistics). The results are largely consistent with the limited fMRI studies in clinical risk populations within the schizophrenia diathesis (see text for references).

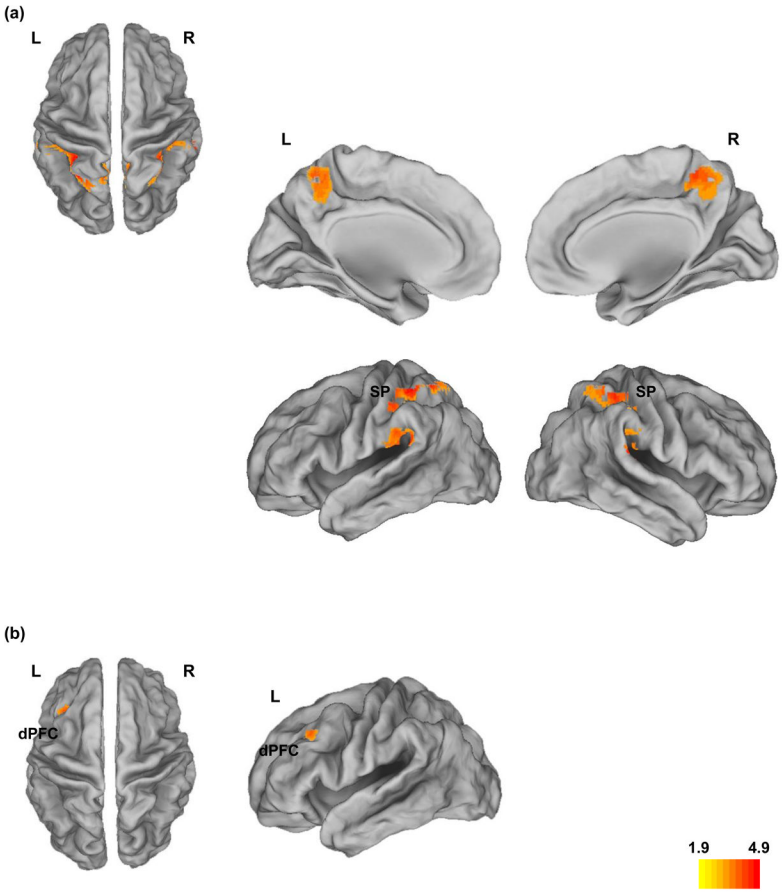

Figure 2. Contrast Differences, HC > HR-S in parietal and frontal cortex

a) Bilateral Parietal Hypo-activity (p_c<.01) during working memory in HR-S. Significantly reduced activity in bilateral superior parietal cortex (BA 7 & 40) during the 2 back task in HR-S relative to controls is projected on dorsal, medial and lateral surfaces of the brain. b) Dorsal Prefrontal Hypoactivity in HR-S. Significantly reduced activity (p_c<.01) in left dorso-lateral prefrontal cortex during the 2 back task in HR-S relative to controls is projected on dorsal and lateral. Peak statistics and cluster extents are shown in the results.

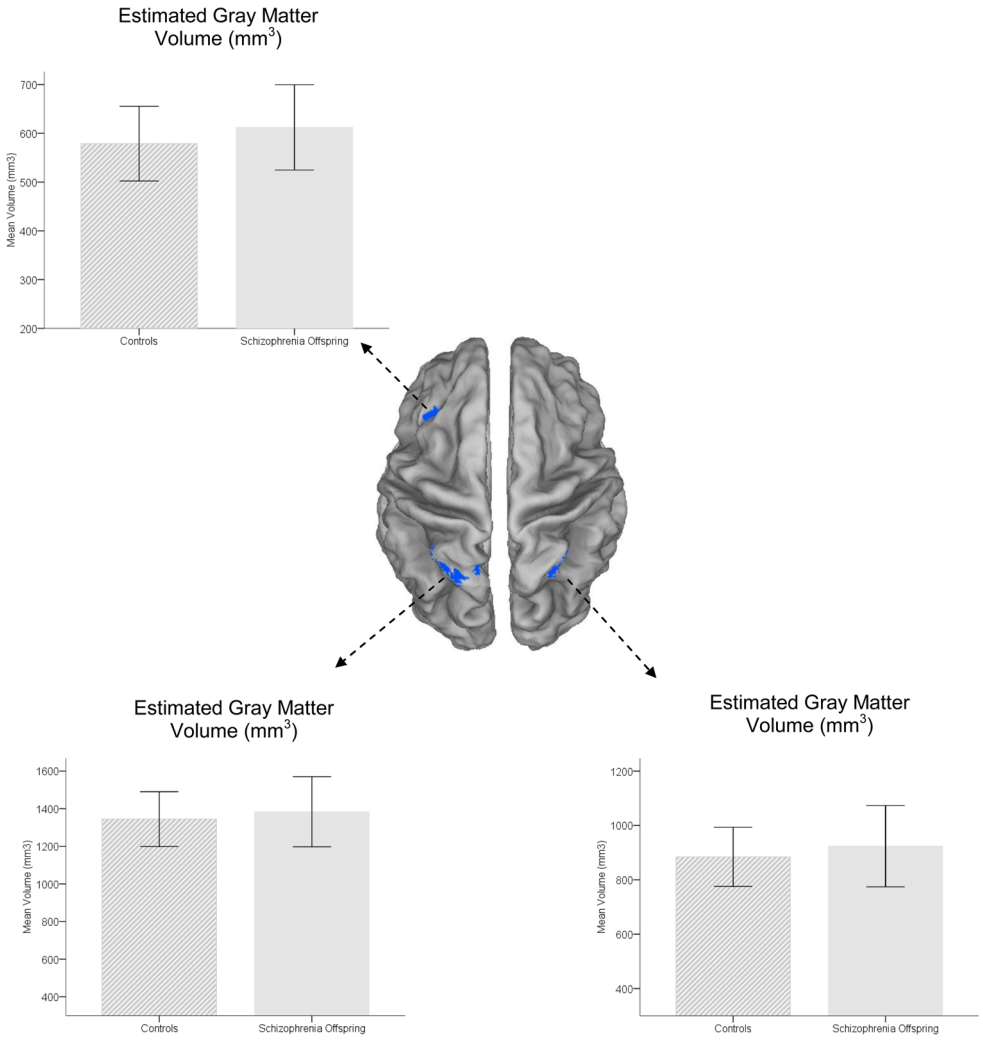

Figure 3. Estimate gray matter under clusters of significance (Figure 2)

Volumetric estimates of gray matter in clusters of maximal difference. Mean estimates of gray matter volume under the significant clusters of interest (depicted on dorsal surface views in the center are depicted. See results for statistical analyses and effect sizes on the main effects. Error bars are ± s.d.

Table 1

Demographic, clinical and behavioral information subjects in the study.

	SCZ-Off (n=19)	**HC (n=24)**
Gender (F/M)	7/12	8/16
Age range (yrs)	8–19	10–19
Mean age (± sd)	14.1 ± 2.85	14.91± 2.84
Mean FSIQ (± sd)	92.05 ± 13.39	92.3 ± 16.46
Mean GAF Score (± sd)	76.2 ± 10.7	85.8 ± 6.6
Performance *d'*	2.91 ± .56	3.05 ± .88
Performance (hit rate)	.86 ± .08	.88 ± .09
Response Latency (s)	.81 ± .29	.68 ± .17

Table 2

Significance peaks (p_u<.10^{-4}, cluster extent:100 voxels) and locations from whole brain analyses under the overall main effect of group (HC vs. SCZ-Offspring). See Figure 1 for cluster renditions.

Peak Statistic ($F_{1,39}$)	k_E (voxels)	Peak (MNI)	Region
23.99	3383	−26, −52, 60	Superior Parietal (BA 7)
18.20	2375	−42, −28, 8	Superior Temporal Gyrus
17.61	970	−4, −12, 36	Cingulate Gyrus (BA 24)
15.01	2158	62, −34, 12	Superior Temporal Gyrus
12.92	210	−50, −66, 0	Middle Temporal Gyrus (BA 37)
8.39	128	−34, 26, 42	Dorsal Prefrontal Cortex (BA 9)