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Increased Anterior Cingulate and Temporal Lobe Activity during Visuospatial Working Memory in Children and Adolescents with Schizophrenia

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Abstract

Objective—Similar to adults, children and adolescents with schizophrenia present with significant working memory (WkM) deficits. However, unlike adults, findings of abnormal activity in the prefrontal cortex in early-onset schizophrenia (EOS) are not consistently reported. Since WkM continues to develop through adolescence and into early adulthood, patterns of activation in adolescents may be different than those found in adults. The goal of this study was to evaluate the functional neurobiology of WkM in patients with EOS.

Method—Participants included 22 patients with EOS (mean age 15 ±2.8 years) and 24 controls (mean age 15.0 ±3.0 years). Diagnoses were confirmed using the KIDDIE-SADS-PL. All subjects underwent a functional MRI paradigm involving a visuospatial working memory task with three separate loads.

Results—The behavioral results demonstrated deficits in EOS patients at all three WkM loads. On functional imaging, EOS patients demonstrated increased activation in the anterior cingulate cortex (ACC), medial temporal lobe structures, the insula, and bilateral lateral temporal lobes.

Conclusions—Patients with EOS demonstrate increased activity in limbic structures and regions involved in processing primary and secondary sensory information. In addition, EOS

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patients had load dependent decreased activity in the parietal lobe. Unlike studies in adults, we did not find that EOS patients had activation differences in frontal cortical regions. One possibility is that abnormalities in PFC function are related to secondary downstream or developmental processes which are 'unmasked' during development. Finally, our findings support growing evidence that EOS patients have aberrations in limbic and temporal lobe regions.

Keywords

fMRI; Working Memory; Early-Onset Schizophrenia; Temporal Lobe; Limbic

1. Introduction

Working memory (WkM) deficits are considered a core feature of schizophrenia (Aleman et al. 1999; Goldman-Rakic 1994; Lee and Park 2005) and have been reported not only in adults and first-episode patients (Lee and Park 2005), but also in children and adolescents with schizophrenia (Cervellione et al. 2007; Haenschel et al. 2007; Karatekin and Asarnow 1998; Kenny et al. 1997; Øie et al. 1999; Vance et al. 2006; White et al. 2006). In addition, WkM deficits are present during the schizophrenia prodrome (Hawkins et al. 2004; Keefe et al. 2006; Pukrop et al. 2007; C. W. Smith et al. 2006; Wood et al. 2003) and there have been reports of pre-prodromal WkM deficits in schizophrenia (Erlenmeyer-Kimling et al. 2000). Since WkM serves as one of the basis elements of higher-order cognitive processing, it is an area that has undergone considerable investigation in schizophrenia.

There have been a number of different definitions of WkM since Baddeley's pioneering work (Baddeley 1986), however, they all appear to have specific core features. For example, they all agree that WkM involves components of encoding, maintenance, and retrieval of information (Miyake and Shaw 1999). Encoding refers to the initial storage of information into memory, after which the information is maintained over a certain period of time. This is followed by the retrieval of the stored information. Retrieval can occur either through either recognition or recall, and the performance using recognition is better than recall.

Electrophysiological and neuroimaging studies have been very effective in mapping the functional regions associated with WkM performance (D'Esposito et al. 1998; Goldman-Rakic 1996; Wendelken et al. 2008). Efficient brain function involves the efficient transmission of information through distributed networks, so it is not surprising that multiple brain regions have been associated with WkM performance. Brain regions most commonly identified during WkM paradigms include the dorsolateral prefrontal cortex (DLPFC, Brodmann's area 9, 46) (D'Esposito et al. 1998; Wendelken et al. 2008), inferior frontal gyrus (BA 6/44) (Buckner and Koutstaal 1998; MacLeod et al. 1998), the superior (BA 7) and inferior (BA 40) parietal lobes (Tuladhar et al. 2007; Wendelken et al. 2008), and the medial temporal lobe (Axmacher et al. 2007). In addition, the anterior cingulate cortex (ACC) (Jansma et al. 2007) and the basal ganglia (Chang et al. 2007) have also been shown to be involved in WkM performance.

These regions have also been shown to have abnormal activity during functional imaging studies in adults with schizophrenia, and notably the DLPFC and the ACC (Barch and Csernansky 2007; Barch et al. 2002; Glahn et al. 2005). One of the early questions that arose

from functional imaging studies in schizophrenia was the question of hyper- versus hypofrontality (Glahn et al. 2005; Ragland et al. 2007). Early H₂ O¹⁵-PET studies demonstrated hypofrontality in patients with schizophrenia performing tasks which engage WkM (Andreasen et al. 1992; Buchsbaum and Wu 1987; D. R. Weinberger and Berman 1988b), but it has since evolved into a complex topic in which multiple variable likely contribute to hyper- or hypoactivity in the prefrontal cortex during WkM tasks. A recent meta-analysis of functional imaging studies executive function demonstrated decreased DLPFC and ACC activation (Minzenberg et al. 2009). However, there is also evidence that once subjects are matched on WkM task performance, patients with schizophrenia demonstrate hyperfrontality (Callicott et al. 2000; Manoach et al. 1999). One thought is that hyperfrontality reflects a greater recruitment of cognitive resources in patients to match their performance with controls and once the task difficulty exceeds their capacity, they demonstrate hypofrontality (Manoach 2003).

Developmental differences in children and adolescents with schizophrenia have undergone considerable less study. These brain regions, and notably the DLPFC and ACC, continue to mature throughout childhood and into young adulthood and display developmental differences in both structure and function. There are developmental differences in gray matter volume, which involves regionally specific differences that move from parietal to frontal regions as children grow into adulthood (Sowell et al. 2004; Sowell et al. 2002). In addition, there are cortical (Shaw et al. 2008) and cerebellar (Tiemeier et al. 2010) differences associated with phylogeny, with phylogenetically older regions demonstrating prolonged or more complex developmental trajectories. Not only do children rely more on subcortical structures (Scherf et al. 2006) during cognitive performance, but there are also developmental differences in trajectories related to brain myelination, especially in prefrontal regions (Yakovlev and Lecours 1967). Finally, children tend to have overall less DLPFC, ACC, and parietal activation during a visuospatial WkM task compared to either adolescents or adults (Klingberg et al. 2002; Scherf et al. 2006). The ACC activations remains less active during adolescence, while DLPFC activation rises sharply (Scherf et al. 2006). These developmental differences become important when evaluating differences in children and adolescents with schizophrenia compared to adults.

There have been three studies to date that evaluate WkM in children and adolescents with schizophrenia, or early-onset schizophrenia (EOS) (Haenschel et al. 2007; Pauly et al. 2008; White et al. (In Press)). Haenschel et al. (Haenschel et al. 2007) reported abnormal activations during a visual WkM paradigm in temporal and occipital regions during both encoding and retrieval, without any patient/control differences in prefrontal regions. Pauly et al. (Pauly et al. 2008) using a verbal n-back paradigm, which included neutral and adverse odors, found that adolescent patients had hypoactivation in the DLPFC, parietal cortex, and the ACC. Finally, we found evidence for aberrant connectivity in the ACC, temporal lobe, and cerebellum during a verbal WkM task (White et al. (In Press)).

Since EOS has been shown to be on a continuum with adult onset illness (Rapoport and Inoff-Germain 2000), and as WkM continues to mature during late adolescence and early adulthood (Luciana and Nelson 2000), a better understanding of the role of prefrontal regions in EOS is crucial for our understanding of the neurobiology of schizophrenia. This is

especially true in light of the considerable research documenting PFC abnormalities in adults with schizophrenia. If EOS patients do not have abnormalities in prefrontal regions, it is possible that aberrant activity related to these structures are downstream, or developmental effects of the illness (White et al. 2008). Our goal was to investigate the neurobiology of spatial WkM in EOS, with a primary interest in studying aberrant PFC function.

2. Methods

2.1. Subjects

The participants included a total of 46 children and adolescents, including 22 patients with a schizophrenia spectrum disorder and 24 controls. The mean age of the patient group was 15.0 (S.D. 2.8) years and consisted of 15 males and 7 females. The mean age of the control group was 15.0 (S.D. 3.0) years and consisted of 16 males and 8 females (Table 1). Both the patients and controls underwent a diagnostic assessment using the Kiddie-SADS-PL (Kaufman et al. 1997). Of the patients, 19 had a diagnosis of schizophrenia, 1 had schizoaffective disorder, and 2 had schizophreniform disorder. Additional clinical measures included the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984).

The control group had no evidence of a past or present psychiatric disorder and no history of schizophrenia or psychosis in a first degree relative. Patients and controls were excluded if they had a history of substance dependence, ongoing substance abuse (within the past month), IQ less than 70, a neurological disorder, head injury, or a medical illness involving the brain. IQ was estimated from the Vocabulary and Block Design subtests from the Wechsler Intelligence Scale for Children, 4th Edition (Wechsler 2003). Valid IQ measures were obtained for 21 of the 22 patients and the mean IQ for the patient group was 100.6 with a standard deviation of 8.9 and a minimum of 85 and a maximum of 109. Due to an administrative error, we do not have IQ data on all the controls, however, there was no history of special education in the control group and no history of poor to failing academic performance.

None of the controls had a history of substance abuse. Of the 22 patients, two had a history of cannabis abuse and one had a history of amphetamine abuse. In addition, two of the subjects had nicotine dependence. Twenty-one of the 22 patients were on medication at the time of the scanning (Table 1). The study was approved by the Institutional Review Board at the University of Minnesota, and informed consent and assent was obtained prior to participation.

2.2. Visuospatial Working Memory Paradigm

The WkM task was a visuospatial adaptation of the Sternberg Item Recognition Paradigm (SIRP) (Sternberg 1966). Each memory block began a fixation bar on the screen for 500 ms. Fixation was followed by the 'Learn' phase (Figure 1), in which subjects were shown either 1, 2, or 3 small black circles which were presented one at a time, each for 2.5 seconds. The locations of the circles were randomly selected from one of 10 different predefined locations on the screen. The participants were to remember the location of the sequentially presented

circles. This was followed by a 5 second delay period. The recall phase consisted of a series of black dots that were presented sequentially, each for 2.5 seconds, in one of the ten different locations on the screen. The participants pushed a button with their right thumb if the location of the dot matched the location of one circles that was presented during the 'learn' phase (target), or their left thumb if the circle was not present during the 'learn' phase (foil). Subjects wore MR compatible gloves, which had a pushbutton under each thumb. The timing for the task is shown in Figure 1.

During the scanning session, subjects rested comfortably in the scanner and viewed the task, which was back-projected on a screen at the end of the scanner bore. Head mobilization was performed using a vacuum bag, which was comfortable for all subjects. Each subject participated in two runs, each lasting five minutes and 30 seconds (Figure 1). Each run contained six memory blocks, two blocks each of the three memory loads (memorizing the location of either 1, 2, or 3 circles). The order of each block within a run was randomly counterbalanced for each subject. The tasks were programmed using E-Prime (version 1.1), a software program for creating and presenting stimulus paradigms for psychological and neuroscience experiments (Psychological Software Tools, Inc., Pittsburgh, PA). E-Prime allows for timing on the order of milliseconds and the 'continuous' setting was used during the task presentation to ensure accurate timing over the course of the fMRI run. The behavioral outcome measures included response time (RT) and the accuracy for each response, and we utilized d' as the primary measure for performance. The stimulus presentation was triggered by the scanner following the fourth repetition time (TR).

Prior to performing the task in the scanner, subjects had two practice sessions. Both practice sessions were performed sequentially and together lasted approximately 45 minutes. The first session was performed while the subject was seated in a chair in front of a computer monitor. The subjects were explained the task using an example and they were allowed to practice in front of the monitor until they were comfortable with the task. They were observed during the practice session and moved to the second session when it was obvious that they understood the task and their performance was better than chance. The second session took place in a mock scanner with the stimuli back-projected on a screen that was placed at the end of the scanner bore. Subjects were told to respond as quickly as possible but try not to make any mistakes.

2.3. MRI Sequence

All MR images were acquired with a 3T Siemens MR System (Erlangen, Germany) at the Center for Magnetic resonance Research in University of Minnesota. A series of localizer sequences were first acquired to orient the functional sequence. Following an initial localizer, a coronal scout image (12 slices; FoV read 224 mm; FoV phase 100%; TR 2000; TE 72 ms; resolution $2.3 \times 1.8 \times 2$ mm) was obtained to locate the coronal midline. Following alignment, sagittal images were acquired along the coronal midline (12 slices; FoV read 224 mm; FoV phase 100%; TR 2040; TE 62 ms; resolution $1.2 \times 0.9 \times 2$ mm). These sagittal slices were used to orient the volume along the anterior/posterior commissure (ACPC) plane.

Functional images were acquired using a gradient echo sequence in 27 axial slices with an in plane resolution of 3.4×3.4 mm and a 4 mm slice thickness and a 25% distance factor. Additional sequence parameters include: TE = 30 ms, TR = 2,000 ms, flip angle = 90° , FoV read = 220 mm and the FoV phase was 100%. A total of 177 volumes were obtained for each of the two runs.

2.4. Image Processing

The functional images were processed using a combination of Analysis of Functional NeuroImages (AFNI, <http://afni.nimh.nih.gov/>) (Cox 1996) and FSL's FMRIB's Software Library (<http://www.fmrib.ox.ac.uk/fsl/>) (S. M. Smith et al. 2004). Following the conversion from DICOM to Nifti format, slice timing correction and motion correction were performed using AFNI (Cox 1996). Subjects who had greater than 2.5 mm of motion in either the x, y, or z directions were excluded from the analyses. An 8-mm FWHM Gaussian spatial filter was applied prior to registration to standard space (White et al. 2001).

Images were oriented to standard MNI space utilizing FSL in a three-stage process. First, a mean EPI image was generated from the fMRI time series for each individual. This mean EPI image was registered to a MNI-152 EPI image through a 12-parameter transformation (Jenkinson et al. 2002; Jenkinson and Smith 2001). Finally, the 12-parameter transform was applied to the entire fMRI time series for each individual and each run.

Single-subject analyses were performed using FMRIB's fMRI Expert Analysis Tool FEAT (<http://www.fmrib.ox.ac.uk/fsl/feat5/index.html>). The time series for the behavioral conditions modeled three different encoding and three different probe conditions, these reflecting the three memory loads. This modeled time series was convolved with the hemodynamic response function (HRF) that was modeled from a linear combination of gamma functions. Next, a general linear model (GLM) was implemented using FMRIB's Improved Linear Model (FILM). A singular value decomposition (SVD) was utilized to assess the fit of each voxel to the design matrix using local autocorrelation (Woolrich et al. 2001). The two within-subject runs were combined using a fixed effects model. The higher-level group analysis, which compared patients and controls for each of the contrasts, was performed using FMRIB's Local Analysis of Mixed Effects (FLAME). The difference images between patients and controls were corrected for multiple comparisons using random Gaussian fields and significance was set at $p < 0.05$, corrected.

In addition to the FLAME analysis, a separate region of interest (ROI) analysis was performed using the z-maps derived from the fixed effects model. These maps had been filtered with an 8 mm FWHM Gaussian filter during the preprocessing stage. The ROI regions consisted of Brodmann area maps that were generated using the Wake Forest University Pickatlas algorithm (Maldjian et al. 2003). The Brodmann regions evaluated included areas 9 and 46 (DLPFC) and area 7 (superior parietal lobe) and were dilated by 2 mm and masked to the gray matter regions. Using an in-house program written in Matlab (Natick, MA, USA), these masks were overlaid on the individual activation z-maps for each load, and for both the encoding and recall contrasts. The peak voxel within each ROI was determined and used for the analyses.

2.5. Statistical Analyses

All statistical analyses were performed using SAS (Cary, NC). The demographic data were assessed using χ^2 for ordinal and t-tests for continuous data. RT was log transformed prior to analyses to fit a normal distribution. The behavioral results and ROI approaches were evaluated using a 2 (diagnosis) $\times$ 3 (load) mixed-model repeated-measures ANOVA using diagnosis and load as the fixed effects, and subject as the random variable. Post-hoc tests on significant findings were performed with mixed-model repeated-measures ANOVAs. One of the main critiques regarding prefrontal activation is that magnitude of the activations are thought to be dependent on task performance. Thus, we repeated the imaging analyses with performance as a covariate.

3. Results

The demographic data was assessed using either chi-square for ordinal and t-tests for continuous data. There were no differences between the age and sex distributions between the two groups (Table 1). There was a significant difference in SES between the patient and control groups ($t = 3.5$, $df = 42$, $p < 0.002$).

3.1. Behavioral Results

A 2 (diagnosis) $\times$ 3 (load) repeated measures mixed-model ANOVA was performed to assess d' for the visuospatial SIRP. There was a main effect of diagnosis ($F_{1,42} = 14.2$, $p < 0.001$) and load ($F_{2,84} = 37.0$, $p < 0.0001$), without a significant load by diagnosis interaction. Measures of d' -prime for the patients and controls are shown in Figure 2.

3.2. Imaging Results

The imaging data was analyzed for encoding and retrieval phases both with and without behavioral performance as a covariate. Several brain regions demonstrated differences between patients and controls irrespective of whether performance was used as a covariate. These regions included increased activity in patients primarily in limbic structures and in the temporal lobes (Table 2 & 3 and Figures 3 & 4). There were no differences in functional activation between patients and controls at the lowest load of 1 spatial location, even though performance was significantly different. When controlling for performance, only the highest load (remembering 3 spatial locations) had significant differences between patients and controls. However, when performance was not used as a covariate, significant differences were present at both the medium and highest load levels (Table 2 & 3).

3.3. Encoding

The anterior cingulate, planum polare, Heschl's gyrus, and regions within the superior, middle and inferior temporal lobe all had significantly greater activity for both the middle load level (not covaried) and for the highest load level (with covarying for performance). However, these structures were not significant for the highest load when performance was not used as a covariate. In fact, for the latter, controls had greater activation in the parietal and occipital lobes (Table 2). The left and right hippocampus and cerebellum had significantly increased activity when not controlling for performance, however, these findings were not present when performance was used as a covariate.

3.4. Retrieval

When performance was not used as a covariate, the results between the middle and highest loads are nearly identical. Both loads show significant differences between patients and controls in the left temporal pole, left middle temporal gyrus, and in the left hippocampus and parahippocampal gyrus (Table 3). Interestingly, when controlling for performance, none of these regions remain significant. Controlling for performance resulted in differences between patients and controls in regions that include the anterior cingulate, planum polare, Heschle's gyrus, the right cerebellum, the left thalamus, and the right hippocampus and amygdala (Table 3).

3.5 Region of Interest Analyses

Analyses performed on the ROI data utilized the same mixed model repeated measures ANCOVA as was performed for the behavioral data. A 2 (diagnosis) $\times$ 3 (load) repeated measures mixed-model ANOVA was performed using the maximum activation within each of the ROI's. Age was used as a covariate for all analyses. During encoding there was a main effect of load for both the left ($F_{2,88} = 9.9$, $p < 0.001$) and right DLPFC ($F_{2,88} = 10.2$, $p < 0.001$). There was also a significant effect of load in the right DLPFC ($F_{2,88} = 4.8$, $p = 0.01$) and a trend effect in the left DLPFC ($F_{2,88} = 3.0$, $p = 0.06$) during recall. However, there was no main effects of diagnosis for either the right or left DLPFC during encoding or recall, nor was there significant load $\times$ diagnosis interactions.

Both the right and left superior parietal lobe (Brodmann area 7) demonstrated a main effect of load in during both encoding and recall ($F_{2,88}$ between 14.8 and 17.7, p 's < 0.001). In addition, a main effect of diagnosis was present during encoding in the left ($F_{1,43} = 10.8$, $p = 0.002$) and right ($F_{1,43} = 9.0$, $p = 0.004$) superior parietal lobe, and during recall in the left ($F_{1,43} = 4.9$, $p = 0.03$) and right ($F_{1,43} = 5.5$, $p = 0.02$) parietal lobe. In addition, there was a load $\times$ diagnosis interaction in for encoding in both the left ($F_{2,88} = 4.9$, $p < 0.01$) and right ($F_{2,88} = 5.8$, $p < 0.01$) superior parietal lobe. Measures of activations for each of the ROI's for the patients and controls are presented in Figure 4.

4. Discussion

We demonstrated that WkM deficits in children and adolescents with schizophrenia were associated with altered brain activity in the anterior cingulate and the medial and lateral temporal lobes. The patients showed increased activation in these brain regions during encoding and retrieval with and without controlling for performance. During encoding, patients had increased activation in the anterior cingulate, the left and right temporal pole, the right insula, and regions encompassing the left superior, middle, and inferior temporal gyri (Table 2). The anterior cingulate also demonstrated increased activation in patients during retrieval, as did the planum polare, Heschl's gyrus, the left thalamus, and the right hippocampus and amygdala (Table 3). In addition, there was a failure to show increased activation with increased load in the parietal lobe during encoding (Figure 5). Interestingly, we did not find significant differences between patients and controls in prefrontal regions using either the voxel-based or the ROI approach.

For decades, neuroimaging studies in adults with schizophrenia have highlighted the role of the DLPFC, first as ‘hypofrontality’ (D. Weinberger and Berman 1988a), then later, when controlling for performance, as ‘hyperfrontality’ (Callicott et al. 2003; Manoach et al. 1999). Considering this wealth of data from adult studies, the lack of differences between EOS patients and controls in prefrontal regions is surprising. Irrespective of whether we covaried for performance, we found no differences in the PFC between EOS patients and controls. A lack of differences in PFC activation between EOS patients and controls has also been reported in two separate studies. Haenschel et al. (Haenschel et al. 2007) studied WkM load using a delayed discrimination task and reported differences in regions of the left middle and superior temporal lobe, the right inferior temporal gyrus and the middle occipital gyrus during encoding. During retrieval, they reported differences in the left middle and right inferior temporal gyrus and in the left and right middle occipital gyrus. We also found differences in connectivity between the anterior cingulate, temporal lobes, and cerebellum in children and adolescents with schizophrenia during a verbal WkM task (White et al. 2010).

A neuroimaging study of WkM in EOS used a verbal n-back task and included negative and neutral olfactory stimuli (Pauly et al. 2008). Evaluating WkM during the neutral olfactory condition, they found hypoactivation in the right and left lateral PFC, anterior cingulate, and inferior parietal lobe. Similar to our findings, they also reported hyperactivation in the superior temporal pole and occipital regions. The differences in these studies could be a result of the influence of the negative emotion paradigm on the WkM task used by Pauly et al. (2008).

The pronounced differences seen in the parietal lobe, the ACC, and the temporal lobe, coupled with the lack of differences in the PFC during visuospatial WkM, raises the question as to whether the finding of abnormal PFC function in adult PET and fMRI studies of schizophrenia are related to a downstream or developmental process. There is now considerable evidence that structural (Sowell et al. 1999), functional (Luciana and Nelson 2000), and neurochemical (Wahlstrom et al. 2007) development of the PFC continues throughout adolescence and into early adulthood. In addition, studies of childhood-onset schizophrenia (COS) find that the loss of GM occurs first in the parietal regions and progresses to encompass the PFC by the time the subjects reach older adolescence (Thompson et al. 2001). One possible explanation for the lack of patient/control differences in the PFC is that these abnormalities are related to connectivity that mature during later adolescence and early adulthood (Benes 1989). As these later developing prefrontal structures mature, disrupted connectivity from earlier developing structures, such as limbic regions, are unmasked (White et al. 2007).

While we found no differences in PFC function in our EOS sample, we did find abnormally increased activity in the anterior cingulate during WkM. This is a finding that has been consistently reported in studies of adults with schizophrenia (Glahn et al. 2005). The increased activation was present during both the encoding and retrieval phases of the WkM task. A review of WkM performance in schizophrenia have highlighted the role of encoding deficits as a primary factor (Lee and Park 2005). Encoding reflects the components of attention and processing speed and the ACC has been linked to attentional control (Davis et al. 2000). Thus, the increased ACC may be related to patients’ impairment in attentional

control. Alternatively, since EOS patients made more errors than controls, especially at higher loads, the increased ACC activation in EOS patients may reflect greater error detection and conflict monitoring (Carter et al. 1998; Taylor et al. 2007). Finally, connections exist between the ACC and PFC (Kondo et al. 2004), and with the continued maturation of the PFC into early adulthood, the EOS patients may be utilizing different neural circuits for task completion. This latter explanation may account for the increased activation in limbic structures in the medial temporal lobe, the insula, and in lateral temporal lobe regions.

It is interesting that there were no brain regions in the controls that showed greater activation during retrieval (Table 3). This was true with or without controlling for performance. Controlling for performance resulted in interesting differences between patients and controls that were seen at only the highest load. When controlling for performance, temporal lobe activation shifted from the left temporal pole, left hippocampal gyrus, and left hippocampus/amygdala to the right hippocampus/amygdala. In addition, the patients had greater activation in the ACC, planum polare/Heschl's gyrus, and the left amygdala. The differences in activation of the ACC may be secondary to greater error detection and conflict monitoring (Carter et al. 1998; Taylor et al. 2007), as described above. Alternatively, the patients may have experienced greater interference via networks tapping the language centers of the brain. Greater temporal lobe activity has been associated with positive symptoms of schizophrenia, and notably in the left superior temporal lobe (Hugdahl et al. 2007). It is possible that the patients utilized more verbal strategies to perform the task, although this is less likely as there were no regions showing greater activation in the controls.

Structural imaging studies of children and adolescents with schizophrenia have found greater GM loss involving regions that include the temporal (Rapoport et al. 1999) and medial temporal lobe (Giedd et al. 1999; Nugent et al. 2007). This loss occurs over adolescence and includes decreases in frontal GM in the frontal lobe as well (Rapoport et al. 1999). Thus, given evidence that there are differences in the developmental trajectory in children and adolescents with schizophrenia, the differences in temporal lobe activation could reflect the underlying changes in connectivity that take place during this period of time. The longitudinal coupling of structural and functional imaging could be useful to study the relationship between structure and function in EOS.

Finally, fairly recently our knowledge of the cerebellum has grown to encompass not only motor function, but higher-order cognitive function as well (Schmahmann and Caplan 2006), and have been shown to be more related to verbal WkM compared to visuospatial WkM (Ravizza et al. 2006). In fact, one network theory of schizophrenia includes the thalamus and cerebellum as key nodes in the pathophysiology of schizophrenia (Andreasen et al. 1998). Thus, the differences in the thalamus and cerebellum could be related to aberrant networks that are related specifically to the verbal cognitive aspects of schizophrenia.

4.1. Limitations

There are several limitations to the current study. All but one of the patients were on an assortment of antipsychotic medications at the time of the study (Table 1). It is possible that

some of the differences between patients and controls may be related to medication effects, although medication is more likely to normalize brain activity (Stephan et al. 2001). Medication effects likely do not account for differences between the adult studies and our sample, since most fMRI studies of adults use medicated patients. Since an ongoing history of substance abuse and dependence was an exclusion criteria for the study, the sample may be biased to some extent. Only three subjects had a history of substance abuse, two having a past history of cannabis abuse and one a history of amphetamine abuse.

Since we are missing IQ data on a number of the control subjects, we were unable to control for the effect of IQ between the two groups. However, since patients with schizophrenia tend to have illness-related global cognitive deficits, controlling for IQ is akin to controlling for specific factors related to the illness. Nevertheless, the ability to separate specific WkM components after controlling for IQ would be very interesting. We did, however, control for task performance. Finally, this paper focused on visuospatial WkM and studies which analyze both visuospatial WkM and verbal WkM will be helpful in teasing apart the role of language in visuospatial WkM paradigms.

While the stimulus presentation paradigm was designed to parse out encoding from retrieval, we did not parse the analysis of the retrieval phase into probes and foils and model only correct answers in the design matrix. A true event related design could parse the task into additional retrieval-related components and test whether the increase in ACC activation was secondary to the greater number of errors made by the patient group (Carter et al. 1998). Finally, we did not have a comparison group of adults with schizophrenia who performed this visuospatial SIRP. Such an adult patient group could assess when in development that neurobiological deficits begin to emerge in the PFC.

4.2. Conclusions

In summary, children and adolescents with schizophrenia demonstrate increased activity in the ACC and regions in the left and right temporal lobes. Unlike studies in adults, we did not find differences in activation in the PFC between patients and controls. One possibility is that aberration in PFC function is related to secondary downstream or developmental processes which are 'unmasked' during development. This work highlights the importance of longitudinal studies, as it would be very interesting to determine when during development abnormal patterns in the PFC emerge. In addition, cross-sectional studies with a greater number of subjects may also help point to developmental differences between patients and controls. Finally, our findings support a growing evidence that EOS patients have aberrations in limbic regions that occur prior to the abnormalities in prefrontal regions (White et al. 2008).

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References

- Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry*. 1999; 156:1358–1366. [PubMed: 10484945]
- Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA: The University of Iowa; 1983.
- Andreasen, NC. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA: The University of Iowa; 1984.
- Andreasen NC, Paradiso S, O’Leary DS. “Cognitive dysmetria” as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull*. 1998; 24:203–218. [PubMed: 9613621]
- Andreasen NC, Rezaei K, Alliger R, et al. Hypofrontality in neuroleptic-naïve patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Arch Gen Psychiatry*. 1992; 49:943–958. [PubMed: 1360199]
- Axmacher N, Mormann F, Fernandez G, et al. Sustained neural activity patterns during working memory in the human medial temporal lobe. *J Neurosci*. 2007; 27:7807–7816. [PubMed: 17634374]
- Baddeley, A. Working Memory. New York: Oxford University Press; 1986.
- Barch DM, Csernansky JG. Abnormal parietal cortex activation during working memory in schizophrenia: verbal phonological coding disturbances versus domain-general executive dysfunction. *Am J Psychiatry*. 2007; 164:1090–1098. [PubMed: 17606661]
- Barch DM, Csernansky JG, Conturo T, Snyder AZ. Working and long-term memory deficits in schizophrenia: is there a common prefrontal mechanism? *J Abnorm Psychol*. 2002; 111:478–494. [PubMed: 12150424]
- Benes FM. Myelination of cortical-hippocampal relays during late adolescence. *Schizophr Bull*. 1989; 15:585–593. [PubMed: 2623440]
- Buchsbaum MS, Wu JC. Hypofrontality in schizophrenia as assessed by PET. *Am J Psychiatry*. 1987; 144:122–123. [PubMed: 2879481]
- Buckner RL, Koutstaal W. Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proc Natl Acad Sci U S A*. 1998; 95:891–898. [PubMed: 9448256]
- Callicott JH, Bertolino A, Mattay VS, et al. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex*. 2000; 10:1078–1092. [PubMed: 11053229]
- Callicott JH, Mattay VS, Verchinski BA, et al. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry*. 2003; 160:2209–2215. [PubMed: 14638592]
- Carter CS, Braver TS, Barch DM, et al. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*. 1998; 280:747–749. [PubMed: 9563953]
- Cervellione KL, Burdick KE, Cottone JG, Rhinewine JP, Kumra S. Neurocognitive deficits in adolescents with schizophrenia: longitudinal stability and predictive utility for short-term functional outcome. *J Am Acad Child Adolesc Psychiatry*. 2007; 46:867–878. [PubMed: 17581451]
- Chang C, Crottaz-Herbette S, Menon V. Temporal dynamics of basal ganglia response and connectivity during verbal working memory. *Neuroimage*. 2007; 34:1253–1269. [PubMed: 17175179]

- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996; 29:162–173. [PubMed: 8812068]
- D'Esposito M, Aguirre GK, Zarahn E, et al. Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cogn Brain Res.* 1998; 7:1–13. [PubMed: 9714705]
- Davis KD, Hutchison WD, Lozano AM, Tasker RR, Dostrovsky JO. Human anterior cingulate cortex neurons modulated by attention-demanding tasks. *J Neurophysiol.* 2000; 83:3575–3577. [PubMed: 10848573]
- Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *Am J Psychiatry.* 2000; 157:1416–1422. [PubMed: 10964857]
- Giedd JN, Jeffries NO, Blumenthal J, et al. Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biol Psychiatry.* 1999; 46:892–898. [PubMed: 10509172]
- Glahn DC, Ragland JD, Abramoff A, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp.* 2005; 25:60–69. [PubMed: 15846819]
- Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *J Neuropsychiatry Clin Neurosci.* 1994; 6:348–357. [PubMed: 7841806]
- Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc Lond B Biol Sci.* 1996; 351:1445–1453. [PubMed: 8941956]
- Haenschel C, Bittner RA, Haertling F, et al. Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging. *Arch Gen Psychiatry.* 2007; 64:1229–1240. [PubMed: 17984392]
- Hawkins KA, Addington J, Keefe RS, et al. Neuropsychological status of subjects at high risk for a first episode of psychosis. *Schizophr Res.* 2004; 67:115–122. [PubMed: 14984870]
- Hugdahl K, Loberg EM, Specht K, et al. Auditory hallucinations in schizophrenia: the role of cognitive, brain structural and genetic disturbances in the left temporal lobe. *Front Hum Neurosci.* 2007; 1:6. [PubMed: 18958220]
- Jansma JM, Ramsey NF, de Zwart JA, van Gelderen P, Duyn JH. fMRI study of effort and information processing in a working memory task. *Hum Brain Mapp.* 2007; 28:431–440. [PubMed: 17133397]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage.* 2002; 17:825–841. [PubMed: 12377157]
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal.* 2001; 5:143–156. [PubMed: 11516708]
- Karatekin C, Asarnow RF. Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. *Psychiatry Res.* 1998; 80:165–176. [PubMed: 9754696]
- Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* 1997; 36:980–988. [PubMed: 9204677]
- Keefe RS, Perkins DO, Gu H, et al. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophr Res.* 2006; 88:26–35. [PubMed: 16930949]
- Kenny JT, Friedman L, Findling RL, et al. Cognitive impairment in adolescents with schizophrenia. *Am J Psychiatry.* 1997; 154:1613–1615. [PubMed: 9356577]
- Klingberg T, Forssberg H, Westerberg H. Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *J Cogn Neurosci.* 2002; 14:1–10. [PubMed: 11798382]
- Kondo H, Osaka N, Osaka M. Cooperation of the anterior cingulate cortex and dorsolateral prefrontal cortex for attention shifting. *Neuroimage.* 2004; 23:670–679. [PubMed: 15488417]
- Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. *J Abnorm Psychol.* 2005; 114:599–611. [PubMed: 16351383]

- Luciana, M.; Nelson, CA. Neurodevelopmental assessment of cognitive function using CANTAB: Validation and future goals. In: Ernst, M.; Rumsey, JM., editors. *Functional Neuroimaging in Child Psychiatry*. Cambridge University Press; Cambridge: 2000. p. 379-397.
- MacLeod AK, Buckner RL, Miezin FM, Petersen SE, Raichle ME. Right anterior prefrontal cortex activation during semantic monitoring and working memory. *Neuroimage*. 1998; 7:41-48. [PubMed: 9500832]
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003; 19:1233-1239. [PubMed: 12880848]
- Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res*. 2003; 60:285-298. [PubMed: 12591590]
- Manoach DS, Press DZ, Thangaraj V, et al. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry*. 1999; 45:1128-1137. [PubMed: 10331104]
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry*. 2009; 66:811-822. [PubMed: 19652121]
- Miyake, A.; Shaw, P. Models of working memory: Mechanisms of active maintenance and executive control. Miyake, A.; Shaw, P., editors. New York: Cambridge University Press; 1999.
- Nugent TF 3rd, Herman DH, Ordonez A, et al. Dynamic mapping of hippocampal development in childhood onset schizophrenia. *Schizophr Res*. 2007; 90:62-70. [PubMed: 17161938]
- Øie M, Sunde K, Rund BR. Contrasts in memory functions between adolescents with schizophrenia or ADHD. *Neuropsychologia*. 1999; 37:1351-1358. [PubMed: 10606010]
- Pauly K, Seiferth NY, Kellermann T, et al. Cerebral dysfunctions of emotion-cognition interactions in adolescent-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry*. 2008; 47:1299-1310. [PubMed: 18827725]
- Pukrop R, Ruhrmann S, Schultze-Lutter F, et al. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res*. 2007; 92:116-125. [PubMed: 17344028]
- Ragland JD, Yoon J, Minzenberg MJ, Carter CS. Neuroimaging of cognitive disability in schizophrenia: search for a pathophysiological mechanism. *Int Rev Psychiatry*. 2007; 19:417-427. [PubMed: 17671874]
- Rapoport JL, Giedd JN, Blumenthal J, et al. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry*. 1999; 56:649-654. [PubMed: 10401513]
- Rapoport JL, Inoff-Germain G. Update on childhood-onset schizophrenia. *Curr Psychiatry Rep*. 2000; 2:410-415. [PubMed: 11122989]
- Ravizza SM, McCormick CA, Schlerf JE, et al. Cerebellar damage produces selective deficits in verbal working memory. *Brain*. 2006; 129:306-320. [PubMed: 16317024]
- Scherf KS, Sweeney JA, Luna B. Brain basis of developmental change in visuospatial working memory. *J Cogn Neurosci*. 2006; 18:1045-1058. [PubMed: 16839280]
- Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. *Brain*. 2006; 129:290-292. [PubMed: 16434422]
- Shaw P, Kabani NJ, Lerch JP, et al. Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci*. 2008; 28:3586-3594. [PubMed: 18385317]
- Smith CW, Park S, Cornblatt B. Spatial working memory deficits in adolescents at clinical high risk for schizophrenia. *Schizophr Res*. 2006; 81:211-215. [PubMed: 16321508]
- Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23(Suppl 1):S208-219. [PubMed: 15501092]
- Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci*. 1999; 2:859-861. [PubMed: 10491602]

- Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. *Neuroscientist*. 2004; 10:372–392. [PubMed: 15271264]
- Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Dev Med Child Neurol*. 2002; 44:4–16. [PubMed: 11811649]
- Stephan KE, Magnotta VA, White T, et al. Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. *Psychol Med*. 2001; 31:1065–1078. [PubMed: 11513374]
- Sternberg S. High-speed scanning in human memory. *Science*. 1966; 153:652–654. [PubMed: 5939936]
- Taylor SF, Stern ER, Gehring WJ. Neural systems for error monitoring: recent findings and theoretical perspectives. *Neuroscientist*. 2007; 13:160–172. [PubMed: 17404376]
- Thompson PM, Vidal C, Giedd JN, et al. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci USA*. 2001; 98:11650–11655. [PubMed: 11573002]
- Tiemeier H, Lenroot RK, Greenstein DK, et al. Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. *Neuroimage*. 2010; 49:63–70. [PubMed: 19683586]
- Tuladhar AM, ter Huurne N, Schoffelen JM, et al. Parieto-occipital sources account for the increase in alpha activity with working memory load. *Hum Brain Mapp*. 2007; 28:785–792. [PubMed: 17266103]
- Vance A, Hall N, Bellgrove MA, et al. Visuospatial working memory deficits in adolescent onset schizophrenia. *Schizophr Res*. 2006; 87:223–227. [PubMed: 16793240]
- Wahlstrom D, White T, Hooper CJ, et al. Variations in the catechol O-methyltransferase polymorphism and prefrontally guided behaviors in adolescents. *Biol Psychiatry*. 2007; 61:626–632. [PubMed: 17014828]
- Wechsler, D. Wechsler Intelligence Scale for Children. 4. San Antonio, Texas: Psychological Corporation; 2003.
- Weinberger D, Berman KF. Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophr Bull*. 1988a; 14:157–168. [PubMed: 3059465]
- Weinberger DR, Berman KF. Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophr Bull*. 1988b; 14:157–168. [PubMed: 3059465]
- Wendelken C, Bunge SA, Carter CS. Maintaining structured information: an investigation into functions of parietal and lateral prefrontal cortices. *Neuropsychologia*. 2008; 46:665–678. [PubMed: 18022652]
- White T, Cullen K, Rohrer LM, et al. Limbic structures and networks in children and adolescents with schizophrenia. *Schizophr Bull*. 2008; 34:18–29. [PubMed: 17942479]
- White T, Ho BC, Ward J, O'Leary D, Andreasen NC. Neuropsychological performance in first-episode adolescents with schizophrenia: a comparison with first-episode adults and adolescent control subjects. *Biol Psychiatry*. 2006; 60:463–471. [PubMed: 16566898]
- White T, Kendi AT, Lehericy S, et al. Disruption of hippocampal connectivity in children and adolescents with schizophrenia--a voxel-based diffusion tensor imaging study. *Schizophr Res*. 2007; 90:302–307. [PubMed: 17141478]
- White T, O'Leary D, Magnotta V, et al. Anatomic and functional variability: the effects of filter size in group fMRI data analysis. *Neuroimage*. 2001; 13:577–588. [PubMed: 11305887]
- White T, Schmidt M, Kim DI, Calhoun VD. Disrupted Functional Brain Connectivity during Verbal Working Memory in Children and Adolescents with Schizophrenia. *Cereb Cortex*. 2010 In Press.
- Wood SJ, Pantelis C, Proffitt T, et al. Spatial working memory ability is a marker of risk-for-psychosis. *Psychol Med*. 2003; 33:1239–1247. [PubMed: 14580078]
- Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*. 2001; 14:1370–1386. [PubMed: 11707093]
- Yakovlev, PI.; Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A., editor. *Regional Development of the Brain in Early Life*. Blackwell; Oxford: 1967. p. 3-70.

Figure 1.

Visuospatial Adaptation of the Sternberg Item Recognition Paradigm. The delay period is followed by the retrieval phase, of which there are ten randomly presented probes that consist of either a 'target' or a 'foil.' An example of a 'target' and a 'foil' within the retrieval phase are presented below.

Figure 2.
Measures of d' between Patients with Early-Onset Schizophrenia and Matched Controls.

Figure 3.

Group Analysis of Visuospatial SIRP ANCOVA. The top row is without controlling for performance and the bottom row is with performance (d') as a covariate. Patients had increased activity in: Blue = Encoding load 3; Red = Retrieval load 3.

Figure 4.

Peak Activation Maps for the Region of Interest Analyses for both Encoding and Recall. The regions include the Dorsolateral Prefrontal Cortex (DLPFC) and the Parietal Lobe.

Table 1

Demographic and Clinical Characteristics for the Patient and Control Groups

	Patients n = 22	Controls n = 24	p
Demographic Measures	Mean/SD	Mean/SD	
Age (years/SD)	15.0 (2.8)	15.0 (3.0)	ns
Sex (M/F)	15/7	16/8	ns
Race			ns
Asian	2	2	
Black	3	0	
Caucasian	17	22	
Ethnicity			
Hispanic or Latino	1	0	
Non-Hispanic/Non- Latino	21	24	
SES	41.5 (14.8)	53.9 (7.5)	0.002
Handedness (R/L/Both)	17/1/1	17/1/3	ns
Clinical Measures			
Psychotic Symptoms (mean/SD)	2.6/1.1		
Negative Symptoms (mean/SD)	2.8/0.8		
Disorganized Symptoms (mean/SD)	1.9/1.0		
Age of Onset (mean/SD)	12.5/2.4		
Duration of Illness (mean/SD)	1.6/1.3		
Clinical Diagnosis			
Schizophrenia – Paranoid Subtype	10		
Schizophrenia – Disorganized Subtype	1		
Schizophrenia – Undifferentiated Subtype	8		
Schizoaffective Disorder	2		
Schizophreniform Disorder	1		
History of Substance Abuse			
Cannabis Abuse	2	0	
Amphetamine Abuse	1	0	
Nicotine Dependence	2	0	
Antipsychotic Medications	Number	Mean Dose	
Aripiprazole	4	25 (12.9)	
Clozapine	4	250 (70.7)	
Olanzapine	1	20	
Ziprasidone	1	40	
Risperidone	8	3.5 (1.4)	
Quetiapine	5	500 (324)	
None	1		

Table 2

Regional Differences in Brain Activation Between Patients and Controls during the Encode Condition of the Visuospatial SIRP

Brain Region	Cluster Size	Cluster z-Maximum	Local z-Maximum	x	y	z
Encode Load = 2 (P > C)						
Anterior Cingulate Gyrus	5,550	3.86		-12	36	-4
Planum Polare/Heschl's Gyrus/Superior Temporal Gyrus			3.69	-50	-14	-2
Left Temporal Pole			3.66	-32	12	-42
Cerebellum/Brainstem	2,587	3.73		-10	-16	-40
Posterior Cingulate Gyrus			3.48	-6	-54	22
Left Anterior Cerebellum			3.42	-2	-52	-6
Left Hippocampus			3.16	-26	-10	-20
Right Middle Temporal Gyrus	2,309	5.59		58	4	-22
Right Orbital Frontal Cortex			3.25	26	14	-20
Right Hippocampus/Amygdala			3.22	24	-6	-22
Encode Load = 3 (C > P)						
Parietal Lobe/Precuneous	3,733	3.27		6	-58	50
Superior Parietal Lobe			3.04	38	-52	46
Lateral Occipital Cortex			3.04	-22	-68	44
Encode Load = 3 (Covaried for Performance) (P > C)						
Anterior cingulate	3,158	5.18		-2	28	-6
Left Orbital frontal cortex			3.39	-12	26	-24
Left Temporal Lobe	2,118	3.96		-44	4	-22
Planum Polare/Heschl's Gyrus			3.75	-46	-20	-4
Left Temporal Pole			3.73	-32	12	-42
Superior Temporal Gyrus			3.54	-52	-10	-6
Left Mid & Inf. Temporal Gyrus			3.24	-56	-8	-26
Planum Polare/Heschl's Gyrus	2,003	3.74		44	-18	-2
Right Temporal Pole			3.3	36	14	-22
Right Sup. & Mid Temporal Gyrus			3.3	50	-6	-18
Right Insula			3.21	36	14	-18

P > C – Regions in which patients had greater activation compared to controls.
C > P – Regions in which controls had greater activation compared to patients.

Table 3

Regional Differences in Brain Activation Between Patients and Controls during the Retrieval Condition of the Visuospatial SIRP. The Children and Adolescents with Schizophrenia had greater activity in all regions and there were no regions in which the controls had greater activity than the patients

Brain Region	Cluster Size	Cluster z-Maximum	Local z-Maximum	x	y	z
Probe Load = 2						
Left Temporal Pole	5,198	3.64		-28	10	-38
Middle Temporal Gyrus			3.43	-56	-8	-24
Left Hippocampus/Parahippocampal Gyrus				-20	-8	-28
Paracingulate Gyrus			3.25	-14	42	-6
Probe Load = 3						
Left Middle Temporal Gyrus	3,632	3.61		-60	-2	-18
Left Temporal Pole			3.46	-46	10	-24
Left Parahippocampal Gyrus			3.31	-16	-14	-22
Left Hippocampus/Amygdala			3.21	-16	-10	-16
Probe Load = 3 (Covaried for Performance)						
Anterior Cingulate	34,262	5.3		-2	32	0
Planum Polare/ Heschl's Gyrus			5.04	44	-18	-2
Right Cerebellum			4.46	20	-74	-34
Left Thalamus			4.42	-6	-28	10
Right Hippocampus			4.4	40	-22	-10
Right Amygdala/Hippocampus			4.36	30	-4	-22