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Hyperactivity of caudate, parahippocampal, and prefrontal regions during working memory in never-medicated persons at clinical high-risk for psychosis

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Abstract

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Contributors

Jill Goldstein, Robert McCarley, Tracey Petryshen, Larry Seidman, Martha Shenton and Tsung-Ung Woo designed the study. Raquelle Mesholam-Gately, Heidi Thermenos, Joanne Wojcik and Kristen Woodberry helped to design and implement the study protocol. Samantha DiChiara, Richard Juelich and Heidi Thermenos managed the literature searches. Samantha DiChiara, Richard Juelich, Susan Whitfield Gabrieli and Heidi Thermenos undertook the statistical analyses. Heidi Thermenos wrote the first draft of the manuscript. All authors commented on the first manuscript and contributed to the writing of subsequent versions. All authors have approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

BACKGROUND—Deficits in working memory (WM) are a core feature of schizophrenia (SZ) and other psychotic disorders. We examined brain activity during WM in persons at clinical high risk (CHR) for psychosis.

METHODS—Thirty-seven CHR and 34 healthy control participants underwent functional MRI (fMRI) on a 3.0 T scanner while performing an N-back WM task. The sample included a sub-sample of CHR participants who had no lifetime history of treatment with psychotropic medications (n=11). Data were analyzed using SPM8 (**2-back > 0-back contrast**). **Pearson** correlations between brain activity, symptoms, and WM performance were examined.

RESULTS—The total CHR group and medication-naïve CHR sub-sample were comparable to controls in most demographic features and in N-back WM performance, but had significantly lower IQ. Relative to controls, medication-naïve CHR showed hyperactivity in the left parahippocampus (PHP) and the left caudate during performance of the N-back WM task. Relative to medication-exposed CHR, medication naïve CHR exhibited hyperactivity in the left caudate and the right dorsolateral prefrontal cortex (DLPFC). DLPFC activity was significantly negatively correlated with WM performance. PHP, caudate and DLPFC activity correlated strongly with symptoms, but results did not withstand FDR-correction for multiple comparisons. When all CHR participants were combined (regardless of medication status), only trend-level PHP hyperactivity was observed in CHR relative to controls.

CONCLUSIONS—Medication-naïve CHR exhibit hyperactivity **in regions that subserve WM**. These regions are implicated in studies of schizophrenia and risk for psychosis. Results emphasize the importance of medication status in the interpretation of task induced brain activity.

Keywords

Psychosis; prodrome; fMRI; clinical high risk; working memory

1. INTRODUCTION

The clinical high risk (CHR) syndrome for psychosis is a putatively prodromal phase preceding the onset of a psychotic disorder, with affected individuals typically presenting with attenuated psychotic symptoms and a decline in social and occupational functioning. Approximately 30-35% of CHR individuals will develop a psychotic disorder within three years (Fusar-Poli et al., 2012; Fusar-Poli et al., 2014; Gee and Cannon, 2011). Neuropsychological and neuroimaging studies of CHR samples have sought to identify biomarkers that predict transition to a psychotic disorder, to inform pathophysiological models and suggest targets for early intervention. Both cognitive and magnetic resonance imaging (MRI)-based markers are useful tools in the potential prediction of psychosis onset (Fusar-Poli et al., 2012; Hoffman et al., 2007; Koutsouleris et al., 2012; Pflueger et al., 2007; Pukrop et al., 2007; Schmidt et al., 2014a; Smieskova et al., 2010; Ziermans et al., 2014).

Functional magnetic resonance imaging (fMRI) has been used to examine brain activity during the CHR state in response to cognitive tasks, such as working memory (WM), that are reliably impaired in participants with frank psychosis (Dutt et al., 2015) (Fusar-Poli et al., 2011b; Giuliano et al., 2012). WM is the capacity for temporary storage, maintenance and manipulation of information in the absence of perceptual stimulation. CHR individuals

exhibit impairments in WM (Giuliano et al., 2012), the largest of which are seen in those who later transition to frank psychosis (Cohen's $d = 0.77$; $d = 0.39$ for those who do not). WM deficits in CHR have also been linked to delusional ideation at follow up (Broome et al., 2012), as well as transition to psychosis (Fusar-Poli et al., 2011b), suggesting that they may be a marker of risk for later conversion.

To our knowledge, 11 fMRI studies of WM in CHR have been reported to date (Dutt et al., 2015; Fusar-Poli, 2012; Fusar-Poli et al., 2010a; Fusar-Poli et al., 2011c; Fusar-Poli et al., 2010b; Morey et al., 2005; Schmidt et al., 2014a; Schmidt et al., 2013; Smieskova et al., 2012; Yaakub et al., 2013). The majority of these studies show reduced activity in multiple frontal and parietal regions, a pattern that has also been reported in a meta-analysis of 10 fMRI studies (Fusar-Poli, 2012) and a quantitative review of 32 fMRI studies of CHR (both of which included a heterogeneous mix of executive function, memory, and other tasks) (Dutt et al., 2015). The quantitative review by Dutt et al. in 2015 included a pooled analysis of 5 studies of the N-back WM task, which showed reduced activity in CHR in the inferior parietal lobule.

One important factor in the examination of potentially predictive biomarkers for psychosis is the impact of antipsychotic and other psychiatric medications on these markers. Cognitive and MRI markers are sensitive to the effects of antipsychotic medication (Fusar-Poli et al., 2013; Radua et al., 2012), and CHR study participants are likely to have varying degrees of exposure to these and other psychiatric medications. The heterogeneity introduced by medication differences may impact cognitive and MRI study results. In the quantitative review by Dutt et al. in 2015, for example, some subjects included in the WM analysis had been exposed to psychotropic medication. Two studies reported that some subjects were on antipsychotic and/or antidepressant medication (Pauly et al., 2010; Smieskova et al., 2012), and three reported that CHR participants were antipsychotic-naïve but did not describe the use of other psychiatric medications. (Broome et al., 2009; Fusar-Poli et al., 2010a; Fusar-Poli et al., 2010b).

Here, we sought to characterize brain activity during WM in CHR, and examine differences in those with and without lifetime exposure to any psychotropic medication. We hypothesized that CHR participants would show altered activity during WM in the classical prefrontal-parietal network, and that these alterations would be associated with attenuated psychotic symptoms (Broome et al., 2009; Morey et al., 2005; Smieskova et al., 2012) and WM performance. Given that psychotropic medication has been shown to normalize function in frontoparietal WM networks (Schmidt et al., 2013), we speculated that medication-naïve CHR would exhibit more pronounced alterations in frontal and parietal regions during WM.

2. MATERIALS AND METHODS

2.1 Participants

The subjects were evaluated at the baseline assessment at entry into the Boston Center for Intervention Development and Applied Research (CIDAR) study (<http://bricweb.bidmc.harvard.edu/bostoncidar/>). Individuals with CHR syndromes ($n = 37$) were

recruited from the general community in the Boston metropolitan area through advertisements, community education and talks to mental health providers. Healthy controls ($n = 34$) were recruited from the general community to be comparable to the CHR sample on age, sex, handedness, years of education, and parental socioeconomic status (SES, (Hollingshead, 1975)). Inclusion criteria for the CHR participants included age 13–35 and syndromal criteria specified in Table 1 (see Supplementary Material for a detailed description of inclusion/exclusion criteria). None of the CHR participants included in this baseline sample developed psychosis during the one-year follow-up period. Of the 37 CHR, 11 CHR had no lifetime history of psychiatric medication exposure (“medication-naïve CHR”). Twenty-three CHR were medicated with one or more psychiatric medications at the time of the study, as well as in the past, and 3 were medicated with one of more medications only in the past. Control participants were medication-naïve. The study was approved by the local institutional review board committees at each institution, including Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts General Hospital (MGH), and Brigham and Women's Hospital, and written informed consent was obtained from all participants.

2.2 Neuropsychological and Clinical Assessments

General intellectual ability (IQ) was prorated using 2 subtests (Vocabulary and Block Design) from the Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler, 1999)). The Word Reading subtest of the Wide Range Achievement Test-4 (WRAT4 (Wilkinson, 2006)) was used as an estimate of premorbid intellectual potential. Handedness was assessed by the Annett scale (Annett, 1970). The Auditory Continuous Performance Test battery (A-CPT), consisting of auditory vigilance, WM and interference conditions (Seidman et al., 1998) with demonstrated relationships to cortical and subcortical activity (Huang et al., 2013), was used to examine effects of WM load and interference filtering during selection and maintenance of auditory information. Prodromal symptoms were assessed using the Structured Interview for Prodromal Symptoms (SIPS)(Miller et al., 1999) and 10 items from the Bonn Scale for the Assessment of Basic Symptoms (Allen et al., 2011; Klosterkotter et al., 2001; Schultze-Lutter, 2007), as implemented in the Schizophrenia Proneness Instrument, Adult Version (Schultze-Lutter et al., 2007). Diagnoses were determined by consensus based on a clinical interview with the Structured Clinical Interview for DSM IV-TR (SCID, Research Version)(First et al., 2002) and available medical records. Social and role functioning were examined using the Global Functioning: Social and Role scales(Cornblatt et al., 2007). Assessment for alcohol and other substance use disorders was with the SCID; lifetime and past month drug and alcohol use were further examined with Drug and Alcohol Rating Scales(Seidman et al.).

2.3 Magnetic Resonance Imaging (MRI)

Participants were scanned on a 3T MRI scanner (TimTrio, Siemens Medical Solutions, Erlangen, Germany) at the MGH Athinoula A. Martinos Center for Biomedical Imaging Boston, MA, using a standard 12 channel head coil. Two sagittal 3D magnetization prepared rapid gradient echo (MPRAGE) (T1-weighted, nonselective inversion prepared, spoiled gradient echo pulse) sequences (repetition time [TR]/echo time [TE]/TI/flip 2530 ms/3.39 ms/1100 ms/7deg, bandwidth 190 Hz/pixel, field of view [FOV] 256 × 256 mm, effective

slice thickness 1.33 mm on a 171 mm slab of 128 partitions) were acquired for anatomical localization of the functional imaging data. fMRI data was acquired during 2 task runs, using a whole-brain gradient echo planar imaging sequence (33 contiguous axial slices parallel to the anterior commissure–posterior commissure line, 3 mm thickness, 1-mm skip, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90deg; field of view (FOV) = 200 mm, voxel size = $3.1 \times 3.1 \times 3$ mm).

2.4 fMRI Working Memory Task

During each fMRI task run, participants performed a block-designed, visual N-back WM task with blocks of rest, 0-back trials, and 2-back trials, as previously described (Thermenos et al., 2005). Briefly, in each run, three 32-sec blocks of the 0-back task alternated with three 32-sec blocks of the 2-back task (16 200-msec trials per block, with a 1800-msec inter-stimulus interval), and each task block was preceded by a 20-sec block of fixation. Hit rate and reaction time were dependent variables.

2.5 Statistical Analysis

All non-fMRI variables were compared using independent sample *t* tests performed in the Statistical Package for the Social Sciences (SPSS v.22, Inc.). fMRI data were analyzed using Statistical Parametric Mapping (SPM)-8 software (www.fil.ion.ucl.ac.uk/spm/) and in-house software (<http://web.mit.edu/swg/software.html>) running under the MATLAB environment (Mathworks, Inc.). For each participant, functional images were realigned, normalized to the Montreal Neurological Institute template supplied with SPM-8, and smoothed with an 8-mm Gaussian kernel. Within-subject analyses used a block-based general linear model. Each block (2-back, 0-back) was modeled using a boxcar function convolved with a canonical hemodynamic response function. Estimated motion correction parameters were included as additional covariates. Contrasts were created for each participant for the 2-back > 0-back (task-related activation) and were submitted to second-level random-effects analyses. Within-group effects were tested using single-sample *t* tests on contrast images for each group separately. Differences in brain activity between the controls, medication-naïve CHR and medication-exposed CHR participants were tested using a 3-group ANOVA *F* test with variances assumed unequal between groups, followed by post-hoc independent samples 2-group *t*-tests. Controls were compared with the combined medication-exposed and medication-naïve CHR sample using an independent samples 2-group *t*-test. Cluster-level inferences for all between-group analyses were corrected across the whole brain, or restricted to *a priori* regions-of-interest (ROI's), in the dorsolateral prefrontal cortex (DLPFC) and the inferior/superior parietal cortex, which were defined anatomically using the Wake Forest University Pickatlas (<http://fmri.wfubmc.edu/software/PickAtlas>). Results surviving family-wise error correction for multiple comparisons, with cluster-level $P < 0.05$, were reported and further analyzed with post hoc *t* tests. ANCOVA was used to test for the potentially confounding effects of IQ and lifetime drug use on between-group differences in brain activity. To characterize group differences further, post hoc two-tailed *t* tests were performed on parameter estimates (levels of task-related activity relative to baseline rest) extracted from significant clusters differentiating the groups for the 2-back and 0-back conditions. To investigate the predicted associations between brain activity, symptoms and WM, we **conducted** bivariate **Pearson** correlations between the fMRI **contrast** estimates (**2-back >**

0-back) and 1) four SIPS summary scores (Positive, Negative, Disorganized, and General Symptoms) and 2) WM performance (2-back task hit rate and reaction time, and A-CPT working memory and interference task hit rate). Correlations were reported when significant at $p < 0.05$, FDR-corrected for multiple comparisons.

3. RESULTS

3.1 Demographic, Clinical and Neuropsychological Characteristics

The total CHR sample ($n=37$) and medication-naïve CHR sub-sample ($n=11$) were comparable to controls in most demographic features (age, gender, race, socioeconomic status, handedness), although the medication-naïve CHR group was marginally older than the medication-exposed CHR group (~21 vs. ~19 years) and had significantly more left-handed participants than the control group (with a similar trend in the total CHR group) (Table 2a).

Compared to controls, both the total and medication-naïve CHR groups had significantly lower scores on measures of current and premorbid intellectual ability, with similar trends in the medication-exposed CHR group (Table 2b). The medication-naïve CHR group also had significantly lower current intellectual ability than the medication-exposed CHR group.

On the A-CPT, the total and medication-naïve CHR groups had significantly reduced performance on only the most difficult version of the A-CPT task (WM with interference) relative to controls. Despite differences in intellectual ability and A-CPT interference task performance, there were no group differences in performance on the N-back WM tasks during fMRI.

The total CHR and medication-naïve CHR groups had significantly more symptoms than controls on all SIPS and lower scores on social and role function scales. In addition, medication-naïve CHR had significantly higher lifetime drug use than controls and medication-exposed CHR. CHR groups did not differ from controls in alcohol use over the lifetime or during the past month. As compared to medication-exposed CHR, the medication-naïve CHR had significantly higher scores on the SIPS grandiosity scale, but significantly lower scores on the SIPS “impaired tolerance to normal stress” scale. There were no significant differences on the other 17 SIPS scales.

3.2 Brain Activity During WM

Relative to controls, the total CHR group showed a non-significant trend toward reduced WM-induced suppression of activity in the left parahippocampus (PHP) (Fig 1a, Table 3). When controls, medication-naïve CHR and medication-exposed CHR participants were compared using a 3-group ANOVA, significant differences were observed in the left parahippocampus ($x = -28$, $y = -8$, $z = -30$; $F = 8.70$, FWE-wholebrain corrected $p = 0.014$) and the left caudate ($x = -7$, $y = 1$, $z = 0$; $F = 12.32$, FWE-wholebrain corrected $p = 0.014$). There was also a significant difference in the right DLPFC [$x = 50$, $y = 43$, $z = 15$; $F = 6.28$, FWE-corrected $p = 0.0001$ over an *a priori* defined small-volume of the DLPFC (BA 46)]. When these differences were further investigated using post-hoc 2-group t-tests, medication-naïve CHR participants exhibited significant hyperactivity (non-suppression) relative to

controls in the PHP as well as in the left caudate (Fig 1a,b, Table 3). These results remained significant when IQ and lifetime drug use scores were used as covariates (notably, the extent of activation in the caudate region was more extensive and included a region of the right caudate). Results were also unaffected when left-handed participants were removed from the analyses.

Relative to medication-exposed CHR, the medication-naïve CHR showed significant hyperactivity in the left caudate and the right DLPFC (Fig 1b,c, Table 3). These results remained significant when IQ and lifetime drug use scores were used as covariates, with the increased DLPFC hyperactivity then significant across the whole brain (FWE error corrected, as compared to the original analysis, when a region of interest approach was used for the DLPFC). Results were also unaffected when left-handed participants were removed from the analyses. Finally, results were replicated when the medication-exposed group was restricted to those exposed to antipsychotic medication.

The medication exposed group showed no significant differences in PHP, left caudate, or right DLPFC relative to controls (Fig 1a-c), and this result was replicated when the medication-exposed group was restricted to those participants exposed to antipsychotic medication.

3.3 Correlations between Brain Activity, Symptoms and Cognition

3.3.1 Symptoms—In medication-naïve CHR (but not the other groups), 2-back induced activity in the left PHP and right DLPFC clusters was associated with SIPS Disorganized summary scores (PHP: $r = 0.69$; DLPFC: $r = 0.63$). Caudate activity, on the other hand, was negatively associated with the SIPS General summary score in medication-naïve CHR ($r = -0.73$) However, these results did not withstand correction for multiple comparisons.

3.3.3 Working memory—In the medication-naïve CHR group, 2-back induced DLPFC activity was negatively associated with 2-back task reaction time ($r = -0.87$, FDR-corrected $p = 0.012$), with similar trend for 2-back hit rate ($r = -0.72$, FDR-corrected $p = 0.060$) (Fig. 2) and the interference WM version of the A-CPT ($r = -0.69$, FDR-corrected $p = 0.080$). There was a similar relationship of 2-back induced PHP activity and 2-back task reaction time in medication-naïve CHR ($r = -0.73$), but this result did not withstand correction for multiple comparisons. These correlations were not seen in the other groups.

4. DISCUSSION

Relative to controls, medication-naïve CHR participants showed hyperactivity in the PHP and the left caudate during performance of the N-back WM task. Relative to medication-exposed CHR, medication naïve CHR exhibited hyperactivity in the left caudate and the right DLPFC. Results were observed in the absence of differences in most demographic features or most importantly, N-back WM performance, and remained significant when IQ and lifetime drug use were used as covariates. Hyperactivity in the DLPFC was significantly associated with reduced WM performance. Activity in the PHP, caudate and DLPFC was strongly correlated with symptoms ($r \sim 0.7$), but results did not withstand correction for multiple comparisons. Medication status affected the study results, as only a trend level

difference from controls was observed in the left PHP when all CHR participants were combined (regardless of medication status), and no significant results were observed in the medication exposed CHR group. Thus, the findings underscore the effect of within-sample heterogeneity (e.g., medication-status) in the interpretation of fMRI data (e.g., see (Schmidt et al., 2013)).

While recent meta-analytic studies of CHR to date report a general pattern of hypoactivity in executive regions in CHR (Dutt et al., 2015; Fusar-Poli, 2012), a large body of work in persons at familial high risk for psychosis and those with schizophrenia suggests that both hypo- and hyperactivity are observed in these populations, with regions of hyperactivity seen as potentially compensatory for deficits in other regions (Minzenberg et al., 2009; Seidman et al., 2006; Thermenos et al., 2013; Whitfield-Gabrieli et al., 2009). The medication-naïve CHR participants in this study were more impaired than the medication-exposed group (e.g., lower intellectual ability and A-CPT interference task performance, lower social and role function, higher SIPS grandiosity scores and higher lifetime drug use), yet they were able to perform the N-back task at a level equal to controls. We have previously shown that non-psychotic first-degree relatives of people with psychosis often show hyperactivity in regions associated with psychosis when their N-back task performance is intact, and hypoactivity when their task performance is impaired (reviewed in (Thermenos et al., 2013)). Thus, it is possible that the medication-naïve sample reported here shows a pattern similar to that observed in non-psychotic first-degree relatives with intact N-back task performance. While speculative, hyperactivity in the context of intact N-back task performance may suggest some ability to compensate for deficits.

Results of this study are provocative, as left PHP, left caudate, and right DLPFC are strongly implicated in studies of CHR, schizophrenia, and familial risk for psychosis (e.g., (Diwadkar et al., 2012; Fusar-Poli et al., 2011d; Kuepper et al., 2013; Seidman et al., 2003; Seidman et al., 2006; Tamminga et al., 2010; Tandon et al., 2013; Thermenos et al., 2013)). Converging evidence points to both structural, functional and/or neurochemical abnormalities in these three regions in CHR. In the frontal cortex, CHR exhibit both structural alterations (e.g., gray matter, cortical surface, integrity) (Bloemen et al., 2010; Fusar-Poli et al., 2011a; Iwashiro et al., 2012; Jung et al., 2012; Kambeitz-Ilankovic et al., 2015; Mechelli et al., 2011; Nenadic et al., 2015; Pantelis et al., 2009) (reviewed in (Brent et al., 2013; Smieskova et al., 2013)) and functional changes in response to WM and other cognitive tasks (Allen et al., 2011; Dutt et al., 2015; Fusar-Poli et al., 2011b; Natsubori et al., 2014). In the PHP and medial temporal lobe (MTL, including the hippocampus, amygdala and surrounding entorhinal and perirhinal cortices), CHR most reliably demonstrate structural alterations (e.g., reduced gray matter, cortical thinning) (Buehlmann et al., 2010; Jung et al., 2011; Mechelli et al., 2011; Mittal et al., 2011; Pantelis et al., 2003; Tognin et al., 2013), with one previous study demonstrating task-induced functional alterations in antipsychotic naïve CHR (Allen et al., 2011). In the striatum, altered striatal activity, as well as altered striatal dopamine (Allen et al., 2012; Fusar-Poli et al., 2011e), glutamate (de la Fuente-Sandoval et al., 2011), GABA (Kang et al., 2014) and 5HT(2A) binding (Hurlmann et al., 2008), have been reported in CHR.

There is also some evidence of links between the structural, functional and neurochemical alterations in these three regions in CHR. For example, reduced prefrontal activity during WM has been associated with reduced prefrontal gray matter (Fusar-Poli et al., 2011a). CHR also exhibit reduced DLPFC-rMTL effective connectivity during WM (Benetti et al., 2009), and reduced frontal connectivity (Jung et al., 2012; Schmidt et al., 2014b) and frontostriatal resting state connectivity (Dandash et al., 2014) in association with positive symptoms. Finally, altered task-induced striatal activity (Sabb et al., 2010), as well as an altered relationship between striatal dopamine and both prefrontal (Fusar-Poli et al., 2010b) (Fusar-Poli et al., 2011e) and MTL activity (Allen et al., 2012), have been reported in CHR.

The DLPFC, caudate, and PHP play unique roles in the temporary storage, maintenance and manipulation phases of WM (Ranganath, 2006). In humans and in animals, WM function is modulated by dopaminergic activity in prefrontal and striatal regions (Castner et al., 2004; Cropley et al., 2006; Harrison et al., 2004; Marie and Defer, 2003; Williams and Castner, 2006). The relationship of prefrontal activity during WM and striatal dopamine follows an inverted U-shaped curve, with prefrontal activity maximal at mid-range levels of striatal dopamine (and attenuated at low or high striatal dopamine levels) (Alexander et al., 1986; Goldman-Rakic et al., 2000; Marie and Defer, 2003; Williams and Castner, 2006). Both the DLPFC and caudate are implicated in the updating phase of WM (Elliott et al., 2003; Murty et al., 2011; Villablanca, 2010; White, 2009). The DLPFC is also implicated in maintenance phase of WM (D'Esposito et al., 1998; Funahashi et al., 1993; Lebedev et al., 2004; Rao et al., 1997) while the caudate is sensitive to WM load (Chang et al., 2007; Grahn et al., 2008; Melrose et al., 2007; Seger and Cincotta, 2005).

The role of the PHP in WM is more controversial. While most research has focused on the role of the MTL in long-term memory (Squire et al., 2004; Squire and Zola-Morgan, 1991), more recent studies implicate the MTL, including the PHP, in encoding and maintenance, but not in the retrieval phases of WM (Luck et al., 2010; Meltzer et al., 2008; Nichols et al., 2006; Ranganath, 2006; Wagner et al., 2009). Recent work demonstrates a role for MTL and PHP in: 1) the binding of multiple pieces of information into a coherent, higher-level representations (Luck et al., 2010) and, 2) the maintenance of that representation in short-term or WM “buffer” during encoding (Axmacher et al., 2008; Luck et al., 2010) (Hasselmo and Stern, 2006) (see (Jonides et al., 2008) and (Kumaran, 2008) for reviews). This is consistent with known roles of the MTL in contextual (Hirsh, 1974), configural (Rudy and Sutherland, 1995), and relational information processing (Cohen et al., 1997). It has also been suggested that the MTL (and long-term memory) only plays a role in performance of short-delay tasks under conditions when immediate memory and WM are insufficient to support performance (e.g., under high complexity or high load conditions) (Jenerson and Squire, 2012).

Ranganath et al. 2006 (Ranganath, 2006) outlined a model of visual WM that involves a distributed network of frontal and posterior cortical areas, in which representations are constructed, maintained and manipulated at multiple cortical levels. This includes a top-down role for the DLPFC [in maintenance, inhibition of distracting information, (Miller et al., 1996; Sakai et al., 2002) and modulation of visual representations based on prior knowledge or goals], as well as top-down roles for the both the MTL and PFC in binding of

relational and novel information between visual objects as higher level representations (e.g., via modulation of activity in primary visual and inferior temporal cortices)(Ranganath, 2006; Ranganath and D'Esposito, 2001; Rolls, 2000).

Taken together, the literature to date suggests that CHR exhibit alterations in frontal, medial temporal and/or striatal regions, which play roles in different components of working memory. There is some evidence of altered connectivity and neuromodulation between these three regions in CHR, as well as more progressive or more severe changes in frontal (Cannon et al., 2015; Fusar-Poli et al., 2011d; Kambeitz-Ilankovic et al., 2015) and striatal regions (Sabb et al., 2010) in those who later transition to psychosis. Consistent with our observation of significant findings in medication-naïve, but not medication exposed CHR, previous studies have demonstrated that antipsychotic medication is associated with normalization of function in frontoparietal WM networks (Schmidt et al., 2013). Antipsychotic medication has also been shown to modulate hemodynamic activity during performance of other (non-WM) tasks. (Smieskova et al., 2015).

4.1 Limitations

Results of this study are considered preliminary in light of some important limitations. First, the medication-naïve CHR sample is relatively small, and thus results require replication in a larger sample. Second, the CHR sample had reduced current and premorbid intellectual ability relative to controls. Notably, all but the medication-naïve group exceeded the average estimated current intellectual ability (IQ = 100) by about 1 standard deviation (with the medication naïve group average about half a standard deviation above average), and findings remained significant when IQ was used as a covariate. The medication-naïve CHR group also evinced higher grandiosity scores, had more lifetime drug use, and better tolerance for normal stress, and was marginally older than the other CHR groups, all of which could be important contributing factors to the findings, in conjunction with medication status [e.g., (Karlsgodt et al., 2014)]. Regarding the effect of lifetime drug use, we note that a current SCID diagnosis of a substance or alcohol use disorder was an exclusion criterion for this study, and that the findings remained significant when lifetime drug use was used as a covariate. Finally, the interpretation of results from cross-sectional studies of CHR is complicated by the normal dynamic changes in brain development during the CHR period (late adolescence and early adulthood) (Pantelis et al., 2009), and thus findings from this study require replication in longitudinal samples.

4.2. Conclusions

Results of this study reveal the potential importance of medication status on brain activity in CHR participants, and converge with other evidence that frontal, striatal, and medial temporal alterations make important contributions to the risk for psychosis. Future studies will use connectivity approaches within our larger, longitudinal dataset, to determine whether or not altered structural and/or functional development in the three regions predicts conversion to psychotic illness or other markers of functional decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a.

Medication-naïve CHR participants showed significant WM-task induced hyperactivity (non-suppression) relative to controls in the left parahippocampus (PHP) (with similar trend observed in all CHR relative to controls). Bar graphs depict parameter estimates extracted from the significant clusters for the 0-back (blue) condition and the 2-back condition (purple) relative to the baseline fixation, and the contrast between the two conditions (green). BOLD: blood oxygen level-dependent signal as measured by functional MRI.

Figure 1b.

Medication-naïve CHR participants showed significant WM-task induced hyperactivity in the left caudate relative to controls and medication-exposed CHR. Bar graphs depict parameter estimates extracted from the significant clusters for the 0-back (blue) condition and the 2-back condition (purple) relative to the baseline fixation, and the contrast between the two conditions (green). BOLD: blood oxygen level-dependent signal as measured by functional MRI.

Figure 1c.

Medication-naïve CHR participants showed significant WM-task induced hyperactivity relative to medication-exposed CHR in the right dorsolateral prefrontal cortex (DLPFC). Bar graphs depict parameter estimates extracted from the significant clusters for the 0-back (blue) condition and the 2-back condition (purple) relative to the baseline fixation, and the contrast between the two conditions (green). BOLD: blood oxygen level-dependent signal as measured by functional MRI.

Figure 2.

In medication-naïve CHR, right DLPFC activity was negatively correlated with 2-back task reaction time ($r = -0.87$, FDR-corrected $p = 0.012$), with a similar trend for 2-back hit rate (-0.72 , FDR-corrected $p = 0.060$).

Table 1

Inclusion criteria for Clinical High Risk (CHR) participants (n = 37).

1. “Late Prodromal Phase” Inclusion Criteria, corresponding to the Criteria of Prodromal States (n = 33)
1.1. Genetic Risk and Deterioration Syndrome (GRDS; also referred to as “trait and state” risk factors) (n = 3): Schizotypal personality disorder or first-degree relative with a psychotic disorder; 30% or greater drop in GAF score within the last month compared with the person’s highest GAF in the prior 12 mo.
1.2. Attenuated Positive Symptoms Syndrome (APSS) (n = 29): Severity rating of 3, 4, or 5 on one or more of the 5 SOPS positive symptom scales; symptom occurs at the above severity level at an average frequency of at least once per week in the past month; symptom(s) must have begun in the past year or currently rate at least 1 point higher than if rated a year ago.
1.3. Brief Intermittent Psychotic Syndrome (n = 1): Severity rating of 6 (psychotic intensity) on any of the 5 positive symptom scales of the SOPS; symptom is present at least several minutes per day at a frequency of at least once a month; symptom(s) must have reached a psychotic intensity in the past 3 mo; symptom(s) have never occurred at least 1 h per day at a minimum average frequency of 4 d per week over 1 mo and been seriously disorganizing or dangerous.
2. “Early Prodromal Phase” Inclusion Criteria (n = 4)
2.1. If under the age of 19 and meets DSM-IV-TR criteria for schizotypal personality disorder (n = 0).
2.2. Modified GRDS Criteria (n = 0): First-degree relative with psychosis and a 10-point drop in the GAF score compared with a year ago (premorbid level); must be sustained over the past 3 mo.
2.3. Modified APSS Criteria (n = 2): The presence of at least 1 attenuated positive symptom (defined as a score of 3, 4, or 5 on any one of the 5 positive symptoms of the SOPS) and must occur at an average frequency of at least twice per month over the past 3 mo.
2.4. Clinical High Risk Negative Symptoms Syndrome (n = 2): The presence of at least 2 negative symptoms (defined as a score of 3 or above on any 2 of the 6 negative symptoms of the SOPS) and must occur at an average frequency of at least once per week for the past month in the context of all positive symptom ratings below a moderate degree of severity (severity rating < 3).
2.5. Basic Symptoms Syndrome (n = 0): Occurrence of one or more of the cognitive-perceptual symptoms, (Schultze-Lutter, 2007) ie, the 10 basic symptoms that were found to have the best predictive validity for a future psychotic disorder (Klosterkotter et al., 2001). Their occurrence is defined as a rating of 3 (several times in a month or weekly) or higher, rated over the past 3 mo, on an abbreviated version of the SPI-A. The 10 symptoms are thought interference, thought perseveration, thought blockages, thought pressure, disturbances of receptive language, decreased ability to discriminate between ideas and perception or fantasy and memory, derealization, unstable ideas of reference, visual, and acoustic perception disturbances.

Note: GAF, Global Assessment of Functioning (Hall, 1995); SOPS, Scale of Prodromal Symptoms (Miller et al., 1999); DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; SPI-A, Schizophrenia Proneness Instrument, Adult Version (Schultze-Lutter et al., 2007)

Table 2a

Demographic characteristics of CHR and control participants.

Variable	Controls (N=34)	All CHR (37)	Medication-naïve CHR (11)	Medication-exposed CHR (26)	Statistic t or X ² (p)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Controls vs. All CHR Controls vs. Medication-naïve CHR Medication-exposed vs. Medication-naïve CHR
Age	20.0 (4.1)	19.6 (4.0)	21.4 (5.0)	18.9 (3.4)	.37 (.71) -.95 (.35) 1.81 (.08)
Gender - % Male	53%	41%	36%	42%	1.10 (.30) .91 (.34) .11 (.74)
Race - % Caucasian	64%	57%	36%	65%	2.98 (.70) 6.50 (.17) 6.11 (.30)
Socioeconomic Status **	1.7 (.9)	2.0 (1.0)	2.3 (1.3)	1.9 (.8)	4.22 (.38) 5.04 (.28) 3.79 (.44)
Handedness -% Left	0%	14%	18%	12%	4.94 (.08) 6.47 (.04) .45 (.80)

*p < 0.05

†Levene's Test for Equality of Variances significant p<0.05

**Hollingshead Four Factor Index of Social Status (values range from 1 to 5).

Table 2b

Cognitive characteristics of CHR and control participants.

Variable	Controls (34)	All CHR (37)	Medication-naïve CHR (11)	Medication-exposed CHR (26)	Statistic t or X ² (p)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Controls vs. All CHR Controls vs. Medication-naïve CHR Medication-exposed vs. Medication-naïve CHR
WASI IQ	120.9 (13.8)	114.1 (14.2)	107.6 (15.1)	116.8 (13.1)	2.04 (.05) [*] 2.71 (.01) [*] -1.88 (.07)
WRAT4-Reading	119.6 (15.9)	111.5 (16.3)	104.8 (15.1)	114.3 (16.3)	2.11 (.04) [*] 2.70 (.01) [*] -1.65 (.11)
Auditory CPT Simple Vigilance Hits – %	97.6 (3.9)	97.7 (3.7)	97.0 (3.9)	97.3 (3.7)	0.49 (.63) 0.47 (.64) -0.20 (.84)
Auditory CPT Working Memory Hits- %	86.4 (10.3)	85.6 (10.4)	84.8 (5.6)	86.0 (12.1)	0.30 (.76) 0.47 (.64) -0.39 (.70) [†]
Auditory CPT Interference Hits- %	66.9 (19.9)	56.3 (21.8)	51.4 (21.5)	58.5 (22.0)	2.13 (0.04) [*] 2.21 (0.03) [*] -.90 (0.37)
In-scanner WM task: 0-Back Hits - %	.93 (.10)	.90 (.11)	.93 (.10)	.88 (.11)	1.21 (.23) -.07 (.95) 1.16 (.26)
In-scanner WM task: 0-Back RT- msec	.556 (.083)	.525 (.106)	.577 (.053)	.504(.116)	1.33 (.19) -.75 (.46) 1.89 (.07)
In-scanner WM task: 2-Back Hits- %	.81 (.21)	.78 (.15)	.74 (.21)	.80 (.11)	.51 (.61) .90 (.37) -.94 (.34)
In-scanner WM task: 2-Back RT- msec	.724 (.193)	.710 (.165)	.765 (.106)	.686 (.181)	.32 (.75) -.65 (.52) 1.29 (.21)

WASI: Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999).

WRAT4: Wide Range Achievement Test-4 Word Reading subtest (WRAT4, Wilkinson and Robertson, 2006).

CPT: Continuous Performance Test

RT: Reaction time

^{*}p < 0.05[†]Levene's Test for Equality of Variances significant p<0.05

Table 2c

Clinical characteristics of CHR and control participants.

Variable	Controls (34)	All CHR (37)	Medication-naïve CHR (11)	Medication-exposed CHR (26)	Statistic t or X ² (p)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Controls vs. All CHR Controls vs. Medication-naïve CHR Medication-exposed vs. Medication-naïve CHR
Structured Interview for Prodromal Symptoms					
Positive Symptom Severity Summary					
P1. Unusual Thought Content	.1 (.2)	3.4 (1.2)	3.5 (.8)	3.4 (1.4)	-16.16 (.0001) [*] -13.57 (.0001) [*] .155 (.88)
P2. Suspiciousness/Persecutory Ideas	.1 (.3)	2.4 (1.5)	2.3 (1.5)	2.4 (1.5)	-9.03 (.0001) [*] -4.76 (.0001) [*] -.211 (.83)
P3. Grandiosity	.06 (.2)	1.7 (1.6)	2.6 (1.6)	1.3 (1.5)	-5.95 (.0001) [*] -5.23 (.0001) [*] 2.49 (.02) [*]
P4 Perceptual Abnormalities	.03 (.2)	2.8 (1.6)	2.7 (1.5)	2.8 (1.7)	-10.27 (.0001) [*] -6.00 (.0001) [*] -.072 (.94)
P5. Disorganized Communication	.06 (.3)	1.9 (1.2)	2.4 (1.4)	1.7 (1.1)	-8.77 (.0001) [*] -5.28 (.0001) [*] 1.56 (.13)
Negative Symptom Severity Summary					
N1. Social anhedonia	.06 (.2)	2.7 (1.7)	2.7 (2.0)	2.7 (1.6)	-9.44 (.0001) [*] -4.42 (.0001) [*] .121 (.91)
N2. Avolition	.09 (.3)	2.6 (1.6)	2.5 (1.8)	2.7 (1.5)	-9.75 (.0001) [*] -4.32 (.0001) [*] -.421 (.68)
N3. Expression of Emotion	.00 (.0)	1.8 (1.5)	1.6 (1.2)	1.8 (1.7)	-6.83 (.0001) [*] -4.50 (.0001) [*] -.29 (.77)
N4. Experience of Emotions and Self	.03 (.2)	2.0 (1.7)	1.9 (1.7)	2.0 (1.7)	-7.08 (.0001) [*] -3.66 (.0001) [*] -.211 (.83)

Variable	Controls (34)	All CHR (37)	Medication-naïve CHR (11)	Medication-exposed CHR (26)	Statistic t or X ² (p)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Controls vs. All CHR Controls vs. Medication-naïve CHR Medication-exposed vs. Medication-naïve CHR
N5. Ideational Richness	.2 (.4)	1.6 (1.5)	1.4 (1.3)	1.7 (1.5)	-5.64 (.0001) [*] -3.08 (.0001) [*] -.59 (.56)
N6. Occupational Functioning	.2 (.6)	3.0 (1.9)	2.5 (1.8)	3.3 (1.9)	-8.60 (.0001) [*] -4.10 (.002) [*] -1.20 (.24)
Disorganized Symptom Severity Summary					
D1. Odd Behavior and Appearance	.00 (.0)	1.5 (1.4)	1.9 (1.6)	1.3 (1.3)	-6.31 (.0001) [*] -3.86 (.003) [*] 1.28 (.21)
D2. Bizarre Thinking	.00 (.0)	1.6 (1.4)	2.0 (1.2)	1.4 (1.5)	-6.82 (.0001) [*] -5.61 (.0001) [*] 1.25 (.22)
D3. Trouble Focus and Attention	.12 (.3)	2.3 (.9)	2.0 (1.2)	2.5 (.8)	-13.75 (.0001) [*] -5.21 (.0001) [*] -1.42 (.16)
D4. Personal Hygiene	.03 (.2)	1.1 (1.2)	.8 (.9)	1.2 (1.3)	-5.23 (.0001) [*] -2.98 (.01) [*] -.789 (.44)
General Symptom Severity Summary					
G1. Sleep Disturbance	.06 (.2)	2.2 (1.0)	1.8 (1.2)	2.4 (.9)	-12.31 (.0001) [*] -4.96 (.0001) [*] -1.46 (.15)
G2. Dysphoric Mood	.06 (.2)	3.4 (1.6)	3.4 (1.6)	3.4 (1.7)	-12.42 (.0001) [*] -6.97 (.0001) [*] -.036 (.97)
G3. Motor Disturbance	.00 (.0)	.8 (.9)	.6 (.8)	.8 (1.0)	-4.80 (.0001) [*] -2.61 (.03) [*] -.48 (.64)
G4. Impaired tolerance to normal stress	.00 (.0)	2.5 (1.9)	1.6 (1.4)	3.0 (1.9)	-8.35 (.0001) [*] -3.56 (.005) [*] -2.25 (.031) [*]
Social Function Summary					
Current Social Function	8.9 (.6)	6.1 (1.3)	6.1 (1.6)	6.1 (1.2)	11.51 (.0001) [*]

Variable	Controls (34)	All CHR (37)	Medication-naïve CHR (11)	Medication-exposed CHR (26)	Statistic t or X ² (p)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Controls vs. All CHR Controls vs. Medication-naïve CHR Medication-exposed vs. Medication-naïve CHR
					5.77 (.0001) ^{†*} .023 (.98)
Lowest Past Year Social Function	8.7 (.8)	5.8 (1.3)	6.0 (1.4)	5.6 (1.2)	11.74 (.0001) ^{†*} 6.00 (.0001) ^{†*} .79 (.43)
Highest Past Year Social Function	9.0 (.7)	6.7 (1.3)	6.9 (1.2)	6.6 (1.4)	9.30 (.0001) ^{†*} 5.48 (.0001) ^{†*} .64 (.53)
Role Function Summary					
Current Role Function	8.7 (.9)	6.4 (2.0)	6.3 (2.1)	6.5 (2.0)	6.27 (.0001) ^{†*} 3.79 (.0001) ^{†*} -.29 (.78)
Lowest Past Year Role Function	8.6 (1.0)	5.8 (2.1)	5.6 (1.9)	5.9 (2.2)	7.17 (.0001) ^{†*} 5.14 (.0001) ^{†*} -.50 (.62)
Highest Past Year Role Function	8.8 (.8)	7.5 (1.5)	7.4 (1.4)	7.5 (1.6)	4.64 (.0001) ^{†*} 3.20 (.007) ^{†*} -.28 (.78)
Drug/Alcohol Use Summary					
Lifetime drug use	.5 (.8)	.8 (1.0)	1.3 (1.2)	.6 (.9)	2.85 (.58) 9.22 (.06) 11.03 (.02) [*]
Past month drug use	.1 (3)	.2 (.4)	.4 (.5)	.2 (.4)	1.35 (.25) 3.44 (.06) 1.83 (.18)
Lifetime alcohol use	.7 (.9)	.6 (.8)	.9 (.9)	.4 (.7)	.62 (.89) 1.29 (.73) 4.40 (.22)
Past month alcohol use	.3 (.5)	.3 (.5)	.5 (.5)	.2 (.4)	.026 (.87) .62 (.43) 1.66 (.20)

* p < 0.05

[†]Levene's Test for Equality of Variances significant p<0.05

Table 3

Differences in hemodynamic activity in CHR and control participants.

Variable	Peak (MNI) ^a coordinate (Cluster extent)	<i>t</i> ^b (FWE-corrected <i>p</i> -value)
Whole-brain^c		
Left Parahippocampus (PHP)	-28 -8 -30 (121)	All CHR > Controls: 3.63 (<i>NS</i>)
	-28 -8 -30 (141)	Med-naïve CHR > Controls: 4.60 (.01) [*]
	-28 -8 -30 (21)	Med-naïve > Med-exposed CHR: ---
Left Caudate		All CHR > Controls: ---
	-4 1 -3 (111) -7 1 -3 (88)	Med-naïve CHR > Controls: 4.69 (.02) [*]
	-7 1 -3 (199) -7 4 6 (131)	Med-naïve > Med-exposed CHR: 4.22 (.008) [*]
Region-of-interest^d		
Right Dorsolateral/ inferior frontal gyrus (BA 46, 10)		
	50 43 18 (5)	All CHR > Controls: ---
	---	Med-naïve CHR > Controls: ---
	50 40 18 (13)	Med-naïve > Med-exposed CHR: 3.96 (.05) [*]

^aMNI = Montreal Neurological Institute Coordinate System^bMaximum voxel-wise *t*-value within the cluster of interest.^cWhole-brain analysis: cluster-wise family-wise error (FWE)-corrected statistic (*p* < 0.05).^dRegion-of-interest analysis: for regions of interest defined *a priori*, the voxel-wise statistic was FWE-corrected for multiple comparisons within the *a priori* region.^{*}*p* < 0.05