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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

*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-naive 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.



## 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.,

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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., 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., 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,

**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 et al., 2007a) i.e., 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., 2007b).

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