Preserved Working Memory and Altered Brain Activation in Persons at Risk for Psychosis

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Objective: Patients with schizophrenia exhibit impairments in working memory that often appear in attenuated form in persons at high risk for the illness. The authors hypothesized that deviations in task-related brain activation and deactivation would occur in persons with an at-risk mental state performing a working memory task that entailed the maintenance and manipulation of letters.

Method: Participants at ultra high risk for developing psychosis (N=60), identified using the Comprehensive Assessment of At-Risk Mental States, and healthy comparison subjects (N=38) 14 to 29 years of age underwent functional MRI while performing a verbal working memory task. Group differences in brain activation were identified using analysis of covariance.

Results: The two groups did not show significant differences in speed or accuracy of performance, even after accounting for differences in education. Irrespective of task condition, at-risk participants exhibited significantly less activation than healthy comparison subjects in the left anterior insula. During letter manipulation, at-risk persons exhibited greater task-related deactivation within the default-mode network than comparison subjects. Region-of-interest analysis in the at-risk group revealed significantly greater right dorsolateral prefrontal cortex activation during manipulation of letters.

Conclusions: Despite comparable behavioral performance, at-risk participants performing a verbal working memory task exhibited altered brain activation compared with healthy subjects. These findings demonstrate an altered pattern of brain activation in at-risk persons that contains elements of reduced function as well as compensation.

in working memory (33, 34)—we hypothesized that the at-risk group would exhibit activation differences that reflect reduced efficiency of brain regions supporting working memory, as well as the compensation for this reduced efficiency (35, 36). The second network that we examined is referred to as the default-mode network (37–39) because the areas are frequently deactivated when a person is focused on a specific task but activated when attention is not focused on the external world. We hypothesized that there would be less task-related deactivation in the default-mode network (40, 41); this would signify reduced ability to disengage from the internal environment to perform the task at hand. Finally, to test the functional relevance of altered activation in at-risk participants, we correlated the magnitude of signal change with several established measures of symptom severity and cognition.

**Method**

**Participants**

We studied 69 persons at risk for psychosis and 40 comparison subjects between the ages of 14 and 29 years. Participants were recruited as part of the Longitudinal Youth At-Risk Study, which sought to identify and follow up ultra-high-risk persons over a 2-year period through psychiatric clinics in Singapore at the Institute of Mental Health, the Singapore Armed Forces, and community mental health services.

Participants were assigned to the at-risk group if they met criteria for any of the following three subgroups, based on the Comprehensive Assessment of At-Risk Mental States: 1) a vulnerable subgroup, comprising individuals with a family history of psychosis in a first-degree relative or with a schizotypal disorder; 2) an attenuated psychosis subgroup, comprising individuals with subthreshold psychotic symptoms; and 3) a brief limited intermittent psychotic symptoms subgroup, comprising individuals with a recent history of frank psychotic symptoms that resolved spontaneously within 1 week. At-risk participants had no history of psychiatric, neurological, or serious medical disorders or mental retardation, and they were not receiving any antipsychotic medications at the time of imaging. Persons with current substance abuse were excluded. Imaging data for three at-risk persons were excluded because of excessive head movement (>3 mm across runs). Data for an additional six at-risk participants were excluded because of poor task performance (<75% accuracy on control and maintenance-of-information conditions). Thus, data for 60 at-risk participants were analyzed. Demographic and clinical characteristics for the at-risk group are summarized in Table 1. The small numbers of participants categorized as vulnerable or as having brief limited intermittent psychotic symptoms made subgroup analyses untenable; however, we did investigate differences in brain activity between vulnerable-only participants (subgroup 1) and those exhibiting psychotic-spectrum symptoms (subgroups 2 and 3). For the results of this analysis, see Figure S1 in the data supplement that accompanies the online edition of this article.

Six at-risk participants were later diagnosed with a psychotic disorder over a follow-up period ranging from 1 year for those recruited later in the course of the study to 2 years for those examined earlier.

In the at-risk group, 35 participants were receiving prescription antidepressants, 24 were not receiving any medications, and one had previously received chlorpromazine at a low dosage but was not receiving any medications at the time of imaging. Aside from the participant who had previously received chlorpromazine, all at-risk participants were antipsychotic naive.

Healthy comparison subjects were recruited through public advertisements in print and online media. They had no history of psychiatric disorders and were matched for age with at-risk participants. One comparison subject was excluded because of excessive head motion, and one was excluded because of poor performance, leaving 38 healthy subjects for inclusion in the analysis.

Participants underwent a battery of neurocognitive tests assessing a range of functions, including working memory, attention, and vigilance. Additionally, at-risk participants were assessed using the Global Assessment of Functioning Scale (GAF), the Positive and Negative Syndrome Scale (PANSS [42]), the Brief Assessment of Cognition in Schizophrenia scale (43), and the Wechsler Abbreviated Scale of Intelligence (44). Because left-handedness is more common in schizophrenia patients, we did not attempt to balance handedness in the groups to avoid introducing bias; however, handedness was assessed using an inventory (45) for inclusion as a covariate in imaging interactions.

The study protocol was approved by the National Healthcare Group Domain Specific Review Board (Singapore). Written informed consent was obtained from participants above age 21 or from a parent or guardian for participants under 21 (with the participant’s assent) after they received a complete description of the study. All participants were reimbursed for their participation in the study.

**Experimental Design**

The working memory experiment (46) was one of four fMRI experimental paradigms administered in the functional neuroimaging battery. The other experiments (to be described in detail in separate reports) assessed associative learning and generalization (47), implicit processing of fearful and neutral male and female faces (48), and anticipation of or motivation to obtain a reward (49). The working memory experiment was always administered third.

The working memory experiment, which we refer to here as the working memory task, comprised three task conditions and one control condition. Briefly, the LTR condition evaluated maintenance of information, while the PLUS and PLUS2 conditions evaluated both maintenance and manipulation of information (Figure 1; see also the online data supplement). Participants were required to achieve an accuracy of at least 75% on both the LTR and control conditions. In the scanner, participants were presented with three runs of alternating blocks of conditions.

Behavioral performance was assessed using accuracy and response time. These measures were entered in separate four-condition-by-two-group mixed-effects analyses of variance testing for main effects of group and condition for each variable. Significant main effects and interactions were decomposed using t tests.

**Image Acquisition and Analysis**

Details of the image acquisition parameters, fMRI data preprocessing steps, and statistical analyses are presented in the online data supplement. The functional images were processed and analyzed using BrainVoyager QX, version 1.10.4 (Brain Innovation, Maastricht, the Netherlands), and custom routines were written in MATLAB (MathWorks, Natick, Mass.). The main effect of group and condition-by-group interactions was assessed using a three-condition-by-two-group mixed-effects analysis of covariance (ANCOVA). These analyses used age, sex, education, handedness, ethnicity, and accuracy as covariates. The resulting F-maps were subject to a corrected
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At-Risk Group (N=60)</th>
<th>Healthy Comparison Group (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
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<sup>a</sup> For continuous and discrete variables, t tests and chi-square tests, respectively, were used to assess group differences.

<sup>b</sup> Twenty-six at-risk participants were receiving selective serotonin reuptake inhibitors, six were receiving tricyclic or tetracyclic antidepressants, and three were receiving a combination of both types of antidepressants.

<sup>c</sup> One at-risk participant was previously treated with chlorpromazine at a low dosage but discontinued prior to entering the study.

<sup>d</sup> Of the six at-risk participants who were later diagnosed with psychosis, four met criteria for subgroup 2, and two met criteria for subgroup 1 based on the Comprehensive Assessment of At-Risk Mental States.

<sup>e</sup> Significant difference between groups.

<sup>f</sup> Data were not available for one at-risk participant and 10 healthy comparison subjects.

<sup>g</sup> Data were not available for one at-risk participant.

<sup>h</sup> The total score is the sum of the severity and frequency scores for the components of unusual thought content, nonbizarre ideas, perceptual abnormalities, and disorganized speech.
FIGURE 1. Examples of Stimuli Used in the Task and Presentation Timings Among Persons At-Risk for Psychosis and Healthy Comparison Subjects

In the LTR condition, participants were presented with four target letters, maintained them in memory for 3 seconds, and then indicated whether any of the targets matched a probe letter. In the PLUS condition, participants were presented with two target letters, shifted each one forward alphabetically by one position, maintained the new targets in memory for 3 seconds, and then indicated whether either of the new targets matched the probe letter. The PLUS2 condition was identical to the PLUS condition except that participants had to shift each target letter forward by two positions. The control condition was designed to match the perceptual and motor elements of the actual task conditions. Four identical letters were presented, followed by a lowercase probe letter. The proportion of matched probes was 50% in all conditions.

cluster significance threshold of p<0.05 (initial uncorrected voxel-level threshold, p<0.001).

The manipulation aspect of working memory was of particular interest, since it involves acting on the contents of short-term memory. We identified activation associated with the manipulation component to investigate group differences in activation within the regions examined. From the conjunction map of each maintenance plus manipulation condition against the maintenance-only condition (PLUS>LTR and PLUS2>LTR), six fronto-parietal regions known to be involved in working memory processes (46, 50) were selected as regions of interest to be considered for between-group analyses. A three-condition-by-group mixed-effects ANCOVA was performed for the parameter estimates at each region of interest. A statistical threshold of p<0.008 (corrected for multiple comparisons for six regions of interest) was applied in this second-level analysis to identify significant condition-by-group interactions.

To evaluate the possible modulatory effects of antidepressant medication on brain signal (51–53), we repeated the above analysis with the at-risk group divided into medicated and nonmedicated subgroups.

Finally, in the at-risk group, we explored the correlation between brain activation and clinical symptom severity (using the GAF scores, the subscale and total scores of the PANSS, and the combined intensity and frequency scores of the Comprehensive Assessment of At-Risk Mental States), as well as measures of cognition (using the symbol coding and digit sequencing scores of the Brief Assessment of Cognition in Schizophrenia and the vocabulary score of the Wechsler Abbreviated Scale of Intelligence). These analyses were conducted for brain regions showing group differences in overall task-related activation and regions involved in manipulation of working memory contents. To ensure that only areas activated during the working memory task entered these analyses, brain areas were masked using the functional activation masks derived from each group for the corresponding condition or contrast.

Results

Behavioral Data

There were no significant differences between the 60 at-risk participants and 38 comparison subjects in age, handedness, sex, or ethnicity (Table 1). At-risk participants had less education on average than comparison subjects. However, there were no significant differences in vocabulary scores between the two groups.

There was a main effect of condition on both accuracy (F=151.9, df=3, 288, p<0.001) and response time (F=459.0, df=3, 288, p<0.001) but no effect of group on either measure of behavioral performance. Increasing difficulty elicited fewer correct responses and longer response times in both groups, but there were no significant group differences. The condition-by-group interaction was not significant for either accuracy or response time.

When the analysis was repeated to take into account use of antidepressant medication, the main effect of condition remained significant (accuracy: F=153.3, df=3, 285, p<0.001; response time: F=455.6, df=3, 285, p<0.001). There was no effect of group, nor were there any condition-by-group interactions (see Table S2 in the online data supplement).

Imaging Data

Engagement of verbal working memory across the different task conditions elicited a common network of left and right fronto-parietal regions in both the at-risk and comparison groups. As expected, activation in these regions increased in magnitude and spatial extent with increasing task difficulty (Figure 2).

Activation in the left anterior insula and posterior cingulate cortex showed a significant main effect of group (Figure 3; see also Table S1 in the online data supplement). The at-risk group exhibited reduced anterior insula activation and increased posterior cingulate cortex deactivation relative to the comparison group in each of the three experimental conditions. The effects remained significant when both medicated and nonmedicated at-risk participants were accounted for (see Figure S2 and Table S2 in the data supplement).

Condition-by-group interactions were identified from a 3×2 ANCOVA. Regions showing significant interaction effects included the right inferior frontal gyrus, right
FIGURE 2. Activation Maps of Significant Task-Related Activations Among Persons At Risk for Psychosis and Healthy Comparison Subjects

At-Risk Group (N=60)

Comparison Group (N=38)

PLUS2 condition

PLUS condition

LTR condition

PLUS2-LTR contrast

PLUS-LTR contrast

a The rows depict activation maps showing regions where MR signal change was significantly different from the control condition in the at-risk and healthy comparison groups for each of the three task conditions and the two manipulation contrasts. All maps were thresholded at p<0.0001 (Bonferroni corrected).
Frontal eye field, right insula, precuneus, left precentral gyrus, posterior cingulate cortex, medial prefrontal cortex, left middle frontal gyrus, and left anterior middle frontal gyrus (see Table S1 in the data supplement). The posterior cingulate cortex, medial prefrontal cortex, left middle frontal gyrus, and left anterior middle frontal gyrus revealed task-related deactivation, while all other regions revealed task-related activation. In the regions where task-related activation was observed, the at-risk group exhibited a greater increase in activation during the manipulation conditions than the comparison group. In the regions where task-related deactivation was observed, the at-risk group exhibited relatively more pronounced deactivation during the manipulation conditions than the comparison group.

Activation associated with manipulation was assessed using a conjunction of the manipulation-related contrasts (PLUS-LTR and PLUS2-LTR). Both the PLUS and PLUS2 conditions elicited greater fronto-parietal activation than the LTR condition in both the at-risk and comparison groups (Figure 2). From the maps showing manipulation-related activity, we analyzed six regions of

\[ \text{Left Insula} \] x=–24, y=20, z=13

\[ \text{Posterior Cingulate} \] x=–3, y=–62, z=31

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\[ a \] The images depict the left insula and posterior cingulate, and the bar graphs show the MR signal change across task condition and group in these regions.
interest that were centered on the locus of peak signals in the frontal and parietal lobes (see Table S1 in the data supplement).

The only region of interest that showed significant condition-by-group interaction was the right posterior dorsolateral prefrontal cortex (F=5.94, df=2, 192, p=0.004) (Figure 4). The at-risk group exhibited greater increase in manipulation-related activity than the comparison group. Both medicated and nonmedicated at-risk participants exhibited greater MR manipulation-related activity than comparison subjects, although the between-group differences were less pronounced (F=3.20, df=4, 190, p=0.02) (see Figure S2 and Table S3 in the data supplement).

**Association Between Brain Activation and Symptom Severity**

There was a significant correlation between manipulation-related activation and PANSS total scores (r=0.40, df=58, p=0.001) in the right dorsolateral prefrontal cortex (Figure 4). Correlations with PANSS positive, negative, and general psychopathology scores in the right dorsolateral prefrontal cortex were positive but nonsignificant. None of the other symptom scales or measures of cognition were correlated with MR signal in contrasts of interest.

**Discussion**

This study represents one of the largest functional imaging studies comparing persons at high risk for developing psychosis with healthy comparison subjects. We observed altered patterns of activation in the at-risk group as they maintained and manipulated letters in working memory. These group differences remained significant after accounting for differences in education and antidepressant use (see the online data supplement).

At-risk participants exhibited reduced activation in the left anterior insula compared with comparison subjects in all task conditions. When manipulating letters, the at-risk group displayed more pronounced task-related deactivation of the default-mode network than the comparison group. A region-of-interest analysis of MR signal in regions known to be involved in working memory found greater manipulation-related activation in the right dorsolateral prefrontal cortex. In the at-risk group, the magnitude of right dorsolateral prefrontal cortex signal during working memory manipulation correlated with PANSS symptom scores.

**Absence of Significant Behavioral Differences Between Groups**

The equivalence of behavior between the at-risk and comparison groups, despite differences in education, across all three conditions allowed us to attribute the altered patterns of activation to the at-risk mental state (23, 29, 31, 54), as opposed to poorer performance in at-risk participants. Additionally, the comparability of performance across medicated and nonmedicated participants reassures us that the imaging findings were unlikely to be a result of antidepressant therapy. The large size of our

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*The bar graph shows the MR signal change across task condition and group in the right dorsolateral prefrontal cortex region of interest. The scatterplot shows the correlation between the MR signal change associated with manipulation in the right dorsolateral prefrontal cortex and Positive and Negative Syndrome Scale (PANSS) total score in the at-risk group. There was a significant correlation between right dorsolateral prefrontal cortex activity and PANSS total score (r=0.34, df=58, p=0.001). The blue circles indicate at-risk participants who later converted to psychosis.*

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**FIGURE 4. Condition-By-Group Interaction and Relationship Between Brain Activation and Symptom Severity**

- Right dorsolateral prefrontal cortex (x=48, y=5, z=25)
- Correlation of right dorsolateral prefrontal cortex activity with PANSS total score in the at-risk group

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**Parameter Estimate**

- At-risk group (N=60)
- Comparison group (N=38)

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**PANSS Total Score**

- At-risk nonconverters (N=54)
- At-risk converters (N=6)
sample allowed us to perform subgroup analysis with reasonable power.

**Reduced Insula Activation in At-Risk Participants**

Reduced anterior insula activity was observed across all task conditions in the at-risk group and was our most robust finding. The anterior insula and anterior cingulate cortex are part of a salience network (55) that supports high-level executive processes. The insula has been proposed as the key region involved in detecting salient stimuli and facilitating switching between the task-positive central executive network and task-negative default-mode network (56). Decreased anterior insula activity in schizophrenia is thought to result in a reduced ability to detect and process salient stimuli and thus an inability to switch between relevant brain networks in order to access attention and working memory resources required for performing the task (57, 58), even under conditions of matched performance (59). This could explain why group differences in insula activation were observed even in the LTR condition, which imposes minimal cognitive load. This finding contrasts with those in the dorsolateral prefrontal cortex and posterior cingulate cortex, where group differences emerged only at higher cognitive loads.

**Greater Task-Related Deactivation in At-Risk Participants**

Task-related deactivation in the default-mode network, in particular the midline nodes, is associated with reallocation of processing resources that occurs when attention is shifted from introspectively oriented mental activity, such as when a participant is at rest, to externally focused goal-directed behavior (60–62).

There has been conflicting reports regarding the direction of altered task-related deactivation within the default-mode network in patients with schizophrenia or their first-degree relatives (63–65). For example, decreased task-related deactivation accompanied by increased resting-state connectivity within the default-mode network has been reported in patients and first-degree relatives (38). Reduced task-related deactivation corresponding with lowered cognitive performance occurs in other settings, such as in Alzheimer’s disease (66) and following sleep deprivation (46), and could be expected in the at-risk group. On the other hand, some patients with schizophrenia exhibit increased task-related deactivation within the default-mode network in association with changes in resting-state connectivity (39). In our at-risk group, increased task-related deactivation during task performance was observed in the default-mode network nodes, including the medial prefrontal cortex, posterior cingulate cortex, and left middle frontal gyrus. While this could reflect the need for greater effort in suppressing self-directed thought in at-risk persons but not in schizophrenia patients, further studies are necessary to clarify this issue.

**Elevated Prefrontal Cortex Activation During Manipulation in At-Risk Participants**

It has been suggested that persons with a schizophrenia spectrum disorder exhibit increases in prefrontal activation as a compensatory change because of deficits in other cortical regions (67). Greater activation in the right dorsolateral prefrontal cortex, a region implicated in executive processes within working memory, could be compensatory for altered recruitment of the anterior insula. Within the prefrontal cortex, the dorsolateral prefrontal cortex contributes relatively more to manipulation of short-term memory, while the ventrolateral prefrontal cortex contributes primarily to information maintenance (68–70). Previous neuroimaging studies suggest that executive functions in working memory, associated with parietal and dorsolateral prefrontal cortex function, may contribute more to working memory impairment in schizophrenia (6, 7, 71) than the impaired maintenance of information.

Most fMRI studies of working memory involving patients with an established diagnosis of schizophrenia and some studies of first-episode schizophrenia have reported reduced performance accuracy. However, the associated functional imaging findings have been mixed. Some studies have reported reduced activation in prefrontal and parietal regions in patients compared with comparison subjects (5, 8, 29), while other studies have reported increased activation in these regions (4, 35, 72).

In a study of patients with schizophrenia, there was a greater increase in activity with elevated cognitive load in patients with good task performance compared with those with poor performance (73). This suggests that in high-performing patients, reallocation of processing resources to prefrontal areas may allow behavioral performance to be maintained at a level comparable to that of comparison subjects. By contrast, in lower-performing patients, this capacity to adaptively recruit additional brain regions has been found to be exceeded and reflected in decreased prefrontal activation (30, 74, 75). This pattern of neuroimaging findings resembles adaptation to cognitive aging (76, 77), in which participants who perform slower exhibit greater activation in the dorsolateral prefrontal cortex. In the present study, our finding of hyperactivation in the right dorsolateral prefrontal cortex in the at-risk group, together with preserved behavioral performance, suggests an adaptive response to the at-risk mental state. While the between-group similarities in performance may reflect a reduced psychometric sensitivity of the task in this population, it is noteworthy that neuroimaging contrasts were sensitive to the at-risk condition when performance measures were not.

Alternatively, the positive correlation between PANSS symptom severity and manipulation-related activation in the right dorsolateral prefrontal cortex may simply denote greater difficulty in engaging task-driven cognition in at-risk participants. Symptomatic individuals may have to
cope with intrusive thoughts or auditory hallucinations. This explanation is supported by studies of patients as well as first-degree relatives that found increased prefrontal cortex activity to be correlated with higher symptom severity (24, 78).

Limitations

While this study suggests altered fMRI activation patterns in at-risk persons without their manifesting overt working memory impairment, these remain baseline results. Six of our 60 at-risk participants presented with a first episode of psychosis after at least 1 year (see Figure S3 in the online data supplement). This low conversion rate is one of the inherent difficulties in prodromal psychosis research. At-risk individuals are heterogeneous, presenting with a range of symptoms, including anxiety and depression (58% of at-risk participants in our sample were receiving antidepressants), and often have functional deficits. Therefore, the group differences could be related to general psychopathology rather than specifically psychosis risk; continued follow-up to identify individuals who convert will be required to relate neuroimaging findings to specific risk of psychosis.

The healthy comparison subjects are likely higher functioning than the at-risk participants based on education level. However, neither task performance nor brain activity was correlated with education, and when education was included as a covariate in the analyses, the results remained significant. Furthermore, the vocabulary scores of the Wechsler Abbreviated Scale of Intelligence, often used as a proxy for IQ, were not significantly different between the two groups.

Conclusions

We found that while not apparent at the behavioral level, individuals classified as being at risk for psychosis manifested functional neuroimaging changes consistent with altered processing of salient stimuli. These may affect the manipulation of working memory contents in a manner resulting in overactivation of the dorsolateral prefrontal cortex, as well as abnormal default-mode network function. Of functional significance, dorsolateral prefrontal cortex signal alteration was associated with symptom severity. Together, these findings highlight the potential utility of detecting early brain changes to facilitate early treatment for at-risk persons.

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SUPPLEMENTAL DATA

Description of the Comprehensive Assessment of At-Risk Mental States (CAARMS)

The CAARMS is a semi-structured interview designed to identify individuals at-risk for psychotic disorders. In this study, we obtained information from the participant and from available medical records. Four sub-scales of the CAARMS are used to identify an at-risk participant. They are unusual thought content, perceptual abnormalities, non-bizarre ideas and disorganized speech. All symptoms must have occurred in the past year, and are rated on a scale of 0 to 6 on both intensity and frequency of occurrence. Functioning in the past year is measured on the Social and Occupational Functioning Assessment Scale (SOFAS) on a scale of 0 to 100.

Participants can be categorized as at-risk if they fulfill any one of the 3 criteria groups; (1) Vulnerable group: family history of psychosis in a first degree relative, or presence of schizotypal disorder in assessed participant, (2) presence of attenuated psychotic symptoms in the past year, (3) brief limited intermittent psychotic symptoms.

Details of working memory task

In the LTR condition, four different uppercase letters were presented for 0.5 seconds, followed by a delay of 3.0 seconds during which a fixation star was displayed. This was followed by the presentation of a lowercase probe letter for 1.5 seconds and another fixation star for an additional 0.5 seconds. Participants were instructed to remember the 4 uppercase letters, match them to the lowercase probe letter, and then signal a match or a non-match by pressing one of two response buttons. Half the probes matched the target letters.
In the PLUS condition, two different uppercase letters were presented, and participants were instructed to shift each letter forward alphabetically by 1 position and to remember the results. For example, if “B” and “J” were presented, participants had to remember “c” and “k” to be matched with the probe. Half the trials were matches. Stimulus presentation sequence and timing were identical to that used in the LTR condition, except that a plus sign replaced the fixation star in the delay periods to denote the PLUS condition. The PLUS2 condition was identical to the PLUS condition except that participants had to shift each letter forward alphabetically by 2 positions, and 2 plus signs were presented during the delay period to indicate the condition.

The control condition was designed to match the perceptual and motor elements of the actual task conditions. Four identical uppercase letters were presented for 0.5 seconds, followed by a delay of 0.3 seconds and then a lowercase probe that matched the target in half the trials. This was followed by a 3.2 second delay during which a fixation star was presented. Participants signaled a match or non-match by using one of two response buttons.

Prior to imaging, participants performed a practice session outside the scanner to familiarize themselves with the task and to ensure that instructions were understood. Each condition was presented in 22-second blocks. Each block consisted of four trials (5.5 seconds per trial). Each experimental run consisted of 10 control blocks alternating with 9 task blocks, with 3 blocks of each condition presented per run in random order. Participants were required to achieve an accuracy of at least 75% on both the LTR and Control conditions.

In the scanner, participants were presented with 3 runs of alternating blocks, each lasting 7 minutes and 10 seconds. Stimuli were projected onto a screen and
viewed by participants using a rear-view mirror. Participants responded by pressing buttons on a MR-compatible response box held in their right hand.

Details of fMRI data acquisition and pre-processing

Images were acquired on a 3T Siemens Tim Trio system (Siemens, Erlangen, Germany). T2*-weighted images were acquired using a gradient echo-planar imaging (EPI) sequence (TR = 2000ms, TE = 30ms, FA = 90°, FOV = 192 × 192 mm, matrix size = 64 × 64 pixels). Twenty-eight oblique axial slices (4 mm thick with a 0.4 mm inter-slice gap) parallel to the anterior commissure-posterior commissure line were acquired. A high-resolution coplanar T1-weighted anatomical image was also acquired for image registration. An additional high-resolution anatomical reference image was acquired using a T1-weighted 3D multi-echo magnetization-prepared rapid-acquisition gradient echo sequence (TR = 2530 ms, TI = 1200 ms, FA = 7°, BW = 651 Hz/pixel, FOV = 256 × 256 mm, matrix size = 256 × 256 mm; resulting voxel dimensions = 1.0 × 1.0 × 1.0 mm) for the purpose of image display in Talairach space.

Intra-run motion correction was performed in-scanner and inter-run motion correction was performed using Brain Voyager QX version 1.10.4 (Brain Innovation), with each run realigned using rigid-body transformation to the first image of the functional run that was acquired closest in time to the coplanar T1-weighted image. Inter-slice timing differences attributable to slice acquisition order were adjusted using trilinear and sinc interpolation. Gaussian filtering was applied in the spatial domain by using a smoothing kernel of 8-mm full-width at half-maximum for group-level activation maps. A high-pass temporal filter (3 cycles) was also applied. The coplanar axial T1-weighted images were used to register the functional data set to
the high-resolution 3D image and the resulting aligned images were transformed into Talairach space.

**Details of statistical analyses**

Group-level analyses were conducted by using a random-effects model with subject as the random effect and task level as the fixed effect. Statistical t-maps were computed from a general linear model with a single predictor for each task condition (LTR, PLUS and PLUS2) by using separate subject predictors. Each predictor was represented by a boxcar function and convolved with a canonical hemodynamic response function. Three functional runs were included per participant. To account for baseline drifts across runs, z-transformation of the signal time-course for each run was performed. Task-induced activation against baseline was assessed using a voxel-level Bonferroni corrected threshold of p<0.0001.

A 3-condition by 2-group mixed-effects ANCOVA, with age, gender, education, handedness, ethnicity, and accuracy as covariates was computed to assess the main effect of group and condition-by-group interactions. A voxel-level threshold of p<0.001 (uncorrected) was applied to the resulting F-maps. To control for Type I errors, voxels surpassing the initial threshold underwent an iterative cluster thresholding procedure that considered the spatial smoothness of the data (1) to compute a spatial map based on a corrected cluster threshold (p<0.05). The significant clusters were masked using a binary mask of all task-related activations and deactivations thresholded at p<0.0001 (Bonferroni corrected).

We identified activation associated with the manipulation component by first contrasting each maintenance plus manipulation condition (PLUS and PLUS2) against the maintenance only condition (LTR) across both groups. The PLUS vs. LTR and PLUS2 vs. LTR contrasts were combined in a conjunction analysis.
(thresholded at p<0.0001, Bonferroni corrected) for increased power. From the resulting conjunction map, 6 fronto-parietal regions known to be involved in working memory processes were selected as regions of interest (ROIs) to be considered for between-group analyses. ROIs consisted of voxels enclosed by a bounding cube of edge length 10mm surrounding an activation peak of interest.

For brain regions showing group differences in overall task-related activation, correlations between brain activity and clinical symptom severity or measures of cognition were calculated by correlating the average beta coefficient of the general linear model (GLM) for each task condition within the region of interest with the clinical or cognitive measures. Correlations between brain activity and clinical or cognitive measures in brain regions showing group differences in the manipulation of working memory contents were calculated by correlating the mean difference in beta coefficients of each manipulation condition and the maintenance only condition (PLUS–LTR and PLUS2–LTR) within the region of interest with the clinical or cognitive measures.

**Effect of education on imaging results**

Although the at-risk and control groups were not matched on education, there were no regions where the effect of the education covariate was significant at p<0.01; cluster level threshold p<0.05.
Subgroup analysis: comparison between the Vulnerable-Only participants (Subgroup 1, n=10) and those with psychotic-spectrum symptoms (Subgroups 2 & 3, n=42)

As it is important to understand subgroups within the at-risk population and to determine if there are any differences in brain activity between the subgroups, we compared activation in at-risk participants in the Vulnerable-Only participants (Subgroup 1) with those that show psychotic-spectrum symptoms (Subgroups 2 & 3).

There were no significant effects of group in either the left insula (Talairach coordinates: -24, 20, 13; \(F_{(1,50)}=0.14\); n.s.) or the posterior cingulate cortex (Talairach coordinates: -3, -62, 31; \(F_{(1,50)}=2.01\); p=n.s.). The parameter estimates across these regions are shown in Figure SF2A. There were no regions significant for condition-by-subgroup interactions.

Among the manipulation-related regions identified for the region of interest (ROI) analysis, the right dorsolateral prefrontal cortex ROI showed no significant task-by-subgroup interactions (\(F_{(2,100)}=0.47\); n.s.; Figure SF2B).

There were no significant differences in brain activity between the two subgroups of at-risk participants. The graphs show trends that could be due to higher variability of parameter estimates in the smaller subgroup (Group 1, n=10).
Figure SF1. Plots comparing MR signal change for the Vulnerable Subgroup (n=10), Psychotic-Spectrum Symptoms Subgroup (n=42) and the Control group (n=38) in the A) left insula, B) posterior cingulate cortex and C) right dorsolateral prefrontal cortex ROI. Plots show the standard error of mean to illustrate higher variability of parameter estimates in the Vulnerable Subgroup. The MR signal change for the control group in each region is shown for comparison. D) The correlation between MR signal change associated with manipulation in the right dorsolateral PFC and PANSS total symptom scores in the at-risk group (r=0.40, p=0.001).
TABLE ST1. Location of activation peaks showing the main effect of group and condition-by-group interactions from whole-brain 3-condition by 2-group ANCOVAs and location of peaks of manipulation-related regions of interest (ROIs) derived from the conjunction of manipulation contrasts.

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>Analysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANOVA: Main effect of group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior insula</td>
<td>-24 20 13</td>
<td>ANCOVA</td>
<td>17.6</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>-3 -62 31</td>
<td>(F)</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>ANOVA: Condition-by-group interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>-21 23 49</td>
<td>ANCOVA</td>
<td>14.8</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>-12 57 7</td>
<td>(F)</td>
<td>11.0</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>-9 -49 22</td>
<td></td>
<td>9.7</td>
</tr>
<tr>
<td>Right posterior insula</td>
<td>30 11 7</td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>48 -4 22</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>Left anterior middle frontal gyrus</td>
<td>-39 35 -5</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>Right frontal eye field 1</td>
<td>33 -4 49</td>
<td></td>
<td>9.3</td>
</tr>
<tr>
<td>Left precentral gyrus</td>
<td>-54 2 10</td>
<td></td>
<td>9.2</td>
</tr>
<tr>
<td>Right frontal eye field 2</td>
<td>33 -4 49</td>
<td></td>
<td>8.7</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-3 -61 31</td>
<td></td>
<td>8.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manipulation-related ROIs</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Analysis (t)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left dorsolateral prefrontal cortex (anterior)</td>
<td>-42</td>
<td>20</td>
<td>28</td>
<td>18.81</td>
</tr>
<tr>
<td>Left inferior parietal lobule</td>
<td>-36</td>
<td>37</td>
<td>17.56</td>
<td></td>
</tr>
<tr>
<td>Left dorsolateral prefrontal cortex (posterior)</td>
<td>-45</td>
<td>34</td>
<td>16.72</td>
<td></td>
</tr>
<tr>
<td>Right inferior parietal lobule</td>
<td>33</td>
<td>37</td>
<td>13.68</td>
<td></td>
</tr>
<tr>
<td>Right dorsolateral prefrontal cortex (posterior)</td>
<td>48</td>
<td>25</td>
<td>12.93</td>
<td></td>
</tr>
<tr>
<td>Right dorsolateral prefrontal cortex (anterior)</td>
<td>45</td>
<td>34</td>
<td>11.75</td>
<td></td>
</tr>
</tbody>
</table>

*Regional peak activation representing BOLD signal change that survived a threshold of p<0.0001, Bonferroni corrected.
Details of analysis and results with at-risk participants grouped according to antidepressant use

Table ST2. Behavioral performance of individuals with At-Risk Mental State who are medicated, ARMS non-medicated and Control participants

<table>
<thead>
<tr>
<th>Behavioral Performance</th>
<th>At-risk Group (medicated) (n = 35)</th>
<th>At-risk Group (non-medicated) (n = 25)</th>
<th>Control Group (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTR condition</td>
<td>90.1</td>
<td>8.8</td>
<td>92.9</td>
</tr>
<tr>
<td>PLUS condition</td>
<td>85.7</td>
<td>11.7</td>
<td>82.8</td>
</tr>
<tr>
<td>PLUS2 condition</td>
<td>78.2</td>
<td>15.2</td>
<td>78.4</td>
</tr>
<tr>
<td>Control condition</td>
<td>98.2</td>
<td>2.4</td>
<td>98.5</td>
</tr>
<tr>
<td>Reaction Time (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTR condition</td>
<td>809.4</td>
<td>104.1</td>
<td>813.2</td>
</tr>
<tr>
<td>PLUS condition</td>
<td>864.2</td>
<td>148.9</td>
<td>885.7</td>
</tr>
<tr>
<td>PLUS2 condition</td>
<td>967.1</td>
<td>187.4</td>
<td>974.8</td>
</tr>
<tr>
<td>Control condition</td>
<td>612.0</td>
<td>90.5</td>
<td>608.6</td>
</tr>
</tbody>
</table>

Table ST3. Location of activation peaks showing a main effect of group and condition-by-group interactions from whole-brain ANCOVAs, taking into account medicated and non-medicated at-risk groups

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td><strong>ANOVA: Main effect of group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior insula</td>
<td>-24</td>
<td>20</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>-3</td>
<td>-61</td>
</tr>
<tr>
<td><strong>ANOVA: Condition-by-group interaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>-21</td>
<td>23</td>
</tr>
<tr>
<td>Precuneus</td>
<td>3</td>
<td>-43</td>
</tr>
<tr>
<td>Left frontal eye field 2</td>
<td>-36</td>
<td>-7</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>-12</td>
<td>59</td>
</tr>
<tr>
<td>Right frontal eye field</td>
<td>30</td>
<td>-13</td>
</tr>
<tr>
<td>Left frontal eye field 1</td>
<td>-21</td>
<td>-16</td>
</tr>
</tbody>
</table>
**Figure SF2.** Plots comparing MR signal change for medicated vs non-medicated at-risk subgroups in regions where there was a main effect of group in the A) left insula and B) posterior cingulate cortex. C) Plot comparing MR signal change for medicated vs non-medicated at-risk subgroups in the right dorsolateral PFC region of interest, which showed a condition-by-group interaction.
Comparison between participants who converted to psychosis (n=6) and those who did not convert to psychosis (n=54)

We compared participants who converted to psychosis (n=6) and those who did not convert (n=54) over a 2-year period for earliest recruits to a 1-year period for later recruits.

There were no significant effects of group in either the left insula (Talairach coordinates: -24, 20, 13; F(1,58)=0.01; n.s.) or the posterior cingulate cortex (Talairach coordinates: -3, -62, 31; F(1,58)=0.39; n.s.). The parameter estimates across these regions are shown in Figure SF3A. There were no regions significant for condition-by-group interactions.

Among the manipulation-related regions identified for the region of interest (ROI) analysis, the right dorsolateral prefrontal cortex ROI showed no significant task-by-group interactions (F(2,116)=0.29; n.s.; Figure SF3B).

There were no significant differences in brain activity between the converted and non-converted at-risk participants.
**Figure SF3.** Plots comparing MR signal change for at-risk participants who converted to psychosis (n=6), those who did not convert to psychosis (n=54) over a minimum of 1-year follow-up period and the Control group (n=38) in the A) left insula, B) posterior cingulate cortex and C) right dorsolateral prefrontal cortex ROI. Plots show the standard error of mean to illustrate higher variability of parameter estimates in the group that converted to psychosis. The MR signal change for the control group in each region is shown for comparison.
References