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Altered Brain Activation During Memory Retrieval Precedes and Predicts Conversion to Psychosis in Individuals at Clinical High Risk

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Memory deficits are a hallmark of psychotic disorders such as schizophrenia. However, whether the neural dysfunction underlying these deficits is present before the onset of illness and potentially predicts conversion to psychosis is unclear. In this study, we investigated brain functional alterations during memory processing in a sample of 155 individuals at clinical high risk (including 18 subjects who later converted to full psychosis) and 108 healthy controls drawn from the second phase of the North American Prodrome Longitudinal Study (NAPLS-2). All participants underwent functional magnetic resonance imaging with a paired-associate memory paradigm at the point of recruitment and were clinically followed up for approximately 2 years. We found that at baseline, subjects at high risk showed significantly higher activation during memory retrieval in the prefrontal, parietal, and bilateral temporal cortices ($P_{\text{FWE}} < .035$). This effect was more pronounced in converters than nonconverters and was particularly manifested in *unmedicated* subjects ($P < .001$). The hyperactivation was significantly correlated with retrieval reaction time during scan in converters ($P = .009$) but not in nonconverters and controls, suggesting an exaggerated retrieval effort. These findings suggest that hyperactivation during memory retrieval may mark processes associated with conversion to psychosis, and such measures have potential as biomarkers for psychosis prediction.

Key words: fMRI/associative memory/memory retrieval/psychosis/clinical high risk

Introduction

Memory impairments are among the most robust correlates of schizophrenia and related psychotic disorders.¹⁻³ Prior work has shown that such deficits are present before the occurrence of clinical symptoms⁴⁻⁶ and are significantly more severe in prodromal subjects who later convert to full psychosis than those who do not.^{7,8} Nevertheless, whether brain physiological measures during memory processing are predictive of future psychotic disorders in individuals at risk remains to be determined.

Compared to memory for single items, episodic memory processing for associated items seems to be particularly impaired in patients with schizophrenia.² Neuroimaging studies have demonstrated that the neural substrates of associative memory involve multiple regions including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), posterior parietal cortex, and medial temporal cortex.⁹⁻¹² Dysfunction in these regions has been widely reported in patients with psychotic disorders, in particular schizophrenia.^{3,6,13-20} Such dysfunction involves altered prefrontal, parietal, and temporal cortical reactivity^{3,14-20} and aberrant functional connectivity in the prefrontal and temporal cortex,^{6,13} during both memory encoding and memory retrieval. In addition, evidence has shown that these functional alterations may further lead to the reorganization of brain network architecture in patients during memory

and cognition, in particular deficits in measures of network efficiency and network segregation.^{21,22} Notably, it has been demonstrated that neural dysfunction during memory processing cannot be fully explained by the severity of clinical symptoms¹⁷ nor medication status,²³ and can also be detected in unaffected first-degree relatives of patients with schizophrenia,^{18,24–27} suggesting that it occurs before the onset of illness. Nevertheless, it remains unclear whether physiological alterations during memory encoding or retrieval are present in individuals at clinical high risk (CHR) and whether such alterations predict conversion to psychosis.

Here, we used functional magnetic resonance imaging (fMRI) during a paired-associate learning and memory task to investigate potential brain activation and network alterations predictive of psychosis in a sample of 155 CHR subjects (including 18 cases who converted to psychosis) and 108 healthy controls (HCs) drawn from the second phase of the North American Prodrome Longitudinal Study (NAPLS-2).²⁸ Specifically, we tested whether subjects at CHR show abnormal neural response during the encoding and/or retrieval phases of the memory task, and whether such baseline abnormalities can potentially predict future psychosis. Moreover, because we have previously reported resting-state network efficiency and network diversity as potential biomarkers for psychosis development,²⁹ we further used a graph-based analysis to examine whether subjects at CHR deviate from HCs on these metrics during the memory task. We hypothesized that similar to patients with psychosis, subjects at CHR may show dysfunction in regions that are pertinent to memory processing during the associative memory task, in particular prefrontal, parietal, and temporal regions, and such changes may particularly be present in those who eventually convert to full psychosis.

Methods and Materials

Subjects

Subjects in this study were drawn from the NAPLS-2 project,²⁸ which included 8 study sites across the United States and Canada. Because fMRI paradigms were introduced half way through the NAPLS-2 project, the present report consisted of 263 subjects with fMRI data available at the initial recruitment point after quality control (155 subjects at CHR, including 18 subjects who converted into psychosis during follow-up, and 108 HCs, see [supplementary material](#) for details). The general exclusion criteria included a prior history of neurological disorders, substance dependence in the last 6 months, and intelligence quotient <70 (assessed by the Wechsler Abbreviated Scale of Intelligence³⁰). The CHR subjects met the Structured Interview for Prodromal Syndromes (SIPS) criteria of prodromal syndromes³¹ at baseline after excluding individuals who had ever met *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders*,

Fourth Edition) criteria for a psychotic disorder.³² The converters met the criteria for an Axis-I psychotic disorder or with the presence of at least one fully psychotic symptom at follow-up. HCs were excluded if they met the criteria for a psychotic disorder or prodromal syndrome, or had a first-degree relative with mental illness. All participants provided written informed consent for the study. The protocol and consent forms were approved by the institutional review boards at each site. Sample details are provided in [supplementary material](#) and [table 1](#). *DSM-IV* diagnoses for all converters are given in [supplementary table S2](#).

All participants (including both CHR and HC) received the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* and the SIPS at baseline and at regular 6-month intervals up to approximately 24 months, and at the point of conversion to psychosis by trained clinicians. At each assessment point, prodromal symptom severity was quantified using the Scale of Prodromal Symptoms (SOPS).³¹

fMRI Paradigm

Subjects underwent fMRI scans while performing a paired-associate episodic memory task,³³ including one run for encoding and another run for retrieval. During encoding, participants were presented a series of semantically unrelated word pairs for objects from 12 different categories (eg, animal, transportation, food) and colored picture pairs depicting each of the presented words. Participants were asked to remember the presented word pair by forming an association between them (eg, for the “rabbit-pail” pair: “put the rabbit in the pail”), and to press a button once the association had been made. Each pair was displayed for 4 seconds followed by a jittered interstimulus interval between 0.5 and 6 seconds. A baseline condition was included in which participants were presented with a series of 1-digit number pairs and colored squared pairs and were asked to sum up the 2 numbers. The session included 32 encoding trials and 24 active baseline trials lasting for 8.3 minutes (250 whole-brain volumes).

The retrieval session ensued directly after the encoding session. During retrieval, a pair of words was presented on the screen on each trial and subjects were asked to indicate whether the given word pair had been presented together during the encoding session by marking their confidence level (sure correct, maybe correct, sure incorrect, maybe incorrect). The word pairs during retrieval were either old pairs (50% of trials) or reorganized new pairs using the words that had been shown during the encoding run (50% of trials). During a baseline condition, participants were instructed to press the button corresponding to a confidence level simultaneously displayed on the screen. The retrieval session consisted of 64 retrieval trials and 16 baseline trials lasting for a

Table 1. Demographic and Clinical Characteristics for the Baseline Sample in This Study

	Converters (<i>n</i> = 18)	Nonconverters (<i>n</i> = 137)	Controls (<i>n</i> = 108)	<i>P</i> Value
Demographic data				
Age (years)	17.22 ± 3.44	19.01 ± 4.19	20.30 ± 4.85	.01 (overall) 0.32 (CHR-C vs CHR-NC)
Sex (M/F)	10/8	81/56	58/50	.65
Education (years)	11.23 ± 2.59	11.58 ± 2.60	12.91 ± 3.48	<.001 (overall) .99 (CHR-C vs CHR-NC)
IQ	110.28 ± 12.37	105.43 ± 14.63	110.99 ± 14.29	.01 (overall) .54 (CHR-C vs CHR-NC)
Site (no. of subjects)	4/3/1/0/4/1/4/1	17/35/15/14/11/12/29/4	15/19/15/16/12/5/14/13	.08 (overall)
Clinical data				
SOPS-positive	12.22 ± 2.51	11.41 ± 3.83	1.25 ± 2.50	<.001 (overall) .96 (CHR-C vs CHR-NC)
SOPS-negative	9.83 ± 6.35	11.31 ± 5.93	1.46 ± 2.03	<.001 (overall) .65 (CHR-C vs CHR-NC)
SOPS-disorganization	7.72 ± 3.91	5.24 ± 3.23	0.67 ± 1.20	<.001 (overall) .001 (CHR-C vs CHR-NC)
SOPS-general	7.33 ± 3.76	8.76 ± 4.43	1.55 ± 2.25	<.001 (overall) .36 (CHR-C vs CHR-NC)
Antipsychotics (% medicated)	33	19	0	<.001 (overall) .16 (CHR-C vs CHR-NC)
Antipsychotics (chlorpromazine equivalent dosage)	107.08 ± 175.22	39.44 ± 108.25	0	<.001 (overall) .01 (CHR-C vs CHR-NC)
Cognitive data				
Hopkins verbal learning test - revised	24.17 ± 6.45	25.82 ± 4.88	28.15 ± 4.11	<.001 (overall) .49 (CHR-C vs CHR-NC)
Brief visuospatial memory test - revised	23.72 ± 7.49	25.49 ± 6.52	28.57 ± 4.68	<.001 (overall) .71 (CHR-C vs CHR-NC)
Task data				
Discrimination index (<i>d'</i>)	1.77 ± 0.93	2.07 ± 1.05	2.44 ± 0.96	.003 (overall) .72 (CHR-C vs CHR-NC)
Hit rate	0.77 ± 0.14	0.81 ± 0.12	0.84 ± 0.11	.02 (overall) .69 (CHR-C vs CHR-NC)
False alarm rate	0.20 ± 0.14	0.18 ± 0.18	0.13 ± 0.14	.03 (overall) .99 (CHR-C vs CHR-NC)
Retrieval reaction time (ms)	1993.41 ± 278.21	1957.39 ± 260.84	1968.58 ± 235.03	.83

Note: M, male; F, female; CHR-C, clinical high risk-converters; CHR-NC, clinical high risk-nonconverters; SOPS, Scale of Prodromal Symptoms; IQ, intelligence quotient.

total duration of 7.3 minutes (219 whole-brain volumes). A figure depicting the task is given in [supplementary figure S1](#).

Data Acquisition

See [supplementary methods](#) for details on data acquisition.

Behavioral Data Processing

Task performance was evaluated based on signal detection theory.³⁴ In particular, the discrimination index (*d'*) was used to assess the subjects' abilities to discriminate between old and reorganized new pairs. This was measured by the left-tail *z* score of the hit rate (Z_{Hit}) minus the *z* score of the false alarm rate (Z_{FA}). In particular, the "hit"

trials (true positive) were defined as those with a positive response (ie, confidence levels at “sure correct” and “maybe correct”) when old pairs were present, and the “false alarm” trials (false positive) were defined as those with a positive response when new pairs were present.

fMRI Data Preprocessing

fMRI data preprocessing followed that of previously published work^{35–37} using the standard procedures implemented in the Statistical Parametric Mapping software (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). In brief, all images were slice-time corrected, realigned for head motion, registered to the individual T1-weighted structural images, and spatially normalized to the Montreal Neurological Institute (MNI) template. Finally, the normalized images were spatially smoothed with an 8-mm full width at half-maximum of Gaussian kernel.

Activation Analysis

The preprocessed images were used for first-level analysis based on the general linear model, where task conditions, 24 head motion parameters (ie, the 6 rigid-body parameters generated from the realignment step, their first derivatives, and the squares of these 12 parameters^{38,39}) and frame-wise displacement^{39,40} were modeled as regressors. The images were then high-pass filtered at 0.008 Hz and individual contrast maps (task condition vs baseline condition) were computed. The computed contrast images were further used for a second-level linear regression analysis, where group was modeled as the regressor of interest, and sex, age, and site were included as nuisance regressors. Notably, a recent study has demonstrated that linear regression with site as regressors can efficaciously and reliably remove site-related effects in imaging data.⁴¹ To control for type I error, significance was determined using family-wise error (FWE) correction across all voxels in the brain⁴² ($N_{\text{voxels}} = 145\,436$).

Network Analysis

Network analysis followed previously published procedures.^{35–37} Here, we investigated 2 network measures that have been reported to be related to psychosis development in our previous work²⁹: network efficiency and node diversity. Node diversity was defined as the connectivity variance between a given node and all other nodes in the network, reflecting the heterogeneity of the connectivity pattern for that node.⁴³ Network efficiency quantified the inverse of shortest path lengths in the network, which can be derived at both global and nodal levels.⁴⁴ Details on network analysis are given in [supplementary material](#).

Linear regression models were used to examine differences in the computed network measures between groups, where group, sex, age, site, and mean frame-wise

displacement (ie, modeling head motion) were included as regressors. Network measures for each node were entered as dependent variables, and statistical significance was determined using FWE correction across all nodes in the brain network ($N_{\text{nodes}} = 270$).

Association Analysis

We further examined whether any observed alterations were related to task performance during scanning as well as clinical symptoms at baseline. For the observed activation differences, we extracted the first eigenvariate from 5-mm spheres around each of the peak coordinates in the group-level contrast map. These eigenvariables were further averaged across all spheres to generate a subject-specific activation metric. Pearson correlations were performed for each group between these subject-specific metrics and performance and symptom variables. Here, task performance was measured using the d' scores and the mean reaction time during the retrieval session. Clinical symptoms were evaluated by the summed scores of each domain in the SOPS (positive, negative, disorganization, and general).

Results

Task Performance

No significant group differences were shown in self-reported response rate during encoding between outcome groups ($P = .07$). There were significant differences in Z_{Hit} , Z_{FA} , and d' scores by outcome group ($P < .02$; [table 1](#)), with both converters and nonconverters showing lower d' scores compared with controls ($P_{\text{Bonferroni}} < .03$); however, converters and nonconverters did not differ from each other. In contrast, there were no significant group differences in retrieval response time ($P = .83$).

Activation Alterations at the Group Level

When controlling for multiple comparisons voxel-wise throughout the brain, there were no significant group differences in activation during encoding. However, during retrieval, a significant group effect on brain activation was observed in 5 brain regions ([figure 1A](#); see [supplementary table S1](#) for coordinates in the MNI space): left superior frontal gyrus (SFG) ($T_{252} = 4.75$, $P_{\text{FWE}} = .034$), left inferior frontal gyrus (IFG) ($T_{252} = 4.99$, $P_{\text{FWE}} = .013$), left inferior parietal lobule (IPL) ($T_{252} = 4.73$, $P_{\text{FWE}} = .035$), left superior temporal gyrus ($T_{252} = 5.71$, $P_{\text{FWE}} = .001$), and right middle temporal gyrus ($T_{252} = 4.89$, $P_{\text{FWE}} = .019$). In each region, subjects at CHR showed significantly higher activation compared with controls, with converters showing significantly higher activation than nonconverters ([figure 1B](#)). Secondary analyses showed that the detected effects were presented for both correct trials and incorrect trials, and for both old word pairs and new word pairs (see [supplementary results](#)), suggesting that hyperactivation

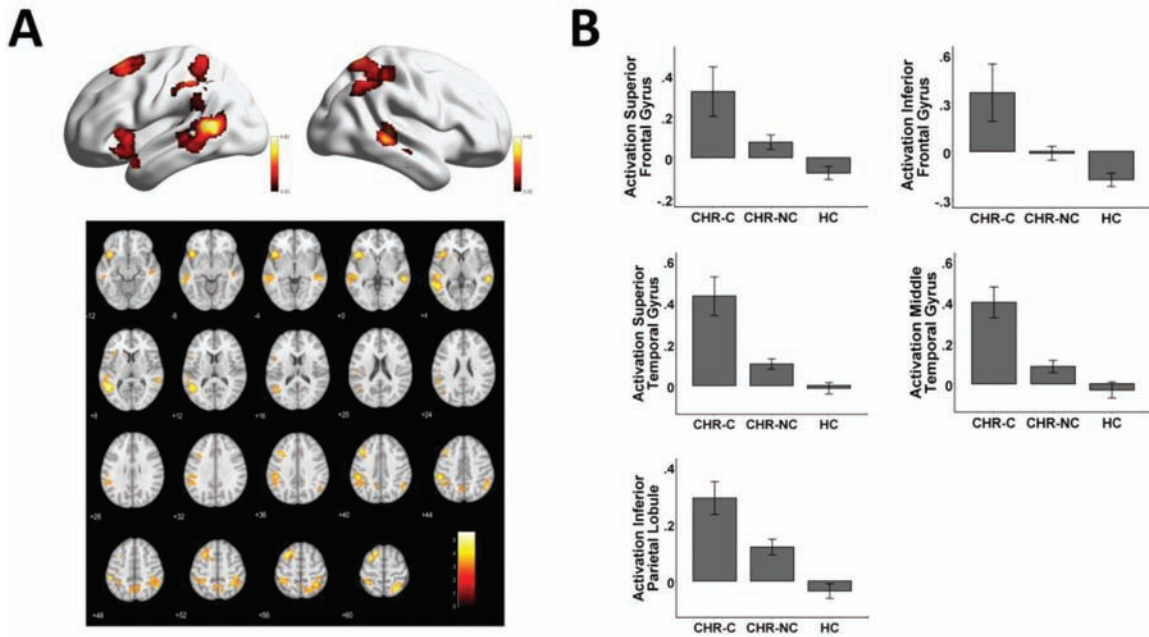


Fig. 1. Between-group activation differences during memory retrieval at baseline scan (panel A). Subjects at CHR showed significantly higher activation in the prefrontal, parietal and temporal cortices compared with controls, with hyperactivation more prominent in converters than nonconverters. For presentation purposes, the activation maps are thresholded at $P < .001$ with cluster size of more than 300 voxels. The mean first eigenvariates across all voxels in each region are plotted in panel B, with error bars indicating the standard error. CHR, clinical high risk; CHR-C, clinical high risk-converters; CHR-NC, clinical high risk-nonconverters; HC, healthy control.

during retrieval is a robust finding not driven by a single trial type in the experiment.

Network Alterations at the Group Level

The network analysis did not reveal any significant differences between groups in terms of network efficiency and network diversity at the global nor nodal levels ($P_{FWE} > .27$).

Associations With Antipsychotic Medications

To determine whether the observed activation findings during retrieval were affected by antipsychotic medications, we extracted mean activation metrics from these 5 regions and compared these metrics between converters and nonconverters separately for unmedicated and medicated participants. The detected activation differences were in fact more pronounced among *unmedicated* subjects than in medicated subjects (figure 2). Specifically, unmedicated converters had significantly higher activation in these regions than unmedicated nonconverters ($P < .001$), whereas no significant differences were found between medicated converters and medicated nonconverters ($P = .21$), suggesting that the pattern of hyperactivation during memory retrieval is not explained by antipsychotic medication.

Associations With Performance Measures and Symptom Severity

There were no significant correlations of activation metrics with d' scores nor with encoding response rate during

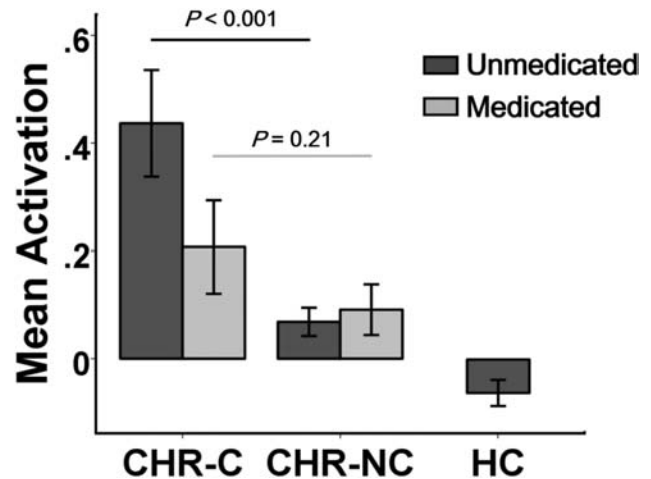


Fig. 2. Mean activation differences between groups during memory retrieval separated by medication status. Significant differences were shown between unmedicated converters and unmedicated nonconverters, but not between medicated converters and medicated nonconverters. The y-axis shows the mean first eigenvariates across all identified regions, with error bars indicating the standard error. CHR-C, clinical high risk-converters; CHR-NC, clinical high risk-nonconverters; HC, healthy control.

scan in any of the 3 groups separately ($P > .16$). However, significant positive correlations were found between activation metrics and retrieval reaction time in converters ($R = 0.61, P = .009$, figure 3), but not in nonconverters and controls. No significant associations were found

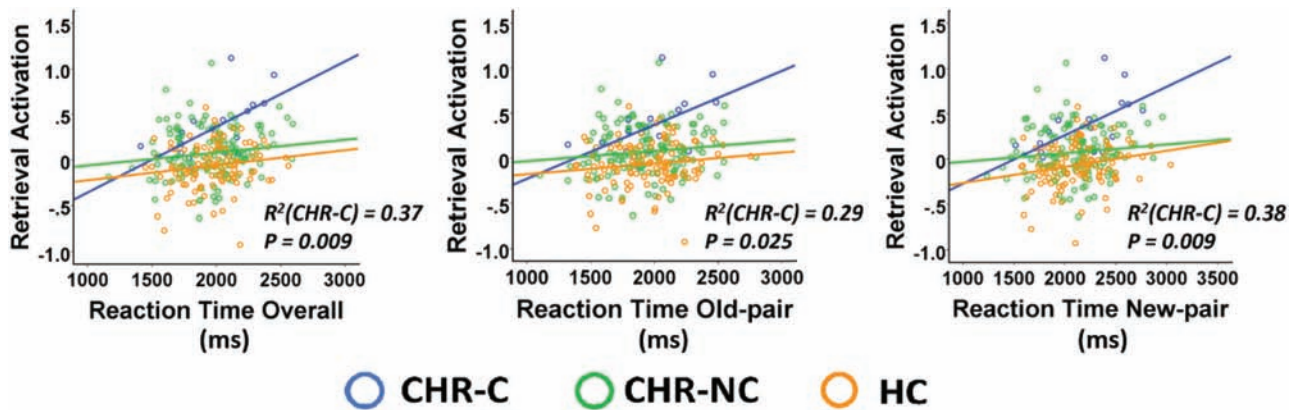


Fig. 3. Association of activation alterations with task performance. Mean activation measures were significantly correlated with task reaction time during memory retrieval in converters. The y-axis shows the mean first eigenvariates across all identified regions, CHR-C, clinical high risk-converters; CHR-NC, clinical high risk-nonconverters; HC, healthy control.

between the activation metrics and symptom severity in any of the groups.

Individual-Level Prediction Analysis

On the basis of these findings, we performed a secondary multivariate receiver operating characteristic (ROC) curve analysis for a logistic regression model to assess individual-level predictability of the activation measures for psychosis. Due to the lack of an independent test sample, we used independent anatomical masks to extract activation-based predictors to minimize potential circularity in the modeling. Here, 5 independent anatomical masks (ie, left SFG, left IFG, left IPL, left superior temporal gyrus, and right middle temporal gyrus) defined by the automated anatomical labeling (AAL) brain atlas⁴⁵ were selected for the analysis based on the group-level activation findings during retrieval. The first eigenvariates for each of the 5 masks were extracted from individuals' contrast maps and were included in the model as predictors. The ROC curves were plotted to illustrate the accuracy of these predictors in distinguishing converters from CHR and from both CHR and controls. The areas under curve (AUCs) were subsequently calculated as the index of accuracy of the prediction models. To test the significance of the derived AUCs, we randomized the sample by 10 000 permutations, where group labels were randomly reshuffled for each subject during each permutation. Empirical *P* values were determined as the proportion of the resampled AUCs in the permutation distribution that were larger than the AUC in the original sample.

The ROC curves using baseline retrieval-related activation measures to distinguish converters from nonconverters and controls are presented in figure 4. The model for predicting converters among the CHR subjects obtained an AUC of 0.768 (*P* = .009), and the model for predicting converters among both CHR subjects and controls had an AUC of 0.773 (*P* = .005).

Discussion

Using data from the NAPLS-2 consortium, we found evidence for memory-associated functional brain alterations in subjects at CHR for psychosis. In particular, CHR individuals showed increased activation during retrieval at baseline compared with controls, a pattern that was more pronounced in individuals who converted to psychosis and was independent of exposure to antipsychotic drugs and performance differences on the underlying memory task.

Five regions were associated with hyperactivation during retrieval in subjects at CHR and in particular among converters: SFG, IFG, IPL, and lateral temporal cortices (LTCs) in both hemispheres. Interestingly, despite inconsistent directions reported in the literature, which may relate to the heterogeneity of samples and tasks used, altered retrieval activation in all of these regions has been found in patients with schizophrenia^{3,15,19,46-48} and has further been summarized in several meta-analyses assessing episodic memory processing in schizophrenia.^{14,16} Here, our results extend prior findings to a sample of CHR subjects before the onset of psychotic disorders. These observations together suggest activation abnormalities in the prefrontal, parietal, and temporal cortices as a biological trait underlying memory retrieval deficits during both the prodromal phase and fully psychotic state. Notably, the observed differences could be robustly detected in subjects who did not receive any antipsychotic medication, indicating that these activation changes are not a secondary phenomenon of clinical treatment but rather reflect neural deficits related to psychosis risk. Although we did not observe a significant difference between converters and nonconverters with antipsychotic medication, which might suggest that antipsychotics have potential to attenuate the hyperactivation in these regions, great caution is warranted in interpreting this result given the small sample size of medicated CHR subjects.

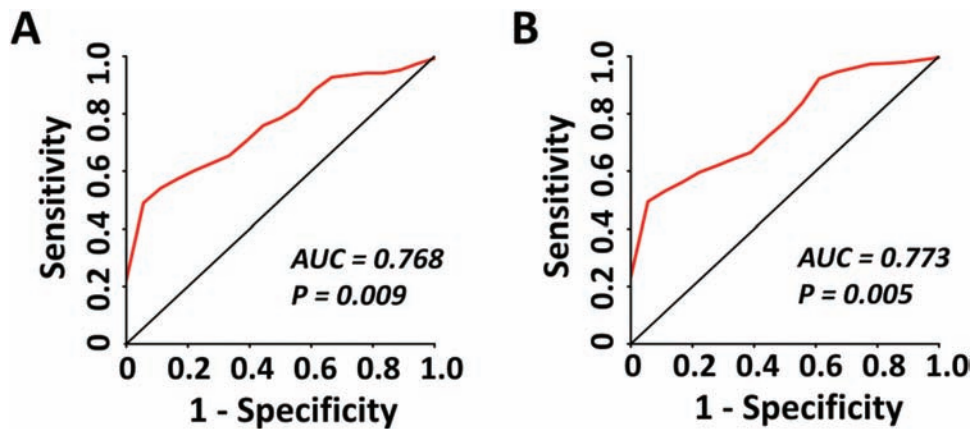


Fig. 4. The multivariate receiver operating characteristic curves for baseline activation measures showed an area under curve (AUC) of 0.768 for distinguishing converters from nonconverters among subjects at clinical high risk (panel A), and an AUC of 0.773 for distinguishing converters from both nonconverters and controls (panel B). For both curves, the AUCs were highly significant from 10 000 permutations, indicating better prediction accuracy than chance.

The detected hyperactivation was exclusively in regions that are crucial for associative and episodic memory processing in humans. Specifically, the SFG as part of the DLPFC has been considered to be involved in cognitive control mechanisms for information retrieval, particularly postretrieval monitoring.^{49,50} The IFG as part of the VLPFC is a key region for the modulation of information input into the memory system and the maintenance of successfully retrieved information.^{51,52} The IPL is related to attention engagement and sense of familiarity during retrieval,^{53,54} and the LTC may play a key role in semantic processing during encoding and retrieval of word pairs.^{55,56} Together, the conjoint hyperactivation of these regions may imply that excessive control is needed for successful information retrieval in subjects at CHR and particular those who will convert to full psychosis. This interpretation is supported by the fact that higher activation in these regions was correlated with longer memory retrieval time but not discrimination ability in converters, a pattern suggestive of greater retrieval effort. The increased effort, in turn, may involve more task-related attention and executive control during the retrieval process and lead to enhanced activation of the aforementioned regions in converters.^{57,58} As a result, these findings suggest that hyperactivation of memory retrieval regions, possibly attributed to increased effortful processing during retrieval testing, marks processes associated with conversion to psychosis. The secondary analyses showing hyperactivation pattern for both correct and incorrect trials and for both old and new word pairs further support this argument.

In contrast to the significant findings in brain activation, brain network analysis did not reveal any significant results in network efficiency nor network diversity in subjects at CHR. This is consistent with our previous work that resting-state functional network configuration disrupts gradually in tandem with the progression of

psychosis but is intact at the baseline scan.²⁹ Although we do not have a sufficient sample tracking the longitudinal change of brain networks during the memory task, the reported baseline findings may suggest that measures of network efficiency and diversity may serve as biomarkers for tracking the development of psychosis rather than biomarkers for predicting psychosis at the early stage of prodromal syndromes. Taken together, it seems that abnormal brain activity may occur before overt network architecture changes in subjects at CHR for psychosis.

Our study has several limitations. First, the sample size for converters was relatively small and the conversion rate among subjects with fMRI data available was relatively low (~12%), thus further replications of the present findings are encouraged using larger sample sizes. Second, as presented in [table 1](#), although demographic variables were matched between converters and nonconverters, the clinical groups differed from controls on some measures. Third, the ROC analysis was not derived from an independent sample. Although we sought to mitigate the effect of this limitation by using anatomical masks that were independent of group-level activation clusters, the resulting AUCs are nevertheless still likely to be overestimated to a certain degree. Fourth, because all participants had their clinical assessments up to approximately 24 months, it is possible that the nonconverter group contains some subjects who might eventually convert to psychosis after the last assessment. However, as previously discussed,⁵⁹ this possibility would actually attenuate the differences between the converter and nonconverter groups, suggesting that the observed effects in this study may be underestimated. Fifth, the detected findings in this study were based on a specific paired-associate memory paradigm and may not necessarily generalize to all tasks used to challenge memory functions in psychosis studies. In particular, the paradigm used in this study

used both verbal (words) and nonverbal (pictures) stimuli during the encoding phase but only verbal stimuli (words) during the retrieval phase. Although including pictures would help participants encode presented word pairs, this design nevertheless introduced additional experimental components that were not exactly matched to the retrieval phase. This discrepancy might to certain degree contribute to the differential activation outcomes between the 2 phases, because impairments of verbal and visual memories might be different in patients with schizophrenia.^{60,61} Finally, the memory deficits in converters may reflect difficulty in recalling the encoded information at retrieval, difficulty in creating the associations during encoding, or both. Although these 2 factors cannot be completely isolated in a memory task as used here, we did not observe a significant between-group difference in self-reported encoding response rate, nor a significant correlation between retrieval hyperactivation and encoding response rate, suggesting that activation differences at retrieval are unlikely to be caused purely by failure in forming an association at encoding.

Conclusion

In summary, this study provides first evidence for functional alterations during associative memory processing in individuals at CHR for psychosis. Our findings support increased baseline retrieval activation as a potential biomarker for psychosis prediction. Further work is encouraged to replicate these findings and to test the predictive power of these findings in independent cohorts.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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