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Intact relational memory and normal hippocampal structure in the early stage of psychosis

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Abstract

Background—Previous studies indicate the transition to psychosis is associated with dynamic changes of hippocampal integrity. Here we explored hippocampal volume and neural activation during a relational memory task in patients who were in the early stage of a psychotic illness.

Methods—41 early psychosis patients and 34 healthy controls completed a transitive inference (TI) task used previously in chronic schizophrenia patients. Participants learned to select the “winner” of two sets of stimulus pairs drawn from an overlapping sequence (A>B>C>D>E) and a non-overlapping set (a>b, c>d, e>f, g>h). During an fMRI scan, participants were tested on the trained pairs and made inferential judgments on novel pairings that could be solved based on training (e.g. B vs. D). Hippocampal volumes were manually segmented and compared between groups. fMRI analyses included 27 early psychosis patients and 30 controls who met memory training criteria.

Results—Groups did not differ on inference performance or hippocampal volume, and exhibited similar activation of medial temporal regions when judging non-overlapping pairs. However, patients who failed to meet memory training criteria had smaller hippocampal volumes. Neural activity during TI was less widespread in early psychosis patients but between-group differences were not significant. Hippocampal activity during TI was positively correlated with inference performance only in control subjects.

Conclusions—Our results provide evidence that relational memory impairment and hippocampal abnormalities, well established in chronic schizophrenia, are not fully present in early psychosis patients. This provides a rationale for early intervention, targeting the possible delay, reduction, or prevention of these deficits.

Keywords

first-episode psychosis; transitive inference; relational memory; associative memory; hippocampus; schizophrenia

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Introduction

Recent research on psychotic disorders has prioritized the discovery of early disease markers to guide the development and delivery of early treatment interventions. Patients with schizophrenia and psychotic bipolar disorder have widespread deficits in brain structure and function (1), but whether these abnormalities are present before disease onset, progress over time, or remain stable are topics of ongoing investigation. Some of the cognitive (2–7) and neural (8–10) deficits observed in chronic schizophrenia patients are already present in the early stage of psychosis. However, longitudinal studies show that the first years of psychotic illness involve progressive reductions in volume across the brain (11–16), perhaps at an accelerated rate compared to more chronic patients (12).

A specific region of interest for studies of early psychosis is the hippocampus, an essential structure for memory and emotional processing (e.g. 17, 18). In chronic schizophrenia patients, small but consistent reductions in bilateral hippocampal volumes are a robust finding (19–21), in addition to selective memory deficits (22–26) and abnormal recruitment of the hippocampus during memory tasks (27, 28). Studies of the early stage of psychotic illness indicate that hippocampal volume changes may coincide with the onset of prominent psychotic symptoms. While a meta-analysis found hippocampal volume to be reduced in first-episode psychosis patients (9), individual studies find more limited and not necessarily consistent volume reductions, e.g. in only the left (21), right (29), or anterior (29, 30) regions of the hippocampus. In addition, studies included in this meta-analysis were not evaluated based on the diagnostic category of the participants or duration of illness, two factors shown to contribute significant variability to hippocampal volumes. Specifically, a large, cross-sectional study of hippocampal volume provided evidence for progressive hippocampal volume loss in schizophrenia patients, finding normal hippocampal volumes in patients with schizophreniform disorder (< 6 months of illness) and first-episode affective disorders, smaller left hippocampal volumes in first-episode schizophrenia patients, and bilateral hippocampal volume loss in patients with established schizophrenia (21). The few studies of individuals at-risk for a psychotic disorder have yielded similarly equivocal results, with some finding evidence for volume loss in specific regions of the hippocampus (31, 32), and others finding no differences from healthy controls (21). Taken together, these studies indicate that dynamic changes of hippocampal volume occur during the transition to psychosis.

Here we explored relational memory, hippocampal structure and hippocampal function in patients in the early stage of psychotic illness. Memory deficits in schizophrenia are not global but selective (22–26), and impairments of associative or relational memory, which require the “binding” together of distinct memory elements, are especially prominent (33–42). Two previous studies of hippocampal function in first-episode psychosis patients provide evidence for subtle functional abnormalities, including decreased functional connectivity between the hippocampus and frontal regions during a working memory task (43) and reduced hippocampal recruitment during relational encoding of arbitrary items (44). In the current study we used a transitive inference (TI) task, a test of relational memory that involves the hippocampus (45–51) and has been used previously to quantify behavioral and neural deficits in patients with chronic schizophrenia (39, 41). TI refers to the ability to make inferential judgments on novel stimulus pairings based on previously learned associations (for example, if one learns that $A > B$, and $B > C$, then $A > C$ can be inferred). TI is impaired in patients with chronic schizophrenia (35, 39, 41) and these deficits have been linked to decreased activity in the hippocampus, parietal cortex, and anterior cingulate cortex (41).

We predicted that early psychosis patients would show impaired TI performance accompanied by reduced recruitment of the hippocampus and parietal cortex during these judgments, similar to chronic schizophrenia patients. We also hypothesized that early psychosis patients would have smaller hippocampal volumes.

Methods and Materials

Subjects

After approval of the study protocol by the Vanderbilt University Institutional Review Board, Nashville, TN we obtained written informed consent from 42 psychotic patients and 35 matched healthy control subjects. Psychotic patients were recruited from the psychiatric inpatient unit and outpatient clinics of Vanderbilt University Medical Center. Healthy controls were recruited from the surrounding community via advertisements. All participants were administered the Structured Clinical Interview for DSM-IV (52) and the National Adult Reading Test as a measure of premorbid IQ (NART; 53). Psychotic patients were also assessed with the 17-item Hamilton Depression Rating Scale (54), the Young Mania Rating Scale (55), and the Positive and Negative Syndrome Scale (56). When available, the assessments of our research team were supplemented with clinical information obtained from the treating physicians. All participants with significant medical or neurological illness, significant head injury, a history of drug or alcohol dependence, and uncorrected vision deficits were excluded. Usable structural MRI data was obtained from 34 control participants (1 excluded for excess motion) and 41 early psychosis patients (1 experienced claustrophobia during fMRI scan). Prior to fMRI analysis, 4 control subjects and 14 early psychosis patients were excluded due to: technical problems during data collection (2 patients), poor compliance with task instructions (2 patients), claustrophobia during fMRI scan which led to early termination of the session (1 patient), poor normalization (1 control) and failure to meet our a priori memory training criteria (3 controls, 9 patients). Our final study group for the fMRI analysis included 30 healthy control subjects and 27 early psychosis patients. The duration of illness and time of last clinical follow-up for the psychotic patients is shown in Table S1. Most patients were studied at the time of their first hospitalization for a psychotic illness and were followed-up in our outpatient clinic. Chlorpromazine equivalent doses were calculated for patients taking antipsychotics (MRI sample $n = 38$, fMRI sample $n = 24$) according to Gardner (57) (Table 1); the remaining 3 patients were unmedicated. Early psychosis and control groups did not differ with respect to age, race, gender, or parental education, for either the structural MRI or fMRI analysis cohorts (Table 1).

Experimental paradigm

The paradigm has been described in detail previously (41, 58). Briefly, prior to the fMRI test session, participants were trained to identify the “winning” stimulus of two sets of visual stimulus pairs: four pairs (A>B, B>C, C>D, D>E) that create a sequence of overlapping stimuli (S condition) and four pairs (a>b, c>d, e>f, g>h) that are non-overlapping stimuli (P condition). During the fMRI scan, participants were tested on the previously learned premise pairs (S, P conditions), and also asked to make inferential judgments on novel pairings from each condition (IS condition: AC, AD, BD, BE, CE and IP condition: ad, af, ch, cf, eh). This 2x2 factorial design (sequence x inference) allows for the study of the neural basis of transitive versus non-transitive inference. The BD pair in the IS condition is the purest test of transitive inference ability as it does not include either of the end items (A, E).

Stimuli

Stimuli in the P condition were pentagonal shapes and stimuli in the S condition were elliptical shapes. Shapes were filled with colored visual patterns that were randomly assigned to pairs for each participant and rotated across subjects.

Training

As detailed elsewhere (41, 58), participants viewed pairs of visual stimuli on a computer screen and were asked to choose via button press which stimulus was “hiding” a smiling face. Participants were first trained on the 4 non-overlapping pairs and then on the overlapping pairs. For each condition there were 3 training blocks, consisting of 60, 60, and 24 trials with equal presentations of each stimulus pair. After training, participants were tested on a single block of 48 pairs that presented 6 instances of each trained pair (both P and S conditions) with no feedback. Subjects who did not correctly select at least 70% of all trials in each condition on the last block (7 patients, 0 controls) received an additional training block of 24 trials of the type they failed (overlapping pairs for all subjects). These subjects were retested on the 48 pair test block before the fMRI scan. Subjects who did not meet the training criterion of at least 66% correct responses on each pair in the S and P conditions were excluded from the final fMRI analyses (9 patients, 3 controls).

fMRI Task

All participants completed two 4.5 minute fMRI scans. Each run began and ended with a 30-second fixation period. In between, eight 25 second memory trial blocks were presented in one of two orders (P, IP, S, IS, P, IP, S, IS or S, IS, P, IP, S, IS, P, IP). Each block included 10 trials, with 2 seconds of stimulus presentation and a 500 ms interstimulus interval. Participants were instructed to indicate with a button press which item they thought would be associated with the smiling face based on prior training and no feedback was given.

Functional MRI

Participants were studied approximately 20 minutes after the completion of training in a 3-T Phillips Achieva MRI scanner (Philips Healthcare, Inc., Best, The Netherlands). Stimuli were presented using Presentation software (Neurobehavioral Systems Inc, Albany, CA) on a personal computer and projected onto a screen. Each scan session began with a high resolution anatomical scan, followed by an initial localizer scan for the fMRI runs. Functional runs lasted 276 seconds; the first 16 seconds of each run were discarded to allow for T1 signal calibration. The remaining acquisition collected 130 blood oxygenation level-dependent (BOLD) functional brain images (echo time=25 milliseconds; repetition time=2000 milliseconds; 36 axial sections, interleaved acquisition [3 mm thick, 0 mm gap]; voxel size, 3×3×3 mm; field of view=108 mm; flip angle=79°). The slice acquisition box was positioned to capture 1–2 slices inferior to the most ventrally visible temporal lobe. Slices were tilted 30° higher anterior than posterior in relation to the anterior commissure-posterior commissure line to minimize medial temporal lobe signal dropout.

Data analysis

Behavioral Data—Accuracy and response latency data during the fMRI session were analyzed with a 2×2 (sequence: overlapping, non-overlapping x inference: trained, novel) repeated measures analysis of variance with diagnosis (control, early psychosis) as a between-subjects factor.

Structural Neuroimaging Data—Volumetric analysis was completed by a single rater (AW) who was blind to experimental group using a previously established hippocampal segmentation protocol (59). Manual segmentations were completed using 3DSlicer (version

3.4) (60). 3DSlicer allows for simultaneous viewing in 3 orientations (coronal, sagittal, and horizontal) and automatically calculates the volumes of manually segmented structures. Reliability statistics were computed by segmenting 10 randomly selected subjects (5 per group) at two different time points to determine Intraclass Correlation Coefficients for right (ICC= 0.85) and left (ICC= 0.96) hippocampi. Hippocampal volumes were corrected with individual intracranial volume calculated with the Freesurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) using a previous detailed method (61). Volumes were analyzed with a 2×2 (hemisphere: left, right x region: anterior, posterior) repeated measures analysis of variance with diagnosis as a between-subjects factor.

Functional Neuroimaging Data—Analysis was performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional data were corrected for head motion, normalized to Montreal Neurological Institute (MNI) template space, high-pass filtered (200 seconds) and smoothed with a 5-mm full-width/half maximum kernel. Functional data were analyzed with a mixed-effects model. At the first level, design matrices were created for each subject to model effects of the 4 experimental conditions (P, IP, S, IS) across the two runs; the fixation period was implicitly modeled as the baseline. The 4 effects of interest were modeled as 25-second blocks with a boxcar function convolved with a canonical HRF. A general linear model was used to quantify BOLD activity in each condition. Effects of interest were investigated with the following contrasts: main effect of sequence (S+IS) vs. (P+IP) and transitive inference (IS – S) – (IP – P) (41, 58).

At the second level, one- and 2- sample t-tests were used to test for within- and between-group effects. For the transitive inference contrast a regression analysis was also performed using inference performance as a predictor. For between-group comparisons, the within-group contrast from the first group was used as a mask (e.g. the control>psychosis contrasts are masked with the contrast in the control group, thresholded at $p<.01$). Hippocampal tracings from the morphometric study were used to create a sample-specific hippocampal ROI. Individual ROIs were coregistered to the subjects' original structural image and normalized to MNI space. Normalized, binary ROIs were averaged across subjects and thresholded at 0.5. A threshold adjustment method based on Monte-Carlo simulations with our whole brain and hippocampal masks (AlphaSim, <http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf>) was used to protect against Type I errors. For whole brain analyses a voxel p-value of .001 and a cluster size of 8 resulted in a family-wise corrected $p<.05$. For the bilateral hippocampal ROI, a voxel p-value of .05 and a cluster size of 14 was required for a family-wise $p<.05$.

Results

Hippocampal Volume Data

Corrected hippocampal volume did not differ between the full sample of early psychosis patients ($n = 41$) and healthy controls ($n = 34$), with numerically larger volumes for the early psychosis group (non-significant main effect of group, $F(1,73)=.74$, $p=.39$) (Figure 1A, Table S2). We found right > left (main effect of hemisphere, $F(1,73)=32.5$, $p<.001$) and anterior > posterior hippocampal volume (main effect of region, $F(1,73)=119.3$, $p<.001$), and a hemisphere x region interaction ($F(1,73)=29.5$, $p<.001$). Hippocampal volume asymmetries did not differ between groups for this or any subsequent analysis, therefore effect sizes were calculated for only left and right hippocampal volumes. Within the early psychosis groups hippocampal volumes did not differ by diagnosis (non-significant main effect of diagnosis, $F(1,38)=.23$, $p=.798$) (Figure 1B, Table S2). Corrected hippocampal volumes and asymmetries were also similar for early psychosis patients ($n = 27$) and control participants ($n = 30$) who met the training criteria for inclusion in the final fMRI analyses

(non-significant main effect of group, $F(1,55)=1.78$, $p=.19$; main effect of hemisphere, $F(1,55)=24.53$, $p<.001$; main effect of region, $F(1,55)=99.40$, $p<.001$; hemisphere x region interaction $F(1,55)=19.9$, $p<.001$) (Figure S1, Table S3).

Interestingly, corrected hippocampal volumes for early psychosis patients who failed to meet training criteria for the memory task had smaller hippocampal volumes compared to patients who passed (5% reduction) (Figure S1, Table S3). While the main effect of group did not reach statistical significance ($F(1,34)=2.02$, $p=.16$), the effect size was moderate (Cohen's d right hippocampus = -0.48 ; left hippocampus = -0.49) (Table S3).

Behavioral Data: Accuracy and Response Latency

Accuracy did not differ between groups (mean percent correct $\pm$ SD for the P, IP, S and IS conditions in control subjects: 99 ± 2 , 92 ± 20 , 92 ± 10 , 74 ± 22 and psychotic patients: 98 ± 3 , 89 ± 19 , 85 ± 11 , 73 ± 22 ; non-significant main effect of diagnosis, $F(1,55)=1.5$, $p=0.22$). Accuracy was lowest when judging novel, inferential pairs (main effect of inference, $F(1,55)=23.86$, $p<.001$) and pairs from the overlapping sequence (main effect of sequence, $F(1,55)=67.8$, $p<.001$) (non-significant interactions with diagnosis). We found a marginally significant sequence by inference interaction ($F(1,55)=3.4$, $p=.07$) indicating accuracy was lowest on novel pairs from the overlapping sequence (IS condition). This pattern indicates equivalent TI performance for both groups. Groups were also matched for performance on the difficult BD inference pair ($F(1,55)=.44$, $p=.51$). There were no correlations between NART scores and accuracy, with the exception of accuracy on the previously learned, non-overlapping pairs in the psychosis group (P condition; $r^2=.30$, $p<.005$).

Groups did not differ in overall response latency (non-significant main effect of group, $F(1,55)=.49$, $p=.49$), and showed similar reaction time patterns by condition (Supplementary Materials). For only control participants, NART scores were negatively correlated with response times for judgments on pairs from the overlapping sequence (S and IS conditions, all $r^2>-.015$, all $p<.032$).

fMRI Data

We were interested to quantify group differences in brain activation related to either relational memory or medial temporal lobe function. Therefore, we explored the neural basis of the main effect of sequence and the sequence x inference interaction effect (transitive inference), which had been linked to medial temporal lobe activation in previous studies (41, 46).

Main Effect of Sequence—Both groups showed greater activation in a network including bilateral frontal and parietal regions when viewing the overlapping pairs compared to the non-overlapping pairs (Table 2, Figure 2) and a direct comparison between groups revealed no significant differences. The inverse contrast (i.e., greater brain activation when viewing non-overlapping pairs) revealed activation of a distributed network in healthy control subjects and more limited activation in psychotic subjects (Table 3, Figure 3). The normal activation pattern included robust medial temporal lobe activation, which was reduced in psychotic subjects, but between group differences were not statistically significant.

Transitive inference (TI)—When making inferential judgments on novel stimulus pairs drawn from the non-overlapping sequence, control subjects activated bilateral frontal, parietal, and temporal (middle and superior) regions, bilateral cingulate, right medial and superior frontal cortex, bilateral cerebellum, and early visual areas (Table 4, Figure 4). The activation pattern in psychotic patients was less widespread, and there were no significant

activations within the frontal lobe. However, despite a marked difference in the strength and extent of activation in the TI network, no clusters survived the stringent statistical threshold used in the between-group comparison. To further explore the neural basis of TI, accuracy on the BD pairs was included as a covariate in the TI contrast. In the control group activation in the left precuneus and precentral gyrus (whole brain analysis) and bilateral hippocampus (ROI analysis) were correlated with inference performance (Figure 5). In contrast, we found no significant correlations in the psychosis group. A similar pattern was found when examining the correlation between raw signal change in the TI contrast, extracted from the group hippocampal ROI, and BD performance (Figure S3).

Predictors of Inference Performance

Inference performance (percent correct on BD pairs) was not correlated with premorbid IQ in either group (both $p > .29$), nor with scores on any of the clinical scales in the psychosis group (all $p > .65$). There was no significant relationship between inference performance and duration of illness ($p = .33$) or medication (CPZ, $p = .96$).

Discussion

We found normal hippocampal structure and function, in the context of intact relational memory performance, in many early psychosis patients. This finding is in contrast to our hypothesis derived from previous studies of chronic schizophrenia patients (35, 39, 41). Our results provide new evidence that some of the well-established abnormalities of brain structure and function found in chronic psychosis patients are not fully present in all early psychosis patients. These findings support the notion that memory deficits and hippocampal abnormalities may be amenable to early intervention and, possibly, prevention.

Previous studies of early psychosis patients have found reductions in hippocampal volume, but results are equivocal. Diagnostic heterogeneity and varied durations of illness likely contribute to these inconsistent findings, as previous studies have shown that patients with a brief (< 6 months) duration of illness, and those experiencing their first episode of an affective psychosis do not exhibit reductions in hippocampal volume (21). While an appropriate diagnosis can be identified at the time of study, it is often difficult to determine the ultimate diagnostic class for early psychosis patients. For example, when followed over 2 years, a significant number of psychotic patients will be reclassified, mainly from the non-affective to the affective psychosis group (62, 63). Future studies which evaluate hippocampal structure and function in early psychosis patients should include these factors in their analyses. In our early psychosis sample we collected follow-up clinical data on 29/41 participants to verify diagnoses (see Table S1). Hippocampal volume did not differ by diagnostic category, though schizophreniform patients had the numerically largest volumes. In our sample, a large number of patients with schizophreniform disorder ($n = 13$) and a relatively short mean duration of illness (about 6 months) likely contribute to the finding of normal hippocampal volumes. While hippocampal volume reductions are not apparent at the group level, the 25% of patients who failed to meet memory training criteria for the final fMRI analysis had the smallest hippocampal volumes. This supports a link between relational memory and hippocampal integrity, and indicates that memory deficits and hippocampal volume reductions are present in some early psychosis patients.

Our study is the first to investigate the neural correlates of relational memory retrieval in early psychosis patients. While a number of studies have documented relational memory deficits in chronic schizophrenia patients (33–36, 38–42), only three have tested relational memory ability in first-episode psychosis patients. Two behavioral studies found normal relational memory performance in first-episode psychosis patients during a pattern-location associative learning test (64) and a brief verbal paired associates task (65). A single fMRI

study investigated brain activation during relational memory encoding in first-episode psychosis patients, finding evidence for reduced activation of the hippocampus and other areas during associative encoding of arbitrary image pairs, and a selective recognition deficit for these pairs (44). In contrast, early psychosis patients included in our final fMRI analysis did not exhibit a selective relational memory deficit, and showed similar medial temporal lobe activity during memory recognition of the non-overlapping pairs. In the TI contrast, neither group showed robust hippocampal activation as predicted based on previous studies (41, 58). Neural activity during TI did not differ between early psychosis patients and healthy controls in the context of matched inference performance. However, only healthy controls showed a significant, positive correlation between inference performance and hippocampal activation.

With respect to overall cognitive function, studies of early psychosis patients find evidence for a broad, stable profile of generalized cognitive deficits (2–5, 66), with the most pronounced impairments on verbal (6) and working (7) memory. While most cognitive studies have focused on non-affective patients, two studies that compared cognition between affective and non-affective first-episode psychosis patients found more selective impairments in memory and executive function in the affective group (7, 67). In our sample, inference performance did not differ between affective and non-affective psychosis patients, making it unlikely that the inclusion of non-affective patients artificially inflated inference performance. Our finding of normal TI performance in early psychosis patients indicates that some cognitive functions may be preserved early in the disease course.

There are several limitations to the study. First, the training performance criteria necessary to test for a selective inference deficit severely limit the generalizability of the findings to all psychotic patients. Over 25% (11/41) of the early psychosis subjects, but only 9% (3/34) of control subjects, who completed the fMRI study were excluded from final analyses based on poor training performance (9 patients, 3 controls) or poor task compliance (2 patients, 0 controls). While isolation of a selective memory deficit is a current goal in schizophrenia research (68), the methods employed to achieve this goal are complicated by differential task difficulty (40) and the exclusion of patients who cannot reach a set inclusion criteria in a baseline condition (34, 39, 41). In the current study our performance criteria excluded patients with smaller hippocampal volumes, which reduced our ability to detect between-group differences. Second, the block design does not allow for analysis of the crucial BD inference pair in isolation, or for an analysis of correct trials only (69). An event-related fMRI version of this paradigm was developed to address this concern (51), but the task proved very difficult for healthy controls, making it impossible to use in psychotic patients. Finally, most of the early psychosis patients were treated with antipsychotic medications; however, only 7/41 patients had a duration of treated illness greater than 6 months, and this factor was not correlated with inference performance ($p>0.4$).

In summary, this study is the first to assess TI, and only the second to directly evaluate hippocampal activation during memory performance, in patients during the early stage of psychosis. In a large sample of well-characterized, early psychosis patients with a short duration of illness we find normal mean hippocampal volume and intact hippocampal activation during relational memory performance. Of note, hippocampal volumes were smallest in those psychosis patients who failed to meet memory training criteria. These findings indicate that hippocampal dysfunction, well-established in chronic schizophrenia patients, is not present at the onset of psychosis in all early psychosis patients, providing an opportunity for clinical intervention and prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Regional hippocampal volumes for the full sample of participants by (A) region and (B) diagnosis. Healthy controls and early psychosis patients do not differ in hippocampal volume or hippocampal asymmetries (A). Within the early psychosis group, there is no significant difference in hippocampal volume by diagnosis, although schizophreniform patients have the largest volumes numerically (B).

Main Effect of Sequence

Figure 2.

Significant clusters of activation for judgments of overlapping pairs relative to non-overlapping pairs, $p < .05$ corrected cluster threshold: bilateral superior and middle frontal gyri (A, B, C), bilateral insula (B), right inferior frontal gyrus (C), bilateral angular gyrus and precuneus (D control), bilateral inferior parietal lobule (D, E early psychosis), and bilateral cerebellum (D, E control). A direct comparison between groups revealed no significant differences.

Inverse Effect of Sequence

Figure 3.

Significant clusters of activation for judgments of non-overlapping pairs relative to overlapping pairs, $p < .05$ corrected cluster threshold: bilateral anterior cingulate (A control), bilateral medial frontal gyrus (B, C control), bilateral precuneus (B, C, D, E control; only left in E early psychosis), bilateral insula/superior temporal gyrus (B, C, D control), bilateral parahippocampal gyrus/hippocampus (B, C), left cingulate (D early psychosis), right inferior parietal lobule (D early psychosis) and right precentral gyrus (B, C, D control). A direct comparison between groups revealed no significant differences.

Transitive Inference

Figure 4.

Significant clusters of activation during transitive inference, $p < .05$ corrected cluster threshold: bilateral medial and superior frontal gyri (A control), bilateral cingulate (B, C, D controls, C early psychosis), middle temporal gyrus (left B, C, D control, bilateral D, E early psychosis), left superior temporal gyrus (B control), left paracentral lobule (B control), bilateral angular gyrus (D control), bilateral precuneus (D early psychosis), bilateral middle/inferior occipital gyrus (E control), and bilateral cerebellum (D, E). A direct comparison between groups revealed no significant differences.

Correlations with Inference Performance: Healthy Controls

Figure 5.

Regions associated with successful transitive inference performance in healthy controls, $p < .05$ corrected cluster threshold at the whole brain level (A, B) and within the group hippocampal ROI derived from our morphometric study (C). With a whole brain analysis, clusters in the left precuneus (panel A; $k = 11$, $z = 3.73$, -15 , -37 , 58) and left precentral gyrus (panel B; $k = 12$, $z = 3.55$, -39 , -10 , 37) were positively correlated with percent correct on the difficult BD inference pair. Within the hippocampal ROI (C), clusters in the left ($k = 22$, $z = 2.73$, -30 , -22 , -14) and right ($k = 19$, $z = 2.73$, -36 , -19 , -17) hippocampus were positively correlated with inference performance. No clusters were correlated with inference performance in the early psychosis group.

Table 1

Socio-demographic and clinical characteristics of participants.

	Full Sample		fMRI Sample	
	Control	Early Psychosis	Control	Early Psychosis
	n = 34	n = 41	n = 30	n = 27
Gender (male/female)	22/12	30/11	18/12	21/6
Race (white/black)	28/6	35/6	26/4	24/3
Age, years	21.79 (2.4)	20.85 (5.0)	21.80 (2.6)	20.78 (5.6)
Participants Education, years	14.24 (2.0)	12.49 (2.0) **	14.37 (2.1)	12.11 (2.2) **
Parental Education, years	14.35 (2.0)	13.68 (2.4)	14.53 (2.0)	13.83 (2.6)
Edinburgh Handedness, # (right/left/ambidextrous)	32/1/1	33/3/5	28/1/1	21/3/3
Premorbid IQ (NART)	112.94 (5.5)	108.48 (7.7) **	112.90 (5.8)	109.24 (8.3) *
HAM-D	-	7.15 (4.8)	-	7.46 (5.4)
YMRS	-	7.33 (8.2)	-	5.19 (5.6)
PANSS_P	-	15.85 (6.1)	-	14.54 (4.7)
PANSS_N	-	13.23 (5.8)	-	13.46 (5.3)
PANSS_G	-	27.56 (7.0)	-	27.58 (7.1)
PANSS_Total	-	56.64 (14.94)	-	55.58 (13.2)
Duration of Illness, years	-	0.54 (0.60)	-	0.69 (0.67)
Prior hospitalizations, #	-	1.22 (0.73)	-	1.04 (0.52)
Duration of treated illness, # (< 1 month/1–6 months/> 6 months)	-	16/15/7	-	6/12/6
CPZ	-	290.79 (150.7)	-	266.04 (149.8)

Values indicate mean (SD) unless otherwise specified

NART = National Adult Reading Test scores

HAM-D = Hamilton Depression Rating Scale scores

YMRS = Young Mania Rating Scale scores

PANSS_P = Positive and Negative Syndrome Scale scores, Positive Subscale

PANSS_N = Positive and Negative Syndrome Scale scores, Negative Subscale

PANSS_G = Positive and Negative Syndrome Scale scores, General Subscale

PANSS_Total = Positive and Negative Syndrome Scale, total score

CPZ = Chlorpromazine Equivalent doses

** Significantly different between Early Psychosis and Control groups $p < 0.01$ * Trend towards significant difference between Early Psychosis and Control groups $p = 0.057$

Table 2

Significant activation clusters for the main effect of sequence (S+IS) > (P+IP)

	Brain Region	Hemisphere	CTL			Early Psychosis		
			# voxels	z score	MNI Peak Voxel	# voxels	z score	MNI Peak Voxel
<i>Frontal</i>	Superior Frontal Gyrus (BA 6)	B	174	6.07	0, 14, 55	149	4.73	-3, 20, 49
	Middle Frontal Gyrus (BA 9)	R/L	23	4.48	48, 35, 22	8	3.5	42, 26, 31
			750	5.84	-45, 32, 28	165	3.97	-15, 17, 37
	Inferior Frontal Gyrus (BA 6/9)	R	47	4.35	51, 8, 31	15	3.64	45, 8, 25
	Insula (BA 13)	R/L	41	4.4	33, 23, 7	10	3.47	33, 26, 4
<i>Parietal</i>			102	4.86	-33, 20, 4	79	4.17	-33, 23, 4
	Angular Gyrus/Precuneus (BA 39/31)	B	1334	7.32	-33, -55, 40			
	Inferior Parietal Lobule/Precuneus (BA 40/31)	R/L				181	4.34	36, -85, 22
						325	5.58	-51, -40, 46
	Posterior Cingulate (BA 23)	L	11	3.7	0, -31, 28			
<i>Occipital</i>	Middle Occipital Gyrus (BA 37)	L	18	4.08	-48, -67, -8			
	Cuneus/Lingual Gyrus (BA 18)	R/L	20	3.53	12, -76, 1			
			39	3.8	-12, -76, -2	18	3.72	-6, -79, 1
<i>Subcortical</i>	Thalamus	L	49	4.5	-12, -16, 10			
<i>Cerebellum</i>		R/L	70	5.47	30, -61, -35	11	4.21	30, -61, -38
			24	4.09	-36, -58, -35			

Table 3

Significant activation clusters for the inverse effect of sequence (P+IP) > (S+IS)

Brain Region	Hemisphere	CTL			Early Psychosis		
		# voxels	z score	MNI Peak Voxel	# voxels	z score	MNI Peak Voxel
Frontal	Anterior Cingulate/Medial Frontal Gyrus (BA 24)	222	4.99	-3, 35, 1			
	Precentral Gyrus (BA 4/6)	910	5.53	57, -4, 7			
	Cingulate Gyrus (BA 31)				26	4.28	-6, -34, 46
Parietal	Precuneus (BA 7)	290	5.35	-6, -43, 58	18	3.6	-15, -43, 46
	Inferior Parietal Lobule (BA 40)				27	3.91	51, -31, 28
	Posterior Cingulate (BA 23/30)	12	3.75	9, -52, 10			
		38	3.82	-6, -52, 10	10	3.57	-6, -52, 10
	Posterior Insula (BA 13)				10	3.8	48, -19, 25
Temporal	Superior Temporal Gyrus (BA 41)	206	4.84	-42, -19, 22			
	Medial Temporal Gyrus (BA 21)	9	4.19	-51, -7, -17			
	Parahippocampal gyrus (BA 28/34/35)				8	3.5	24, -16, -14
		42	4.82	-21, -16, -20	19	4.03	-30, -25, -17
	Fusiform Gyrus (BA 19)	12	3.84	30, -79, -11			
Occipital	Lingual Gyrus (BA 17/18)	46	4.79	21, -97, 1	82	5.07	18, -97, 1
	Inferior Occipital Gyrus (BA 17)	71	4.7	-27, -94, -8			

Table 4

Significant activation clusters for the transitive inference contrast (sequence x inference) (IS>S) > (IP>P)

	Brain Region	Hemisphere	CTL			Early Psychosis		
			# voxels	z score	MINI Peak Voxel	# voxels	z score	MINI Peak Voxel
<i>Frontal</i>	Superior Frontal Gyrus (BA 6)	L	11	3.88	-15, 47, 46			
	Medial Frontal Gyrus (BA 8)	R	457	4.98	3, 44, 37			
	Paracentral Lobule (BA 4)	L	12	4.05	-15, -28, 61			
	Precentral Gyrus (BA 44)	R	18	3.88	54, 17, -2			
<i>Parietal</i>	Angular Gyrus/Middle Temporal Gyrus (BA 39/40)	R/L	96	4.23	45, -64, 37			
			330	5.16	-48, -67, 34			
	Precuneus (BA 31)	R/L				12	3.74	12, -55, 28
						15	3.68	-3, -34, 46
	Cingulate (BA 31/23)	B/R	888	6.11		15	3.62	6, -43, 34
	Posterior Cingulate (BA 23)	B				65	4.03	-9, -55, 4
<i>Temporal</i>	Superior Temporal Gyrus (BA 39/41)	L	8	3.71	-15, -16, -11			
	Middle Temporal Gyrus (BA 21)		80	4.97	-57, -34, -5	102	4.36	-42, -58, 22
	Fusiform Gyrus (BA 19/37)	R/L				9	3.69	36, -82, -11
						14	3.44	-48, -52, -14
<i>Occipital</i>	Inferior Occipital Gyrus (BA 19)	R/L	14	3.93	42, -82, 4			
			30	4.09	-27, -94, -8			
<i>Subcortical</i>	Thalamus	R/L	8	3.72	6, -16, 10			
	Putamen	R	10	3.85	33, -16, -5			
<i>Cerebellum</i>		R/L	69	4.05	27, -76, -26	56	3.87	33, -55, -20
			82	4.98	-30, -73, -26	169	4.8	-24, -58, -11