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Hippocampal network modularity is associated with relational memory dysfunction in schizophrenia

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Abstract

Background—Functional dysconnectivity has been proposed as a major pathophysiological mechanism for cognitive dysfunction in schizophrenia. The hippocampus is a focal point of dysconnectivity in schizophrenia, with decreased hippocampal functional connectivity contributing to the marked memory deficits observed in patients. Normal memory function relies on the interaction of complex cortico-hippocampal networks. However, only recent technological advances have enabled the large-scale exploration of functional networks with accuracy and precision.

Methods—We investigated the modularity of hippocampal resting-state functional networks in a sample of 45 patients with schizophrenia spectrum disorders and 38 healthy control subjects. Modularity was calculated for two distinct functional networks: a core hippocampal-medial temporal lobe cortex (MTLC) network; and an extended hippocampalcortical network. As hippocampal function differs along its longitudinal axis, follow-up analyses examined anterior and posterior networks separately. To explore effects of resting network function on behavior, we tested associations between modularity and relational memory ability. Age, sex, handedness, and parental education were similar between groups.

Results—Network modularity was lower in schizophrenia patients, especially in the posterior hippocampal network. Schizophrenia patients also showed markedly lower relational memory ability compared to control subjects. We found a distinct brain-behavior relationship in schizophrenia that differed from control subjects by network and anterior/posterior division—while relational memory in control subjects was associated with anterior hippocampal-cortical modularity, schizophrenia patients showed an association with posterior hippocampal-MTLC network modularity.

Conclusions—Our findings support a model of abnormal resting-state cortico-hippocampal network coherence in schizophrenia, which may contribute to relational memory deficits.

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Keywords

psychosis; resting-state fMRI; functional connectivity; graph theory; posterior hippocampus; cognitive dysfunction

INTRODUCTION

Schizophrenia has long been characterized as a disorder of brain dysconnectivity (1; 2). The hypothesis of widespread miswiring, rather than the focal dysfunction originally supported by anatomical studies, has now been broadened using modern neuroimaging methods (3–6). Resting-state functional magnetic resonance imaging (rs-fMRI) has revealed widespread functional dysconnectivity in schizophrenia (7–9). Among the most consistent findings are connectivity deficits in the hippocampus (10–12), a region central to the pathophysiology of schizophrenia (13; 14). Correspondingly, a large body of evidence indicates robust structural deficits in temporal lobe white matter (15), suggesting a structural foundation for decreased cortico-hippocampal functional connectivity. However, functional connectivity findings are mixed—while the majority suggest hippocampal dysconnectivity (10–12), recent evidence also shows increased connectivity in components of hippocampal circuits (16–18), suggesting a complex picture across the network.

A hippocampal dysconnectivity model of schizophrenia needs to consider the anatomy of cortico-hippocampal circuits. Direct inputs from sensory cortices provide the foundation for rich relational memories (19; 20), while connections with association and prefrontal cortices are critical for memory storage and retrieval (19; 21). Structural connections and function are substantially segregated along the hippocampal longitudinal axis (22–27), with the anterior and posterior hippocampus implicated in familiarity-based item recognition (28; 19; 29–31) and spatial/contextual memory, respectively (32; 33). The hippocampus is densely interconnected with the adjacent medial temporal lobe cortex (MTLC), including the entorhinal, parahippocampal, and perirhinal cortices. Together, these structures form a core hippocampal-MTLC network supporting formation and retrieval of memory for items (34). The hippocampal-MTLC network is situated within a broader neocortical network, comprised of sensory and association regions in the prefrontal, anterior temporal, and parietal cortex that support memory-guided behavior (22).

Schizophrenia is associated with a profound deficit in the ability to flexibly integrate information into cohesive relational memories (30; 35–37). This deficit has been linked to abnormalities in anterior and posterior hippocampus (38–41) and in both core hippocampal and extended cortical circuits (28; 30). However, while previous studies have investigated the association between memory function and individual components of hippocampal networks, it remains unclear whether functional connectivity findings reflect widespread disruption in the function of networks.

Advances in network modeling techniques are particularly well-suited to investigate this question (42). In the healthy brain, neural networks are organized into modules, i.e., communities of densely interconnected regions (43; 44). Modules allow for rapid and efficient information processing among brain regions that share similar functional

specialization, while restricting cross-talk with regions with different specialization (43; 45), and are thought to evolve in order to increase both efficiency of communication and adaptability of to new environments (46). Recent findings have shown substantially decreased modularity across cortical networks in schizophrenia (6; 47). Additionally, abnormal modularity has been noted in genetic models of schizophrenia (48), suggesting the network dysfunction may be a core feature of the illness.

Here, we examined connectivity in both a core hippocampal-MTLC and extended hippocampal-cortical network in schizophrenia. To characterize network interactions, we used the graph theory metric of modularity, an index of the balance between functional integration and segregation of networks. Higher modularity scores indicate greater cohesion of memory regions into a distinct network, while lower modularity scores indicate lower cohesion across memory regions. We hypothesize that hippocampal network modularity be lower in schizophrenia relative to controls. To test the hypothesis that anterior and posterior hippocampus may be differentially affected in schizophrenia, we conducted planned follow-up analyses within anterior and posterior hippocampal networks, separately. Finally, resting-state differences in modularity likely reflect inherent individual constraints in network biology; therefore, we expected resting-state modularity to predict relational memory performance. To test this question, we performed correlations between modularity and relational memory ability in schizophrenia patients and control subjects.

METHODS AND MATERIAL

Participants

We studied 45 patients with schizophrenia spectrum disorder (i.e., schizophreniform disorder, schizophrenia, schizoaffective disorder) and 38 healthy control subjects (Table 1). Patients were recruited from the inpatient units and outpatient clinics of the Vanderbilt Psychiatric Hospital into a registered neuroimaging repository from 2008 through 2013 ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00762866); NCT00762866). All participants were assessed by a trained rater using the Structured Clinical Interview for the DSM-IV (SCID I-P) (49), and diagnoses were confirmed by a senior clinician (S.H.) through patient interview, consensus conference, and available hospital records. At the time of participation, 19 patients were diagnosed with schizophreniform disorder. Follow-up diagnoses were available for 14 of these patients: 13 patients converted to schizophrenia and 1 patient converted to schizoaffective disorder. Healthy control subjects were recruited from the surrounding community. Participants were assessed for current mood, psychotic symptom severity, and intellectual function (see Supplementary Methods). There were no significant differences in age, sex, handedness, and years of parental education by group (Table 1).

Participants were selected for this analysis based on the following criteria: 1) successful completion of an eye tracking memory study; and 2) completion of a high-quality resting-state functional connectivity scan (see quality methods below). Twenty-eight of the 38 healthy control subjects and 23 of the 45 schizophrenia patients had been included in a previous behavioral study (35). Exclusion criteria were age less than 16 or greater than 65, a history of significant head injury, major medical (i.e., HIV, cancer) or neurological illness, any contraindication for MRI scanning (e.g., pregnancy, metal implants, claustrophobia),

current alcohol or substance abuse within the past 3 months, and uncorrected vision deficits (see Supplementary Methods for full repository sample details). Healthy control subjects were excluded for any history of Axis I disorders or prior psychotropic medication use, or a first-degree relative with a psychotic illness.

Participants in both groups were predominantly white (69%), although groups differed by racial composition ($\chi^2 = 7.86$, $p = .005$). Secondary analyses were performed to test for potential effects of race on modularity results. This study was conducted in accordance with the Vanderbilt Human Research Protection Program and all participants provided written informed consent prior to study procedures. Participants received financial compensation for their time.

Relational memory behavior

Eye movements were recorded to assess memory performance during a face-scene pair task (35; 50). During testing, participants were shown three previously-seen faces superimposed over a previously-seen background scene. One of the three overlaid faces (Match face) had been previously paired with the background scene (for further details see Supplementary Methods). During the first 2 s of test trials, schizophrenia patients spent less time fixating on faces and scenes compared to control subjects (Schizophrenia mean = 1.24 s, SD = .16 s; Control mean = 1.48 s, SD = .22 s; $F = 29.46$, $p < .001$), suggesting more time spent on blinks or looking away from the monitor; therefore, element viewing times were corrected for total viewing time.

Previous findings have shown that preferential viewing associated with hippocampal function occurs within the first 2 s of face-scene test viewing (28). Therefore, relational memory performance was characterized as the change in the proportion of time spent viewing the Match face (slope) during the first 2 s of each Match trial. Slopes were corrected for between-subject differences in initial eye position (first 250 ms) following face presentation (51; 52).

Imaging data acquisition and pre-processing

Imaging data were collected on two identical 3T Philips Intera Achieva magnetic resonance imaging (MRI) scanners located in the Vanderbilt University Institute for Imaging Science. A high-resolution T1-weighted fast field echo (FFE) structural scan (Supplementary Methods) and a 7-minute echo-planar imaging resting-state functional scan (rs-fMRI) were collected for each subject. The rs-fMRI was collected with the following parameters, which provided whole-brain coverage: 28 axial slices; FOV = 240 mm; matrix = 80×80 , $3 \text{ mm} \times 3 \text{ mm}$ in-plane resolution, slice thickness = 4 mm; volumes = 203; TR = 2 s; TE = 35 ms; SENSE = 1.8. Participants were instructed to relax and close their eyes and to remain awake during the scan. The rs-fMRI was acquired following the structural scan and was not preceded by any cognitive tasks. Resting-state data were motion corrected, coregistered to the subject's structural image, and normalized to an MNI T1 template image in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) (Supplementary Methods). Functional quality measures were computed using an in-house quality assurance toolbox (53); data with motion greater than 2 mm translation or 2° rotation, or with median framewise displacement (FD) greater

than 0.6 mm were not selected for analysis. Overall, motion was low (translation [max] = .82 mm, rotation [max] = 1.27°, median FD [max] = .55) across subjects and similar between groups (all p 's > .2).

Functional connectivity and network modularity analysis

Network connectivity was calculated at two levels: the hippocampal-medial temporal lobe cortex (MTLC) network, a core hippocampal network comprised of proximal connections central to memory function, including the hippocampal formation and adjacent entorhinal, perirhinal, and parahippocampal cortices; and the hippocampal-cortical network, a broader network including prefrontal, temporal, and parietal cortical regions that support memory function (Figure 1). Because memory function and connectivity vary along the longitudinal axis of the hippocampus, follow-up analyses were conducted for the anterior and posterior hippocampus separately (19; 22; 54). To capture individual variation of hippocampal structure, hippocampus region of interest (ROI) masks were created for each participant using in-house multi-atlas segmentation techniques (55; 56). Each ROI was manually segmented into an anterior and posterior mask by a trained rater (S.A.). The anterior lateral and posterior medial entorhinal cortex were delineated by high-resolution functionally-derived masks (57). For the remaining cortical ROIs, a regular 12 mm grid containing 1068 spheres (58) was overlaid on each subject's anatomically-segmented brain. Using anatomical atlases, spheres were selected within the perirhinal cortex ($n = 2$, bilateral) and parahippocampal cortex ($n = 4$, bilateral). The remaining cortical spheres were chosen based on coordinates from an independent sample that show resting-state functional connectivity with the hippocampus (19; 24) (see Supplementary Table S1 for sphere coordinates). In total, the hippocampal-cortical network consisted 72 nodes (ROIs) and 2,556 possible edges (connections), while the core hippocampal-MTLC network consisted of 20 nodes and 190 possible edges.

Connectivity analyses were performed in the Functional Connectivity (CONN) toolbox (59) v16.a (www.nitrc.org/projects/conn). Connectivity matrices (Supplementary Methods) were calculated for each subject and connections were analyzed for laterality differences. Connectivity strength was similar across hemispheres; therefore, left and right hemisphere connectivity values were averaged. To enhance contrast between relevant (strong) and irrelevant (weak) networks, graph matrices were thresholded to include only moderate to strong connections ($|r| \geq .5$). The number of retained connections (edges) was similar between groups (sparsity ~2%, $p = .74$) (Supplementary Methods). Thresholded functional connectivity matrices are displayed in Supplementary Figure S1. To explore the stability of networks over different levels of sparsity, graph matrices were also thresholded at values ranging from mild to strong connectivity ($r = .3, .4, .6, .7$), corresponding to network sparsity of ~13%, 6%, 1%, and .5% (Supplementary Figure S2). Connection matrices were binarized for each participant to create unweighted networks. Secondary analyses using only the positive connectivity network were also conducted to determine stability of findings. Connection matrices were collapsed by anatomical region for the purposes of visual display (Figure 1).

Modularity (Q) was calculated for *a priori* hippocampal networks (Figure 1) according to Newman's metric (43). Modularity can be described as the quality of the partition of the network, or the fraction of connections that fall within the network minus the expected fraction if connections were distributed at random. Higher modularity values indicate a tightly knit community (modules) with dense inter-connections, while a modularity value of zero indicates no greater community structure than would be expected by chance.

Hippocampal asymmetry scores were calculated to examine the relationship between anterior and posterior networks. Modularity values were converted to z-scores (mean = 100, SD = 25) and asymmetry was calculated as the difference in modularity between anterior and posterior networks, with higher scores indicating an anterior > posterior asymmetry in modularity strength. Anterior and posterior hippocampal functional connectivity may be differentially affected by age (60); therefore, all within-group asymmetry analyses were corrected for potential age effects. Modularity calculations were conducted using Matlab R2016b (The MathWorks Inc., Natick, MA).

Statistical analysis

One-way analysis of variance (ANOVA) tested for between-group comparisons of hippocampal network modularity ($p = .05$). Properties of the functional connectivity matrix were calculated to describe patterns contributing to modularity; means and standard deviations are presented for descriptive data. To assess whether memory network modularity was associated with relational memory function, Spearman correlations between modularity and relational memory slope were examined ($p = .05$). Spearman correlations do not assume a linear relationship, but rather measure the monotonic relationship between variables, including non-linear relationships. *A priori* follow-up comparisons of individual anterior and posterior networks were Bonferroni-corrected ($p = .025$). To ensure modularity distributions did not influence findings, all between-group results were confirmed using non-parametric tests. Statistical analyses were performed using SAS software v9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Modularity of hippocampal networks in schizophrenia

Modularity values were lower in schizophrenia patients than control subjects, with significant differences detected in the hippocampal-MTLC network (hippocampal-MTLC, $F = 6.14$, $p = .02$; hippocampal-cortical, $F = 1.53$, $p = .22$). In schizophrenia patients, evidence for a modular hippocampal-cortical network was no greater than chance (modularity ~ 0). Follow-up analyses of anterior and posterior hippocampal-MTLC networks showed a similar, yet non-significant, pattern of lower modularity in patients (p 's $> .08$) (Figure 1). Hippocampal anterior/posterior asymmetry scores were similar between groups for both the hippocampal-MTLC and hippocampal-cortical network (p 's $> .40$). Secondary analyses examining only positive connectivity values ($r \geq .5$) revealed similar modularity differences between groups (hippocampal-MTLC, $F = 5.47$, $p = .02$; hippocampal-cortical, $F = 1.77$, $p = .19$). Together, these findings indicate low modularity of hippocampal networks in schizophrenia.

Functional connectivity within networks

To better understand modularity results, we calculated the functional connectivity properties for each *a priori* hippocampal network (Figure 2). Because modularity calculations were conducted on absolute connectivity values, group differences in either positive or negative connections, or both, could contribute to modularity findings; therefore, we examined both positive and negative connectivity values. In the core hippocampal-MTLC network, schizophrenia patients had a pattern of fewer connections at both positive and negative connectivity strengths relative to control subjects. In the hippocampal-cortical network, schizophrenia patients displayed a more mixed positive connectivity pattern, but a greater number of strong negative connections than control subjects. Mean functional connectivity strength was similar across groups for both positive and negative connections (positive, control mean = .63, SD = .09, schizophrenia mean = .69, SD = .18, $F = 3.03$, $p = .09$; negative, control mean = -.54, SD = .04, schizophrenia mean = -.53, SD = .02, $F = .42$, $p = .53$). Functional connectivity within and between networks is displayed in Supplementary Table S2.

Associations between hippocampal network modularity and relational memory

Relational memory was significantly impaired in the schizophrenia group. Patients were slower in recognizing face-scene pairs than control subjects, as indexed by shallower relational memory slopes (Control mean = 56.51, SD = 27.81; Schizophrenia mean = 13.61, SD = 32.7; $X^2 = 30.18$, $p < .0001$) during Match trials. Schizophrenia patients also had lower explicit recognition of face-scene pairs compared to control subjects (Control mean = 91%, SD = 19%; Schizophrenia mean = 62%, SD = 31%; $X^2 = 20.82$, $p < .0001$). Relational memory slopes were strongly correlated with explicit recognition measures ($r = .64$, $p < .001$) across participants.

To determine whether modularity was associated with differences in behavior, we tested for correlations between modularity and relational memory ability (Figure 3). Correlations were examined in patients and control subjects separately to avoid confounding effects of between-group differences in relational memory and modularity. In control subjects, better relational memory was associated with lower modularity values in the hippocampal-cortical network ($r = -.43$, $p = .007$). Follow-up analyses of the anterior and posterior hippocampus showed a negative correlation between relational memory and the anterior hippocampal-cortical network ($r = -.48$, $p = .004$). In contrast, in patients, better relational memory was associated with lower modularity in the hippocampal-MTLC network ($r = -.35$, $p = .02$). Follow-up analyses suggested the correlation was primarily driven by posterior network scores ($r = -.32$, $p = .07$). In addition, we found that higher asymmetry scores (anterior > posterior) in the hippocampal-cortical network were correlated with better relational memory in schizophrenia patients (hippocampal-cortical network, $r = .30$, $p = .05$), but not in control subjects ($r = -.23$, $p = .18$). To determine whether schizophrenia patients and control subjects showed a divergent brain-behavior relationship, we compared correlation coefficients between networks for each group. Both groups showed evidence for a divergent brain-behavior correlation between networks, with a significant difference detected in schizophrenia patients ($z = 2.09$, $p = .02$; control trend, $z = 1.59$, $p = .06$). The association between hippocampal-cortical modularity and relational memory was stronger in control

subjects compared to schizophrenia patients ($z = 1.62$, $p = .05$); hippocampal-MTLC correlations did not significantly differ between groups ($z = 1.25$, $p = .11$).

We did not see evidence that group differences in modularity were confounded by race (hippocampal-MTLC, $X^2 = .38$, $p = .54$; hippocampal-cortical, $X^2 = 1.15$, $p = .29$). Neither length of illness (schizophreniform vs. schizophrenia, p 's $> .12$) nor affective symptoms (schizophrenia vs. schizoaffective disorder, p 's $> .12$) were associated with modularity differences. Because modularity analyses require thresholding the connectivity matrix at a researcher-defined threshold, we examined the stability of results at alternative thresholds. Between-group modularity differences were consistent across moderate to strong connectivity values (Supplementary Results, Supplementary Figure S2).

DISCUSSION

In the current study, we used graph theory to examine modularity of resting-state hippocampal networks in schizophrenia. Schizophrenia was associated with a pattern of lower modularity in a localized hippocampal network relative to control subjects, consistent with the hypothesis that schizophrenia is a disorder of network dysconnectivity. A similar, though non-significant, trend was observed in an extended hippocampal network, suggesting the existence of broad hippocampal dysconnectivity; notably, evidence for a modular extended hippocampal network was no greater than chance in patients. Furthermore, schizophrenia patients showed a divergent brain-behavior relationship: while modularity of the extended hippocampal-cortical network was associated with relational memory ability in control subjects, modularity of the core hippocampal-medial temporal lobe cortical (MTLC) network predicted relational memory ability in schizophrenia patients. Together, these findings indicate that hippocampal network function is disrupted in schizophrenia and that disruptions are associated with relational memory ability.

The conceptualization that schizophrenia results from disconnection of the hippocampus from association cortices has gained support in recent years (13; 61–63). Brain networks are mediated by the constant dynamic interactions between regions, with the pattern of connections a function of activity-dependent synaptic plasticity. Deficits in one region can propagate as signaling deficits across the network, resulting in abnormal network function. One of the most consistent findings in schizophrenia is a deficit in hippocampal signaling, including increased glutamatergic signaling (13; 64), decreased GABAergic inhibitory control (13; 65–67), and impaired neural plasticity (68). Structural and functional deficits in cortico-hippocampal pathways have also been repeatedly demonstrated in schizophrenia patients (7–9; 15), supporting a dysconnectivity hypothesis. Our findings are in line with this mechanistic framework. Schizophrenia patients had lower modularity than control subjects across hippocampal networks (19) at both a narrow and broad spatial scale. Follow-up analyses revealed lower modularity was likely driven by overall fewer positive and negative connections in hippocampal networks. However, patterns across connection strengths were mixed, particularly in the broader hippocampal-cortical network, where there was some evidence for a greater number of positive connections in patients. These findings may inform discrepancies in the literature showing both increased and decreased functional connectivity in cortico-hippocampal circuits (10–12; 16–18).

Network dysconnectivity has been proposed as a major mechanism underlying cognitive dysfunction in schizophrenia (69). Here, we provide initial evidence that hippocampal network connectivity is associated with relational memory. Furthermore, we show a divergent brain-behavior relationship. In control subjects, relational memory ability was associated with lower modularity of the anterior hippocampal-cortical network, while relational memory in schizophrenia patients was associated with lower modularity within the posterior hippocampal-MTLC network. These results are in line with recent memory findings that showed higher modularity during a memory task was associated with worse performance (70). Extreme segregation of networks may reflect inability to integrate between regions in accordance with task demands. Unexpectedly, this relationship was detected even in the context of lower overall modularity in patients. One possibility is that relational memory also requires a balance between anterior and posterior hippocampal networks. In healthy brains, relational memory is associated with activity across anterior hippocampal network regions (28). Consistent with this, we found that higher anterior vs. posterior modularity in patients was associated with better relational memory. These findings suggest that some patients may rely on a relatively spared anterior temporal lobe memory network to compensate for a dysfunctional posterior network (40). Future studies examining changes in anterior and posterior hippocampal network connectivity in schizophrenia patients before and after interventions that increase relational memory performance, such as exercise (71), will aid in clarification of these findings.

Our findings suggest that abnormalities in resting-state integration across memory regions reflect biological constraints on relational memory ability. It is now well established that the function of brain networks at rest can reveal individual differences in biology that relate to behavioral ability (9; 72–74). Prior task-based findings have identified abnormalities in recruitment of both posterior and anterior hippocampal connections during relational memory judgments (40). We now extend these findings to show that the balance between anterior and posterior hippocampal network function at rest is critical. Resting-state analyses provide distinct advantages in the study of schizophrenia (9)—notably, the ability to study patients who may struggle to perform a memory task (75), as resting-state connectivity is not confounded by task performance deficits.

The study has several limitations. First, brain networks do not function in isolation. The hippocampal network is situated within a broader context of partially overlapping cortical networks (e.g. default mode, attention) that show varying degrees of disruption in schizophrenia (6). Observed modularity values for the hippocampal network were lower than those typically seen when modularity is optimized across multiple networks (48; 76; 77). The signals of nodes in a single network are expected to be comparatively similar, thus producing lower estimates of within-network modularity. The difference that persists between groups suggests the hippocampal network is less functionally integrated in patients relative to controls, an interpretation supported by follow-up descriptive analyses of functional connectivity values. Future studies are necessary to understand interactions between the hippocampal and cortical association networks and relative disruption of the hippocampal network compared with other networks in schizophrenia. Second, there are commonalities among schizophrenia patients that differentiate them from control subjects, including current and past use of psychoactive medications, stress, anxiety and mood

alterations, and educational attainment. Thus, we cannot determine whether lower modularity in schizophrenia is due to a common neural phenotype or these other factors. Third, examining patients across early and later stages of illness could obscure differences in biology related to the progression of illness (78). Although modularity was similar across patients in our sample, longitudinal studies are necessary to make definitive statements about hippocampal network modularity over the course of schizophrenia.

The idea that the brain ceases to function as a set of cohesive, inter-related networks is among the most important and earliest theories linking neurobiology with the phenomenology of schizophrenia (2; 79). Here, we found evidence for lower hippocampal network modularity in schizophrenia patients relative to control subjects, suggesting lower cohesion of hippocampal network connections. Additionally, modularity was associated with relational memory ability, a central and relatively selective cognitive marker of schizophrenia (50; 80). These findings suggest that resting hippocampal network modularity may be an important marker of neuropathology in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Hippocampal network regions are shown on the medial and lateral surface of the brain. Colors indicate individual hippocampal networks. (B) Network graphs are visualized for the control and schizophrenia group separately. Individual nodes are denoted by the color of their assigned network. Network connection lengths are scaled to reflect functional connectivity strength using ForceAtlas2, Gephi Software (<https://gephi.org/>). (C) Mean modularity values for hippocampal networks are compared across schizophrenia and control groups. Modularity was significantly lower in schizophrenia patients in the hippocampal-MTLC network, with findings primarily driven by lower modularity within posterior

hippocampal nodes. (D) Schizophrenia patients had generally lower modularity in both anterior and posterior hippocampal-cortical networks, although there were no significant differences between groups.

Figure 2.

The functional connectivity matrix was examined to describe patterns that may have contributed to modularity results. Histograms are shown for the hippocampal-MTLC network and hippocampal-cortical network in control subjects and schizophrenia patients. Matrices are thresholded at $|r| \geq .5$ to show only values included in modularity calculation. Schizophrenia patients showed a pattern of fewer positive and negative connections in the core hippocampal-MTLC network. In contrast, connectivity patterns in the broader hippocampal-cortical network were mixed; while schizophrenia patients had generally fewer

positive connections than control subjects, patients also had a slightly greater number of strong negative connections than control subjects.

Figure 3.

Correlations between modularity and relational memory ability are plotted for control subjects (blue) and schizophrenia patients (red). Shaded areas show the 95% confidence interval. (A) In control subjects, better relational memory was associated with lower modularity in the hippocampal-cortical network. These results were driven by a negative correlation between modularity and relational memory in the anterior hippocampal-cortical network. (B) In schizophrenia patients, better relational memory was associated with lower modularity of the hippocampal-MTLC network. The relationship was driven by a negative correlation between modularity and relational memory in the posterior hippocampal-MTLC network. There was a significant difference in modularityrelational memory correlations between networks in the schizophrenia group, with a similar trend in the control group, suggesting a divergent brain-behavior pattern in patients and control subjects.

Table 1

Participant demographics and clinical characteristics.

	Healthy controls (n = 38)	Schizophrenia (n = 45)		
	<i>n</i>		χ^2	<i>p</i>
Sex (m/f)	26/12	32/13	0.07	.79
Race (w/aa/o)	32/6/0	25/19/1	7.86	.005
Handedness (r/l)	32/6	38/7	0.0009	.98
	<i>Mean (sd)</i>		<i>F</i>	<i>p</i>
Age, years	30 (10)	31 (13)	0.18	.68
Parental education, years	14 (2)	14 (3)	0.09	.77
Education, years	16 (2)	13 (2)	20.18	< .001
Premorbid IQ, WTAR	113 (10)	94 (17)	34.96	< .001
Motion, FD	.17 (.06)	.19 (.12)	0.73	.39
HAM-D score	--	10 (8)	--	--
YMRS score	--	4 (6)	--	--
PANSS-Total score	--	68 (18)	--	--
PANSS-Positive score	--	19 (7)	--	--
PANSS-Negative score	--	17 (8)	--	--
PANSS-General score	--	32 (8)	--	--
CPZ equivalent dose	--	458 (283)	--	--
Duration of illness, years	--	10 (13)	--	--

m = male; f = female; w = white; aa = African American; o = other; r = right; l = left; sd = standard deviation; WTAR = Wechsler Test of Adult Reading; FD = median framewise displacement; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; PANSS = Positive and Negative Syndrome Scale; CPZ = chlorpromazine.