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Hippocampal network dysfunction in early psychosis: a 2-year longitudinal study

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ABSTRACT

Background. Hippocampal abnormalities are among the most consistent findings in schizophrenia. Numerous studies have reported deficits in hippocampal volume, function, and connectivity in the chronic stage of illness. While hippocampal volume and function deficits are also present in the early stage of illness, there is mixed evidence of both higher and lower functional connectivity. Here, we use graph theory to test the hypothesis that hippocampal network connectivity is broadly lowered in early psychosis and progressively worsens over two years.

Methods. We examined longitudinal resting-state functional connectivity in 140 participants (68 individuals in the early stage of psychosis, 72 demographically similar healthy control individuals). We used an anatomically-driven approach to quantify hippocampal network connectivity at two levels: 1) a core hippocampal-medial temporal lobe cortex (MTLC) network; and 2) an extended hippocampal-cortical network. Group and time effects were tested in a linear mixed effects model.

Results. Early psychosis patients showed elevated functional connectivity in the core hippocampal-MTLC network, but contrary to our hypothesis, did not show alterations within the broader hippocampal-cortical network. Hippocampal-MTLC network hyperconnectivity normalized longitudinally and predicted improvement in positive symptoms, but was not associated with increasing illness duration.
Conclusions. These results show abnormally elevated functional connectivity in a core hippocampal-MTLC network in early psychosis, suggesting selectively increased hippocampal signaling within a localized cortical circuit may be a marker of the early stage of psychosis. Hippocampal-MTLC hyperconnectivity could have prognostic and therapeutic implications.
INTRODUCTION

Hippocampal deficits are among the most robust and well-replicated brain abnormalities in schizophrenia (1–3). Postmortem and neuroimaging studies have demonstrated involvement of the hippocampus at all stages of illness (4–9), and implicated a fundamental relationship between smaller hippocampal volumes and elevated hippocampal metabolism in the progression of psychosis (10–13). Early hippocampal dysfunction begins in the CA1 region (13–15) and may remain relatively stable from psychosis onset through the early course of illness (6; 7; 16; 17), followed by a spread to other subfields (13; 15) and cortical regions by way of long-range efferent projections (18) during a period of progressive deterioration (15; 19–21). These findings place the hippocampus as a critical early biomarker for detection and therapeutic intervention (12; 22; 23). However, the emergence and progression of hippocampal functional connectivity remains to be fully characterized.

Disrupted functional integration across brain regions has been proposed as a mechanism underlying psychosis (24; 25). Widespread dysconnectivity is considered a hallmark feature of chronic schizophrenia (26), and many studies indicate this view extends to hippocampal connections (27–32). In contrast, in early psychosis, functional connectivity studies have produced mixed results, including findings of higher (33; 34), lower (34; 35), and normal (35) hippocampal-cortical connectivity. Mixed connectivity findings may stem from interneuron hypofunction in the hippocampus, resulting in increased hippocampal metabolism, glutamatergic tone, and disinhibition (36). In the early stages of psychotic illness, this hippocampal disinhibition may contribute to both elevated and lowered connectivity (34),
consistent with the disruptive and compensatory connectivity patterns identified in temporal lobe epilepsy (37). Investigation of hippocampal network connectivity as a whole, as opposed to individual connections, may clarify the patterns associated with specific illness stages. The introduction of quantitative network analysis has facilitated examination of aberrant connectivity across entire networks (38). These studies have suggested that with advancing stages of psychotic illness, aberrant connectivity patterns may change from mainly hyperconnectivity to hypoconnectivity (33), although it remains unclear whether this shift in connectivity patterns is also present in the hippocampal network.

One reason for this gap in knowledge may be due to the distinct architecture of hippocampal connections. The hippocampus binds sensory information from distributed parts of the cortex to form holistic representations of experiences. Polymodal sensory information converges on the hippocampus via medial temporal lobe cortices (MTLC; perirhinal, parahippocampal, and entorhinal) (39; 40), culminating in highly integrated information processing at the level of the hippocampus. Processed information is then relayed to a distributed cortical network via return circuits through the MTLC (40), suggesting the hippocampus occupies an important position in whole-brain networks. Yet, data-driven whole-brain network analyses often do not identify the hippocampus as a central hub, as its unique connectional architecture results in neither a disproportionately high number of structural connections nor a central location in the whole-brain connectome (41–43). For example, data-driven approaches have generally partitioned the default mode network, which includes a number of regions that support hippocampal memory, into three distinct subnetworks (44): a hippocampal-MTLC subnetwork; a midline cortical
subnetwork; and a subnetwork comprised of dorsal medial prefrontal, lateral temporal, and ventrolateral prefrontal cortex (45). Although early research included the hippocampal-MTLC subnetwork as a key component of the default mode network (46; 47), recent findings have largely focused on cortical subnetworks. However, when communication capacity is considered, the centrality of the hippocampal-MTLC network embedded in the whole-brain connectome becomes clear (48–50).

To address this gap, we used an anatomically-guided approach to examine hippocampal network connectivity in both a core hippocampal-MTLC network and an extended hippocampal-cortical network in a cohort of early psychosis patients. 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 into a distinct network, while lower modularity scores indicate lower cohesion. Using a similar approach, we previously demonstrated decreased modularity and broad hypoconnectivity in hippocampal networks in chronic schizophrenia patients (28). Because hippocampal deficits are already prominent at the earliest stages of illness, we hypothesized that early psychosis would also be associated with decreased modularity and widespread network hypoconnectivity. To determine whether hippocampal network connectivity changes during the early stage of illness, we used a prospective 2-year longitudinal study design to examine hippocampal network function across the initial years of illness. Patients completed a neuroimaging assessment within the first two years of illness and follow-up assessments every 8 months for two years. We hypothesized early psychosis patients would show greater
hippocampal network hypoconnectivity over two years, in line with findings of broad hypoconnectivity in chronic illness.
METHODS AND MATERIALS

Participants

Participants (N=140) were 68 individuals in the early stage of a psychotic disorder and 72 healthy control participants enrolled between May 2013 and February 2018 into a prospective 2-year longitudinal neuroimaging study. Most participants (57 early psychosis, 66 healthy control) were included at two or more visits. Details regarding participant attrition are included in the supplement. Groups were recruited with the goal to have similar age, gender, race and parental education (Table 1). Early psychosis patients included in the analysis had similar demographic and clinical characteristics as those who were excluded.

Patients in the early stage of a psychotic disorder (< 2 years following psychosis onset) were recruited from the Vanderbilt Psychiatric Hospital inpatient units and outpatient clinics. To specifically target early neuropathology (51), the majority of early psychosis patients were recruited during the initial months following onset (mean = 7 months ± 6, range = 1-24 months). Diagnoses were determined using the Structured Clinical Interview for the DSM-IV-TR (SCID) (52; 53), augmented by extensive review of all available medical records, and finalized by a senior psychiatrist (SH) during diagnostic consensus meetings. Patients were required to meet criteria A for schizophrenia at study entry. Only patients with either schizophreniform disorder or schizophrenia/schizoaffective disorder (referred to as schizophrenia going forward) at 2-year follow-up were included in this analysis. Healthy control participants were recruited from the community via advertisements. Exclusion criteria for all participants were < 16 or > 65 years of age, premorbid IQ < 75, a history of significant head injury, major medical or neurological
illness, any contraindications for MRI scanning, substance abuse within the past month, and uncorrected vision deficits. In addition, healthy control participants were excluded for any history of Axis I disorders or prior psychotropic medication use, or a first-degree relative with a psychotic illness.

Data from participants in this cohort have been included in previous reports (6; 7; 19; 54–60), but the functional connectivity analyses presented here are novel. All participants provided written informed consent and received monetary compensation for their time. The study was approved by the Vanderbilt University Institutional Review Board, Nashville, TN.

**Clinical measures**

Diagnostic assessments were collected during in-person interviews at study entry and 2-year visits. The onset of psychosis symptoms was determined using the Symptom Onset Scale (SOS) (61). The duration of psychosis was calculated as the time between symptom onset and study enrollment. Chlorpromazine (CPZ) equivalent doses were calculated for patients on antipsychotic medication (62; 63). Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001) (64; 65). Clinical symptom severity was assessed at each study visit using the Positive and Negative Syndrome Scale (PANSS) (66; 67), the Hamilton Depression Rating Scale (HAM-D) (68), and the Young Mania Rating Scale (YMRS) (69). Clinical and cognitive characteristics are reported in Table 1 and Supplementary Table 3.

**Imaging data**
**Acquisition and preprocessing.** High resolution T1-weighted structural and 7-minute echo-planar resting-state functional magnetic resonance imaging (rs-fMRI) data were collected at each study visit. Imaging data were acquired on two identical 3T Philips Intera Achieva MRI scanners using a 32-channel head coil at the Vanderbilt University Institute for Imaging Science. Images were processed on the Vanderbilt University Institute of Imaging Science Center for Computational Imaging XNAT platform (70) in MATLAB (version 2018a) using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Resting-state data were motion corrected, coregistered to the subject’s structural image, and normalized to an MNI T1 template image (see supplement for full preprocessing details).

**Data quality.** Data quality and exclusions are detailed in the supplement. Overall motion in the sample was low (median framewise displacement (FD) = .042 mm) and was higher in healthy control participants than patients ($p = .002$). To ensure differences did not influence graph theory comparisons, FD was included as a covariate of no interest for all between-group comparisons.

**Modularity analysis**

**Regions of interest.** Hippocampal network connectivity was calculated for two pre-defined networks: 1) a core hippocampal-MTLC network consisting of the hippocampus, rhinal cortex, and parahippocampal cortex (71); and 2) an extended hippocampal-cortical network consisting of functionally-connected prefrontal, posterior parietal, temporal, thalamic, and amygdala regions that interact with the core hippocampal network to support hippocampally-guided...
behavior (72–74). The hippocampal-MTLC network had 12 regions of interest (ROIs) divided into two a priori modules/communities (left and right, separately). The hippocampal-cortical network had 66 ROIs divided into 4 modules/communities (left-right and anterior-posterior, separately). Community assignments are detailed by anatomical brain region in Supplementary Table 1 and visualized in Figure 1. To provide a comparison to the hippocampal network, connectivity was also calculated for the visual network (75) (Supplementary Table 2). The visual network was chosen in light of considerable visual processing (76) and visual ROI connectivity (77; 78) deficits in schizophrenia.

**Network construction.** Networks were calculated for a 66 x 66 region connectivity matrix. For each subject, temporal connectivity was obtained by extracting the average time-series for each ROI and calculating the ROI-to-ROI Pearson’s correlation coefficients. To remove potential sources of noise, fMRI signal was bandpass filtered (0.01 to 0.10 Hz) and 12 motion parameters, 6 principle components of white matter and CSF, and mean gray matter timeseries signal were removed (79). Correlation coefficients were Fischer r-to-z transformed and corrected for the number of time points. Both positive and negative connections were considered connectivity in brain networks. The absolute value of connections was calculated to create a non-negative graph matrix. Connectivity matrices were thresholded for noise ($r \geq .2$) and binarized to create unweighted networks. The number of retained edges was similar between groups ($p = .99$). Functional connectivity matrices are displayed in Supplementary Figure 2.
Network architecture. The architecture of hippocampal networks was investigated as described below. First, communities were assigned a priori as shown in Supplementary Table 1 and modularity (Q), or cohesion, of each network was calculated according to Newman’s metric (80). Second, to examine communication within hippocampal networks, we calculated characteristic path length, global efficiency, and degree density. Short characteristic path length, high global efficiency, and low degree density indicate ability to communicate quickly across the network as a whole (81; 82). Finally, we calculated the nodal descriptive statistics of degree (number of connected edges) and local efficiency to identify ROIs with altered nodal properties associated with module integrity. To evaluate the stability of networks over connection strengths, graph matrices were thresholded 80-99% sparsity, corresponding to values ranging from mild to strong connectivity (|r| ~ .34-.57). For all network measures, area under the curve (AUC) across sparsity levels and served as the dependent variables in the models described below. Visual network modularity was calculated using methods described above (see Supplement for full details).

Statistical analysis

Statistical analyses were conducted in Statistical Analysis System (SAS Studio, version 3.8). Hippocampal network modularity served as the dependent variable in the primary analysis. Effects of group, time, and the interaction of group by time were modeled using linear mixed effects analyses, with group included as a fixed factor, time included as a repeated factor (t0 = study entry, t1 = t0 + 8 months, t2 = t0 + 16 months, t3 = t0 + 24 months), and participant as a random factor. FD, race, and scanner were included as covariates of no interest. For linear
mixed effects models, hypothesis tests were performed using Satterthwaite’s adjustment for degrees of freedom and Cohen’s $d$ effect sizes were calculated according to (83). Secondary analyses of network communication (characteristic path length, global efficiency, and degree density) and nodal characteristics (degree and local efficiency) were conducted using the primary model described above, with each serving as the dependent variable. Three exploratory linear mixed effects analyses were conducted to examine associations between clinical features and hippocampal network modularity, with modularity entered as the dependent variable, clinical feature (duration of illness, PANSS subscale scores, or HAM-D score) and time included as the independent variable, and FD, race, and scanner included as covariates of no interest. Duration of illness models did not include a time covariate. Spearman correlations tested for associations between modularity, demographic variables, and clinical features within visits. Associations were considered significant at $p \leq .05$. 
RESULTS

Demographic and clinical features

Demographic and clinical characteristics are presented in Table 1. For simplicity, comparisons of study entry vs. 2-year clinical characteristics are presented; comparisons across all four study visits produced similar results and can be found in Supplementary Table 3. The early psychosis sample was young (mean age = 21, range = 16 – 31), primarily male (79%), white (76%), and educated (mean years of education = 13, range = 9 – 22). Psychosis and depression symptom severity decreased significantly over time ($ps \leq .007$). Fewer patients were taking antipsychotic medication at follow-up visits compared to study entry ($p = .02$), although among those taking medication, chlorpromazine equivalent dosage was similar across visits ($p = .34$).

Hippocampal networks

Modularity. Modularity values were higher in early psychosis patients than healthy control participants, with significant differences detected in the hippocampal-MTLC network ($F_{1,136} = 3.95$, $\beta = -0.005$, StdErr = 0.003, $d = 0.29$, $p = 0.05$; Figure 1). Higher modularity in patients was largely driven by elevated group values at study entry ($t_0$, control vs. patient: $t = -1.77$, $d = .25$, $p = .08$); later time points were similar across groups ($t_1–t_3$, control vs. patient: $ps \geq .39$).

Hippocampal-MTLC network modularity decreased over time in all participants ($F_{3,240} = 2.79$, $\beta = 0.014$, StdErr = 0.005, $d = 0.39$, $p = 0.04$; no group x time interaction), with the largest decrease occurring between $t_0$ and $t_1$ ($t_0$ vs. $t_1$: $t = 3.02$, $p = .003$; $t_1$ vs. $t_2$: $t = -1.53$, $p = .13$; $t_2$ vs. $t_3$: $t = 0.59$, $p = .56$). In contrast, modularity of the hippocampal-cortical network was similar between groups and did not differ over time ($ps \geq .12$). In comparison, visual network modularity was
stably elevated in early psychosis patients (F_{1,136} = 10.27, β = -.009, StdErr = 0.003, d = 0.60, p = .002; no time or time × group interaction, ps ≥ .59). Comparing elevations at study entry, between-group effects were similar for the hippocampal-MTLC (d = .25) and visual networks (d = .30) (Supplementary Results).

Network characteristics. To understand the dynamics that contribute to elevated hippocampal-MTLC network modularity in early psychosis, we next examined measures of network communication. Early psychosis patients had a greater number of connections per node (degree: F_{1,136} = 7.38, β = -0.17, StdErr = 0.08, d = 0.42, p = .007) and greater local efficiency of connections (F_{1,136} = 12.23, β = -0.01, StdErr = 0.004, d = 0.56, p < .001) compared to healthy control participants (Figure 2). The overall density of connections also tended to be higher in patients than healthy control participants (degree density: F_{1,136} = 3.66, β = -0.016, StdErr = 0.01, d = 0.27, trend p = .06; Supplementary Figure 5). Similar to modularity, local efficiency was highest at study entry and lower at all subsequent visits (F_{3,242} = 9.28, β = 0.03, StdErr = 0.005, d = 0.84, p < .001). Hippocampal-MTLC modularity was strongly correlated with the number and local efficiency of connections (ps ≤ .001). Full statistical results are detailed in the supplement. Together, these findings indicate the hippocampal-MTLC network is more densely integrated in early psychosis patients than in healthy individuals.

Clinical correlates of hippocampal network modularity

To understand why hippocampal-MTLC network modularity was elevated in patients at study entry but normalized over follow-up visits, we performed exploratory analyses to test two
competing hypotheses: that network modularity 1) varied with symptom severity (i.e., clinical state); or 2) decreased with greater duration of illness (i.e., clinical stage). Analyses across PANSS subscales (positive, negative, general) revealed that positive symptom severity was selectively associated with modularity values (PANSS-positive, $F_{1,105} = 5.16, p = .03$; PANSS-negative and general subscale $p_s \geq .25$; Figure 3). Follow-up analysis of the PANSS positive subscale showed that higher PANSS-positive symptoms significantly predicted higher modularity ($F_{1,104} = 5.81, p = .02$; Figure 3). There was no linear interaction between positive symptoms and time. To determine whether higher PANSS-positive symptoms at study entry drove associations, PANSS-positive scores at study entry were included as a covariate in the linear mixed model. Controlling for the association between modularity and positive symptom severity at study entry, higher positive symptoms significantly predicted higher modularity across visits in patients (PANSS-positive, $F_{1,90} = 4.31, p = .04$). This suggests higher modularity at any visit was associated with higher positive symptom severity, regardless of severity at study entry. The association was similar when including duration of illness or HAM-D score as a covariate, and neither covariate independently predicted modularity in patients (duration of illness: $F_{1,106} = 1.03, p = .31$; HAM-D: $F_{1,101} = 1.45, p = .23$). Examining correlations at individual time points, we found that positive symptom severity was positively correlated with hippocampal-MTLC modularity at study entry and 16-month follow-up ($t0: r = .31, p = .02$; $t1: r = -.02, p = .92$; $t2: r = .36, p = .04$; $t3: r = .10, p = .48$, Supplementary Table 11). Duration of illness was not correlated with hippocampal-MTLC modularity ($p_s \geq .20$). Taken together, these findings suggest variation in hippocampal-MTLC connectivity over visits is explained by changes in positive symptom severity, not increasing duration of illness. Hippocampal-MTLC network
modularity was also positively correlated with CPZ dose at study entry (t0: $r = .30, p = .05$), but was not correlated with age, subject education, premorbid IQ, duration of illness, or mood symptoms ($ps \geq .27$). Including CPZ dose as a covariate in the model did not alter the association between positive symptoms and modularity.
DISCUSSION

Our goal was to characterize hippocampal network connectivity over two years in the early stage of psychosis. We found that resting-state hippocampal functional connectivity in a core MTL network was strengthened in acute early psychosis patients, with stronger connectivity positively correlated with severity of positive symptoms. In contrast, we did not observe alterations within a broader hippocampal-cortical network. Hippocampal-MTLC network hyperconnectivity normalized longitudinally and was associated with improvement in positive symptoms. Collectively, these results highlight a potential neuroimaging marker for identifying abnormal connectivity in early psychosis patients that relates to clinical symptom severity and clinical improvement, and provides insights into hippocampal network dynamics during the early stages of psychosis.

Schizophrenia is associated with progressive, but likely non-linear, declines in hippocampal structure across different illness stages (6; 15; 17; 19; 20). Hippocampal function may also vary by illness stage (84; 85). A primary goal of this study was to determine whether hippocampal network connectivity was disrupted in the early stage of a psychotic disorder. Contrary to our hypothesis of predominantly lowered connectivity, we identified a pattern of elevated hippocampal-MTLC network cohesiveness in early psychosis patients, with the magnitude of elevations similar to that of the visual network. Visual processing deficits (76) and connectivity abnormalities in early visual processing regions(77; 86; 87) are prominent in schizophrenia. Hippocampal network elevations are consistent with findings of interneuron hypofunction in patients with schizophrenia (5; 18; 88) which could lead to hippocampal hyperactivity (7),
elevated glutamatergic tone (13), and sustained hippocampal signaling (55; 56) in early illness. Given that hyperconnectivity has been associated with psychosis symptoms and cognitive impairments (89), abnormally elevated integration of hippocampal-MTLC functional connections is likely indicative of a pathological state arising from disinhibition in the hippocampus.

Contrary to our hypothesis of widespread deficits, we did not detect connectivity differences across the broader hippocampal-cortical network. One possible explanation is widespread deficits develop in later illness stages as a result of a prolonged period of abnormal hippocampal signaling which entrain abnormal communication within cortical regions (90), culminating in widespread asynchronous communication (24). Alternatively, it’s possible that medication effects normalize hippocampal-cortical interactions during early illness (34; 35; 91; 92). As the vast majority of patients in this study were taking antipsychotic medication during one or more study visit (94%), we were unable to test whether hippocampal-cortical modularity values differed in those not exposed to antipsychotics, although modularity values were not associated with antipsychotic dose. Importantly, connectivity within the MTL may not be normalized even with antipsychotic treatment (91), suggesting hippocampal-MTLC connectivity may represent a core illness-related feature of psychosis.

The second key goal of the study was to determine whether hippocampal network connectivity changes over two years of follow-up. Longitudinal analyses revealed three key findings: 1) hippocampal-MTLC hyperconnectivity normalized in our longitudinal sample, with connectivity
in early psychosis patients resembling that of healthy control participants at two-year follow-up; 2) connectivity was not associated with duration of illness at study entry and normalization was not associated with progression of illness; and 3) connectivity normalization was correlated with improvement in psychosis symptoms over longitudinal follow-up. Together, these findings suggest hippocampal-MTLC network hyperconnectivity may be a marker of current clinical state. Alterations in hippocampal function and connectivity have been proposed as a foundational mechanism in the formation of psychotic symptoms (93–95). Abnormally elevated resting activity in the hippocampus and MTLC, particularly parahippocampal cortex, has been associated with the presence or severity of positive symptoms in schizophrenia by a number of studies (96–100). Additional findings have linked alterations in hippocampal structure and function to the pathophysiology of positive symptoms in traumatic brain injury (101; 102), stroke (103), Alzheimer’s disease (104), and temporal-lobe epilepsy (105–107), indicating a central, transdiagnostic role for the hippocampus in the formation of positive symptoms. Longer duration of active psychosis has been associated with lower rates of remission and delayed treatment response (108), indicating acute psychosis may reflect an ongoing pathophysiological process (109; 110). Our findings suggest hippocampal-MTLC network connectivity may be a neurobiological process amenable to early interventions (90).

We need to consider several limitations to our study. First, given the drawbacks of data-driven approaches in delineating the hippocampal network, we used an anatomically-guided approach. Cortical nodes were comprised of regions that showed functional connectivity with the parahippocampal and perirhinal cortex in an independent sample (72). This approach excluded some direct hippocampal connections (e.g., ventral striatum) (111) that are altered in
early psychosis. Second, hippocampal-MTLC network connectivity decreased across visits in all participants, which may reflect hippocampal habituation (112) to repeated scanning and/or lowered state anxiety (113) across visits. Future longitudinal studies may consider using naturalistic viewing during resting state acquisitions to limit arousal confounds (114), and the collection of state-based anxiety measures during scanning. Third, graph theory metrics show increased reliability with longer rs-fMRI acquisitions (i.e., 20-100 minutes) (115). Future studies may consider longer acquisition times, although shorter acquisitions (e.g., 7 minutes, as acquired here) can be helpful in minimizing in-scanner head motion, a major confound for rs-fMRI analyses (116). Finally, as the majority of patients were taking antipsychotic medications during the study, alterations in connectivity related to disease state and medication use are intrinsically linked. As antipsychotic use affects hippocampal connectivity (34; 35), additional longitudinal studies of hippocampal network function in medication-naive patients are warranted.

In conclusion, this study established functional connectivity was elevated within a core hippocampal-MTLC network in early psychosis and associated with the severity of positive symptoms. Hippocampal hyperconnectivity normalized longitudinally and predicted clinical improvement. These results suggest hippocampal-MTLC hyperconnectivity may be a useful biomarker development target (23). Quantitative metrics of hippocampal network function may be particularly useful in the classification of psychosis patients by clinical stage (117) and prediction of treatment response (35). Longer-term prospective studies are necessary to
determine whether additional hippocampal connectivity changes occur during progression to chronic stages of psychosis.
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FINANCIAL DISCLOSURES

The authors report no biomedical financial interests or potential conflicts of interest.
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FIGURE LEGENDS

Figure 1. (A) Hippocampal networks are visualized on medial and lateral brain surfaces. (B) Area under the curve (AUC) of modularity values across sparsity thresholds (80 – 99%) are plotted as lsmean by group and time. Early psychosis patients had higher modularity than healthy control participants in the hippocampal-MTLC network driven by elevated modularity at study entry (t0). (C) Modularity values increased at higher sparsity thresholds across participants and for both hippocampal networks. Elevations in early psychosis patients were greater at higher thresholds. (D) Modularity values in the hippocampal-MTLC network significantly decreased over time in early psychosis patients, with the largest decrease occurring between study entry (t0) and 8-month follow-up (t1). Modularity remained stable from 8-month through 2-year follow-up (t1-t3). Error bars are 95% confidence intervals. Asterisks indicate significant effects.

Figure 2. (A) Network graphs are displayed for the early psychosis and healthy control groups at study entry (t0). Graphs were drawn in Gephi (https://gephi.org/) using the Yifan Hu Multilevel layout algorithm on the weighted network at 90% sparsity. Node sizes and connection weights are scaled by number and weight of connections, respectively. Node color denotes the assigned network. To reduce the number of connections visualized, displayed connections are present in ≥ 20% of individuals. (B) On average, mean degree and local efficiency of the hippocampal-MTLC network was higher in early psychosis patients than healthy control participants. Error bars are 95% confidence intervals.
Figure 3. (A) Positive symptoms were highest at study entry (t0) and were significantly lower at all subsequent visits (t1-t3). (B) Associations between hippocampal-MTLC modularity, clinical state, and illness duration are visualized across visits. More severe positive symptoms in individual participants were associated with corresponding elevations in modularity of the hippocampal-MTLC network. In contrast, increasing duration of illness over study visits was not associated with changes in hippocampal-MTLC modularity. Dotted lines are 95% confidence intervals. Asterisks indicate significant effects.
Table 1. Participant characteristics.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Early Psychosis, n = 68</th>
<th>Healthy Control, n = 72</th>
<th>Early Psychosis vs. Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, years</td>
<td>21 ± 3.3</td>
<td>22 ± 2.8</td>
<td>( F_{1,110} = 0.76 ) ( p = .38 )</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>79%</td>
<td>74%</td>
<td>( \chi^2 = 0.65 ) ( p = .42 )</td>
</tr>
<tr>
<td>Race, White/Black/Other</td>
<td>52/15/1</td>
<td>56/12/4</td>
<td>( \chi^2 = 2.17 ) ( p = .34 )</td>
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<tr>
<td>Ethnicity, % Non-Hispanic</td>
<td>99%</td>
<td>93%</td>
<td>( \chi^2 = 2.55 ) ( p = .11 )</td>
</tr>
<tr>
<td>Handedness, % right</td>
<td>94%</td>
<td>92%</td>
<td>( \chi^2 = 0.32 ) ( p = .57 )</td>
</tr>
<tr>
<td>Premorbid IQ, WTAR</td>
<td>103 ± 15.0</td>
<td>113 ± 9.7</td>
<td>( F_{1,130} = 19.67^* ) ( p &lt; .001^* )</td>
</tr>
<tr>
<td>Participant’s education, years</td>
<td>13 ± 2.2</td>
<td>15 ± 1.9</td>
<td>( F_{1,120} = 13.66 ) ( p &lt; .001^* )</td>
</tr>
<tr>
<td>Parental education, years</td>
<td>15 ± 2.8</td>
<td>15 ± 2.3</td>
<td>( F_{1,120} = 0.54 ) ( p = .66 )</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Study entry, n = 52(^a)</th>
<th>2-year follow-up, n = 56</th>
<th>Study entry vs. 2-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, SZF/SZ/BP(^c)</td>
<td>35/14/3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duration of illness, months</td>
<td>7.2 ± 5.9</td>
<td>1 – 24</td>
<td>31.8 ± 5.7</td>
</tr>
<tr>
<td>CPZ, mg</td>
<td>337 ± 155.9</td>
<td>75 – 750</td>
<td>299 ± 197.2</td>
</tr>
<tr>
<td>Antipsychotic treatment, %</td>
<td>85%</td>
<td>–</td>
<td>64%</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>66 ± 20.7</td>
<td>34 – 114</td>
<td>52 ± 15.1</td>
</tr>
<tr>
<td>PANSS-Positive</td>
<td>16 ± 7.0</td>
<td>7 – 36</td>
<td>13 ± 4.7</td>
</tr>
<tr>
<td>PANSS-Negative</td>
<td>17 ± 7.1</td>
<td>7 – 33</td>
<td>12 ± 6.2</td>
</tr>
<tr>
<td>PANSS-General</td>
<td>32 ± 9.6</td>
<td>18 – 59</td>
<td>27 ± 7.0</td>
</tr>
<tr>
<td>HAM-D</td>
<td>11 ± 8.0</td>
<td>1 – 29</td>
<td>7 ± 6.3</td>
</tr>
<tr>
<td>YMRS</td>
<td>2 ± 4.1</td>
<td>0 – 19</td>
<td>2 ± 3.0</td>
</tr>
</tbody>
</table>

Demographic data are presented for included study participants. Note: WTAR, Wechsler Test of Adult Reading; SZF, schizotypal form; SZ, schizophrenia; BP, bipolar disorder with psychotic features; CPZ, chlorpromazine equivalent; PANSS, Positive and Negative Syndrome Scale; HAM-D, Hamilton Depression Rating Scale-17 item; YMRS, Young Mania Rating Scale. Asterisk (\(^*\)) denotes significant \( p \)-values (\( p \leq 0.05 \)).

\(^a\) All data meeting quality thresholds were included. Exclusions are detailed by visit and group in the supplement.

\(^b\) All participants met criteria for a schizophrenia-spectrum disorder diagnosis at 2-year follow-up.

\(^c\) WTAR scores are reported for native English speakers (early psychosis, \( n = 66 \); healthy control, \( n = 65 \)).

\(^d\) One patient missing HAM-D and YMRS at study entry.