Medial Temporal Lobe Structures and Hippocampal Subfields in Psychotic Disorders
Findings From the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study

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IMPORTANCE Structural alterations in the hippocampus and other medial temporal lobe regions have been observed in schizophrenia. How these alterations and hippocampal subfields might differ across the psychosis spectrum remains unclear.

OBJECTIVES To characterize medial temporal lobe structures, including hippocampal subfields, using magnetic resonance imaging and to examine their relation to psychosis and cognitive function across the psychosis spectrum.

DESIGN, SETTING, AND PARTICIPANTS Case-control, cross-sectional neuroimaging study in a large series of probands with psychotic disorders and healthy volunteers as part of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Patients with psychotic disorders (schizophrenia, n = 219; schizoaffective disorder, n = 142; and psychotic bipolar disorder, n = 188) and healthy controls (n = 337) were recruited across ambulatory clinics at university health centers in the B-SNIP consortium.

MAIN OUTCOMES AND MEASURES Medial temporal lobe and hippocampal subfields were quantified with an automated parcellation approach using FreeSurfer software. Memory and other cognitive parameters were assessed using standardized neuropsychological tests.

RESULTS Hippocampal volume reductions were seen in all 3 diagnostic groups when compared with healthy controls; alterations in the entorhinal cortex and parahippocampal regions were limited to schizophrenia and schizoaffective disorders (P < .001). Smaller volumes across the hippocampal subfields were seen in all 3 psychotic disorders, with the most prominent differences being in cornu ammonis 2/3 (P < .001). Hippocampal volumes were positively correlated with psychosis severity, declarative memory, and overall cognitive performance (P < .05).

CONCLUSIONS AND RELEVANCE Alterations in the hippocampus were evident across psychotic disorders. Hippocampal subfields that participate in memory-related processes supporting pattern separation and pattern completion might be abnormal and may underlie the pathophysiology of psychosis.
Despite more than a century of research, the pathophysiology of psychotic disorders remains unclear. 1-4 Neuroanatomical5-7 and functional (in vivo neuroimaging) studies have identified the medial temporal lobe (MTL) as a key area of alteration in psychoses, especially schizophrenia (SZ). 6-10 Volumetric alterations in the hippocampus have been characterized as a hallmark feature of SZ, although alterations have been observed in the parahippocampal gyrus and the entorhinal cortex (EC) as well. 3,4,11-13 These alterations appear in first-episode SZ,10,11 and in those at familial risk for this illness,13,14 and may progress in severity during the course of illness. 15,16

Psychosis has been theorized to result from cognitive mistakes that may stem from a hippocampally mediated failure to discriminate between present and past memory experiences; 7,18; the MTL and its subregions, which have been classically implicated in declarative memory; 19,20 (which is impaired in SZ), are therefore of particular relevance in studies of pathophysiology of psychoses. The hippocampus comprises cornu ammonis 1 through 4 (CA1-4), dentate gyrus (DG), and subiculum. The parahippocampal cortex (PHC) and EC surround the hippocampus and serve as its primary inputs. Subfields in the hippocampal formation such as the DG and CA3 play key roles in encoding distinct representations (pattern separation) and associating previous memory traces with current input (pattern completion). 17 The EC stores modulatory sensory input, while the aforementioned input is compared with older memory traces to distinguish between novel and familiar information. 6,7 The parahippocampal region assimilates novel information with longer-term contextual information. 19,21,22 It has been suggested that deficits in these regions, ie, a failure of DG-mediated pattern separation, and increased CA3-mediated pattern completion may result in spurious associations of memories, ultimately manifesting as psychosis. 17 Verbal declarative or explicit memory (the conscious recollection of words, stories, or events), known to be impaired in SZ, is of importance in understanding the neural substrates of psychoses. 7,23 Investigating structural alterations among the subfields of the hippocampal complex may therefore help in understanding the pathophysiology of psychoses.

Alterations in the MTL in patients with bipolar disorder are inconsistent, with most studies showing either modest or no change. 3,25,26 However, smaller hippocampi have been observed among patients with psychotic bipolar disorder (BPP) but not in patients with nonpsychotic bipolar disorder. 9 This raises the question of whether MTL and hippocampal alterations cut across a range of psychosis spectrum disorders or whether they align with the traditional separation between SZ and bipolar disorder, a dichotomy whose biological validity remains to be established after more than a century of study. 1 Interestingly, there appears to be a medication effect, with patients with bipolar disorder taking lithium showing no hippocampal reductions. 7,27 Larger well-characterized samples are clearly needed to address this question.

The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, which assessed endophenotypes across the psychotic spectrum, provided a unique opportunity to study the relationship between psychosis, cognition, MTL, and hippocampal subfields in a large sample of individuals with psychotic disorders. Recent advances in image processing28 allow precise parcellation of the hippocampal subfields. We hypothesized that (i) the hippocampal subfield alterations would be most prominent in SZ and schizoaffective disorder (SZA) and least in BPP, (ii) patients with psychosis would demonstrate significant alterations in the volumes of the DG, CA2/3, PHC, and EC, with the most widespread alterations in SZ, and (iii) deficits in these regions would correlate with positive symptoms and declarative memory. To test these hypotheses, we examined volumes of the hippocampal subfields, PHC, and EC in patients with SZ, SZA, and BPP.

Methods

Study Participants
This study included clinically stable probands with SZ (n = 219), SZA (n = 142), or BPP (n = 188) as well as 337 healthy controls (HCs) recruited as part of the B-SNIP consortium, a 6-site collaboration (Wayne State University, Harvard University, Maryland Psychiatric Research Center, University of Chicago/University of Illinois at Chicago, University of Texas Southwestern Medical Center at Dallas, and the Institute of Living/Yale University).

Inclusion criteria were the following: (1) ages 15 to 65 years; (2) sufficient proficiency in English at the sixth-grade level or higher; (3) no significant neurologic disorders including those secondary to head injury; (4) no history of substance abuse within the last month or substance dependence within the last 6 months; and (5) negative urine toxicology screening results on the day of testing. The HCs met the following additional criteria: (1) no personal or family history (first degree) of psychotic or bipolar disorders; (2) no personal history of recurrent mood disorder; (3) no lifetime history of substance dependence; and (4) no history of any significant cluster A Axis II personality features defined by meeting full criteria or within 1 criterion of a cluster A diagnosis using the Structured Interview for DSM-IV Personality. 29 Institutional review boards at each of the 6 sites approved the study, and all sites used identical diagnoses, clinical, and recruitment techniques. 30 All participants provided written informed consent. All but 88 patients (SZ, n = 17; SZA, n = 19; BPP, n = 52) were taking antipsychotics and 82 patients (SZ, n = 13; SZA, n = 16; BPP, n = 53) were taking lithium. Antipsychotic dosing equivalents were computed using the method of Andreasen et al.31

Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders. 32 Symptom ratings were completed using the Positive and Negative Syndrome Scale (PANSS), 33 the Montgomery-Asberg Depression Rating Scale, 34 and the Young Mania Rating Scale. 35 Cognition was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS). 36 The BACS composite score indexed overall cognition, and the list-learning measure was used to assess verbal declarative memory.
Structural Magnetic Resonance Imaging

High-resolution isotropic T1-weighted magnetization-prepared rapid acquisition with gradient echo scans were performed (scanning parameters are listed in eAppendix in Supplement). All images underwent rigorous data quality control, which was performed blind to participant identity. Fifty-one participants were excluded from this analysis owing to severe motion artifacts or scanner inhomogeneity (HC, n = 10; SZ, n = 22; SZA, n = 10; BPP, n = 9). Images were converted to Neuroimaging Informatics Technology Initiative format and checked for scanner artifacts by trained raters. Images were then run through a first-level autoreconstruction in FreeSurfer version 5.1 software. The skull-stripped brains were checked for remaining dura or sinuses that could interfere with accurate segmentation. When nonbrain tissue was found, trained raters blinded to clinical data edited images manually. All raters (I.M., N.T., A.N.F.) had interrater reliabilities and intrarater reliability (intraclass r) greater than 95%. When deemed sufficiently clean for segmentation by an independent rater, images were run through second- and third-level autoreconstruction, in which gray matter surface area, thickness, and volume measures were extracted.

Automated hippocampal subfield segmentation was carried out using a separate processing pipeline included in the FreeSurfer software package. The subfield regional volumes that are extracted include CA1, CA2/3, CA4/DG, presubiculum, subiculum, hippocampal fissure, and fimbria. This method, which uses a Bayesian probabilistic model to automatically segment the hippocampus, has been validated with manual morphometric measurements of ultra-high-resolution magnetic resonance imaging scans. The model uses prior distributions from hippocampal image data to generate predictions about where neuroanatomical labels typically occur throughout the image. Voxel measurements of the subfields were \(0.5 \times 0.5 \times 0.5\) mm\(^3\).

Statistical Analysis

Outliers were handled by removing participants with data showing more than 4 SDs from the mean (HC, n = 5; SZ, n = 5; SZA, n = 0; BPP, n = 2). Participants between the third and fourth SD (HC, n = 18; SZ, n = 16; SZA, n = 7; BPP, n = 11) were winsorised to the third SD. When appropriate, a 1-way analysis of variance and \(\chi^2\) tests were used to test for differences between groups in demographic and clinical variables. First, contrasts comparing HCs with probands were run on the MTL region using age, sex, site, race and intracranial volume as covariates. The mean age of our sample was 37.3 years (HC, 37.2 years; SZ, 35.1 years; SZA, 35.7 years; BPP, 36.1 years). The groups did not differ by age \((F = 1.32; \ P = .27)\) but showed significant sex \((F = 54.6; P < .001)\), race \((F = 48.1; P < .001)\), and site \((F = 62.1; P < .001)\) effects; thus, these variables were included as covariates in our analysis. There were group differences in intracranial volume \((F = 6.5; P < .001)\). No site by group or sex by group interactions were seen for any regional gray matter measures.

MTL Volumes

Hippocampal volumes were significantly reduced bilaterally when comparing all probands and HCs (Table 1). Bilateral hippocampal volume reductions were also present between individual diagnostic groups and HCs. Somewhat smaller bilateral reductions in mean parahippocampal gyrus volume were observed in all probands when compared with HCs. The SZ and SZA groups showed a bilateral reduction in parahippocampal gyrus volume but the BPP group showed no difference when compared with HCs. Reductions in mean EC volumes were observed only on the left side for the SZA group compared with HCs. No differences in bilateral EC volumes were observed when SZ and BPP groups were compared with HCs.

Hippocampal Subfields

Having observed significant group differences in the hippocampus, we proceeded with subfield analyses. Bilateral hippocampal subfields showed widespread differences across all probands with statistically significant reductions of mean volume in CA1, CA2/3, CA4/DG, presubiculum, and subiculum (Table 2 and Figure 1).

When individual diagnostic groups were compared with HCs, significant volume reductions were found in the SZ group bilaterally in CA2/3, CA4/DG, presubiculum, subiculum, and CA1. Compared with HCs, the SZA group displayed statisti-
We did not find any correlations between chlorpromazine equivalent antipsychotic dosage and hippocampal subfield volumes ($r = -0.02$ to $0.07$). A total of 495 probands (SZ, n = 129; BPP, n = 172) had imaging and PANSS data (Table 3 and Figure 2). We observed significant (Hochberg-corrected) negative correlations between hippocampal volume and symptom severity. The left hippocampus, CA4/DG, presubiculum, and subiculum correlated negatively with PANSS positive subscale and hallucinations item scale scores ($r = -0.16$ to $-0.11$). There was a significant negative correlation between the left CA2/3 and hallucinations item scale score ($r = -0.12$ and $-0.13$, respectively). The right hippocampus and subiculum were also negatively correlated with PANSS positive subscale score ($r = -0.12$ and $-0.13$, respectively). The right subiculum negatively correlated with delusions item scale score ($r = -0.12$).

**Clinical and BACS Correlations**

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A total of 472 probands (SZ, n = 192; SZA, n = 119; BPP, n = 161) and 286 HCs had imaging and BACS data. We observed a significant difference between HCs and probands in BACS composite ($P < .001$) and BACS list-learning ($P < .001$) scores. Positive significant correlations between hippocampal volumes, BACS composite score, and BACS list-learning score were seen in probands but not HCs. The hippocampus and all hippocampal subfields demonstrated significant positive correlations with the BACS composite score ($r = 0.09$ to 0.19). Bilaterally, the hippocampus positively correlated with BACS list-learning score ($r = 0.14$). The left CA1, CA2/3, CA4/DG, and subiculum also positively correlated with BACS list-learning score ($r = 0.11$ to 0.14).

Discussion

We observed widespread volumetric reductions in the hippocampus and its subfields in probands with psychosis compared with HCs, consistent with and extending numerous previous observations.41-43 Widespread MTL volumetric reductions were seen in SZ and SZA consistent with prior literature.42,44 While patients with BPP did not show alteration in other MTL regions, hippocampal volume reductions were evident; this observation in a large sample is particularly important and helps address the inconsistent findings in previous BPP literature.45

The observed volume reductions in the hippocampus and hippocampal subfields across diagnostic groups suggest that smaller hippocampal volumes may be a common trait shared across the psychosis spectrum. Consistent with a recent study by Kühn et al,46 we observed a significant relationship between hippocampal subfield volumes and psychotic symptoms. However, these correlations were weak, perhaps resulting from the relatively small variance in psychotic symptoms in our sample, which consisted mainly of patients stabilized with antipsychotics.

As predicted, we noted an association, albeit modest, between bilateral hippocampal volumes and composite cognitive score as well as verbal declarative memory in probands. The association was strongest for the overall hippocampus and for the subiculum. However, all subregions other than the
Figure 2. Relationship of Left Hippocampal Volume With Brief Assessment of Cognition in Schizophrenia (BACS) Composite and List-Learning Scores

Scatterplot of individual-specific data for all participants and diagnostic group correlations. A, Correlation between BACS composite scores (z scale) and left hippocampal volume, with healthy controls (HCs) separate from probands. B, Correlation between list-learning scores (z scale) and left hippocampal volume, with HCs separate from probands. BPP indicates psychotic bipolar disorder; SZ, schizophrenia; and SZA, schizoaffective disorder.
presubiculum showed significant associations in the predicted direction in the probands (smaller volumes, worse performance) and not in HCs, suggesting that hippocampal volumes are linked to the cognitive deficits associated with psychosis.

The observed relationships between hippocampal structure and psychosis on the one hand and with declarative memory on the other hand are consistent with the view that psychosis may be related to alterations in a number of nodes of the associative memory network in the hippocampal formation. While all subfields showed structural volume reductions across probands, these were most prominent in the CA2/3, DG, and subicular regions. The hippocampus mediates the encoding of new memories and the retrieval of old memories. Distinct hippocampal structures may play different roles in the process of memory encoding and retrieval. Pattern separation, the flexible distinction of multiple memory constructs from highly similar stimuli, is thought to be carried out by the DG and CA2/3 and establishes distinct memory. Pattern completion involves retrieval of full memory from partial stimuli cues via the process of associative recognition thought to be mediated through CA2/3 and CA1 augmented by the trisynaptic pathway. Spurious associations may arise owing to a partial failure of the DG, thus leading to increased and inaccurate CA2/3 activity and consequently to the production of psychotic symptoms. The subiculum is thought to serve 2 functions salient to the manifestation of psychosis: (1) hippocampal gating of dopamine-mediated information flow from the prefrontal cortex, and (2) inhibition of the hypothalamic-pituitary-adrenal axis. Both systems have been described extensively elsewhere. The altered subiculum function might lead to (1) failure of dopaminergic gating with a net increase in mesolimbic dopaminergic activity, and (2) dysregulation (exaggeration) of the hypothalamic-pituitary-adrenal axis-mediated stress response. Excessive hypothalamic-pituitary-adrenal axis activity may in turn contribute to hippocampal atrophy. These changes together may be part of the causative chain leading to psychosis in the context of spurious information processing and the attendant misinterpretation of neutral sensory inputs caused by the EC, PHC, DG/CA4, and CA2/3 regions. Structural alterations in the parahippocampus and EC, which provide most of the input to the hippocampus, may also be pertinent in the manifestation of psychosis, although their precise role remains to be understood.

Causal mechanisms involved in the pathogenesis of the observed hippocampal abnormalities remain unclear. We found that bilateral volume reductions in CA2/3 were shared across all diagnostic groups, with the SZ and SZA groups showing the most impairment. Hippocampal alterations have been thought to result from developmentally mediated disruptions in glutamatergic excitatory and/or inhibitory interneurons leading to synaptic or dendritic pathology. Recent reports identify glutamate genes to be implicated in both SZ and BPP. Interestingly, another recent study suggests that hippocampal volume reduction in SZ is correlated with increases in glutamatergic metabolites (glutamine/glutamate). While focused investigations into hippocampal glutamate among patients with BPP are still needed, perturbations in hippocampal glutamate may play a part in the shared CA2/3 volume reductions observed across the psychosis spectrum. Imaging studies in SZ have identified increases in baseline blood perfusion and decreases in task-related activation in the hippocampus, thought to be related to impaired glutamatergically mediated synaptic plasticity. Such neuropathological alterations could potentially result from genetic factors interacting with environmental influences.

Few studies have definitively examined whether in vivo hippocampal subfield morphology can serve as an endophenotypic marker. Evidence for hippocampal alterations in unaffected relatives, evidence for moderate heritability of hippocampal volumes, and our recent observation of hippocampal subfield alterations among first-degree relatives of patients with SZ support this view. Investigation of genomic correlates of brain structure can help further examine this question.

To our knowledge, this is the first report of changes in hippocampal subfield volumes and related MTL structures across the psychotic spectrum. A major strength is the use of an automated parcellation approach. While manual region-of-interest tracing remains the gold standard for morphometric studies, it is time-consuming, making it impractical for large-sample studies. Semiautomated FreeSurfer whole-brain and hippocampal subfield segmentations have been rigorously tested and proven to produce reliable measurements. Larger subfields such as CA2/3 and CA4/DG correlate well with manual volume segmentations; smaller subfields produced less reliable segmentations and were not considered for analysis. Another strength is the large, clinically well-characterized sample of patients across DSM diagnoses within the psychosis spectrum.

Our study was cross-sectional and most patients were receiving medications. Because medication effects may not necessarily be linear, use of chlorpromazine equivalents alone as a way to address this confound has limitations. Future studies need to examine hippocampal subfield data prospectively before and after introduction of antipsychotics in previously untreated patients. We did not have a sample of patients with nonpsychotic bipolar disorder, which could have more definitively clarified the nature of hippocampal alterations in bipolar disorders. Finally, our imaging parameters were not optimized for imaging hippocampal subfields as in the study by Van Leemput et al, which used long acquisition times and frequent averaging to yield high signal-noise ratios. Future studies of hippocampal structure need to use more rigorous image acquisition and multimodal techniques to elucidate structure-function relationships. Despite these limitations, our samples are some of the largest to date, we tested specificity among the psychoses, and we used the most sophisticated tool for subdividing the hippocampus to date.

Conclusions

This study firmly establishes the hippocampus as one of the key nodes in the pathway to psychosis. Understanding the functional consequences and etiological underpinnings of these alterations will likely facilitate better prediction and targeted intervention in psychoses.
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