Hippocampal Subfield Alterations Across the Psychotic Disease Spectrum

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Hippocampal Subfield Alterations
Across the Psychotic Disease Spectrum

Tova M. Gardin
Abstract

Psychiatry stands at a pivotal point of development. With the advent of brain imaging modalities, descriptive diagnostic criteria have been called into question. Psychotic disorders, historically dichotomized into “schizophrenia” and “bipolar disorder,” and the intermediate “schizoaffective disorder,” have been shown to overlap in clinical symptomatology, familial inheritance, and genetic association studies. Scientific investigation of disease pathogenesis provides an opportunity to develop biological diagnostic criteria from the ground upwards – correlating anatomy, pathophysiology, genetics, and symptomatology. In this context, structural MRI studies have the capacity to shed light on structural abnormalities underlying psychotic disorders (schizophrenia, schizoaffective disorder, and psychotic bipolar disorder) and contribute to the development of a comprehensive mechanistic model of disease. Neuropathological and in vivo neuroimaging studies have identified the temporal lobe as a key area of alteration in schizophrenia, but large-scale studies examining the hippocampal volumes of patients across the psychotic spectrum have not yet been performed. Further, until recently, the manual labor and error involved in parcellating hippocampal subfield volumes made the task unfeasible. New automatic parcellation techniques enable the analysis of hippocampal subfield volumes among patients with schizophrenia, schizoaffective disorder, and bipolar disorder.

The objectives of our study were to: (1) investigate using magnetic resonance imaging hippocampal volume in addition to entorhinal cortex volume, parahippocampal gyrus volume, and hippocampal subfield volumes in patients with schizophrenia, schizoaffective disorder, and bipolar disorder; and, to (2) correlate volumetric alterations with clinical metrics of psychosis and cognition. We utilized a case-control cross-sectional design to collect data from patients with schizophrenia (n=219), patients with schizoaffective disorder (n=142), patients with psychotic bipolar disorder (n=188), and healthy controls (n=337). Freesurfer image analysis software was utilized to automatically parcellate and quantify hippocampal, hippocampal subfield, entorhinal cortex, and parahippocampal gyrus volumes. Clinical ratings and neuropsychological tests were administered as well to assess positive symptoms and cognition. Bilateral hippocampal volume alterations were noted among patients with all three psychotic disorders, while alterations in the surrounding medial temporal lobe regions were noted only in schizoaffective disorder and schizophrenia, but not in patients with bipolar disorder. While widespread hippocampal subfield volume alterations were noted in schizophrenia and schizoaffective disorder, only the cornu ammonis 2/3, dentate gyrus, and subicular regions were noted to be altered across all three psychotic disorders. The most prominent alterations were noted in the cornu ammonis 2/3. Hippocampal volumes were negatively correlated with psychosis and positively correlated with measures of declarative memory. Findings suggest that alterations in the hippocampus are present across psychotic disorders and may contribute to the pathogenesis of psychosis. In particular, alterations in the cornu ammonis, an area which supports memory pattern completion, and in the dentate gyrus, an area which supports memory separation may play a role in the pathophysiology of psychosis.
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Glossary

ADNI  Alzheimer’s Disease Neuroimaging Initiative
ANOVA  Analysis of Variance
BACS  The Brief Assessment of Cognition in Schizophrenia
BPP  Bipolar Disorder with Psychosis
CA  Cornu Ammonis
DG  Dentate Gyrus
DNMS  Delayed Nonmatch to Sample Task
DSM  *The Diagnostic and Statistical Manual of Mental Disorders*
EC  Entorhinal Cortex
HC  Healthy control
MADRS  Montgomery Asberg Depression Rating Scale
MPRAGE  Magnetization-prepared rapid acquisition with gradient echo
MTL  Medial temporal lobe
NIFTI  Neuroimaging Informatics Technology Initiative
NMDA  N-methyl-D-aspartate
NS  Not significant
PANSS  The Positive and Negative Syndrome Scale
SD  Standard deviation
<table>
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Summary

Psychosis presents across a wide range of psychiatric conditions, and yet, its pathophysiologic mechanism remains principally an enigma. Whether presenting as a cardinal feature of schizophrenia and schizoaffective disorder or as an associated symptom of bipolar disorder, the clinical presentations are remarkable in their consistency across a myriad of disease spectrums. Given the similarity of the phenotypic presentation of psychosis across dissimilar clinical syndromes, further exploration into the etiology of psychosis is warranted.

This paper suggests the presence of common and distinct medial temporal lobe structural abnormalities within the psychotic disease spectrum. This pattern has not been previously elucidated due to an unavailability of advanced neuroscientific imaging tools. With the use of recently developed, improved voxel-wise analysis tools, our group was able to conduct a detailed study of differentiated regions in the hippocampus, which we hypothesized together comprise a core localization of abnormality across differing clinical psychotic syndromes. We identified a marked decrease in hippocampal volume in the cornu ammonis 3 and dentate gyrus across patients experiencing psychotic symptoms, regardless of the specific DSM disorder with which they had been formally diagnosed. These findings lend support to the theory that psychosis is generated as a result of dysfunction in the glutamate-driven “trisynaptic pathway” via a decrease in pattern separation in the dentate gyrus and an increase in pattern completion in the cornu ammonis 3. Our findings further highlight the hippocampus’ unique role in processing...
spatially bound memory, distinguishing between representations, and completing memory traces from partial inputs, and the possible role of alterations in these functions in the generation of delusions and hallucinations. With the generation of psychotic thought content, individuals suffering from schizophrenia are unable to recognize that these erroneous pattern completions, translated as psychotic memories, are self-generated and not in accord with reality.

Further research has suggested that the inability to distinguish self-generated stimuli from external stimuli is associated with dysfunction of the frontal lobe and the connections between the frontal and medial temporal lobes in individuals with schizophrenia\textsuperscript{1–5}. Related abnormalities of corollary discharge have also been described\textsuperscript{6}. Taken together, this constellation of findings suggests that psychosis is related to an aberrant activation in specific hippocampal subregions, coupled with a failure of insight due to dysfunction in the frontal lobe. Support for a model of psychosis based on dysfunction in the glutamate driven trisynaptic pathway of the hippocampus may provide targets for novel antipsychotics that aim to increase glutamatergic activity in the dentate gyrus and decrease neuronal firing in the cornu ammonis 3.
Introduction

Epidemiology of Schizophrenia and Bipolar Disorder

Psychotic disorders confer significant morbidity and mortality, with schizophrenia and bipolar disorder each independently accounting for two of the top ten leading causes of disability in the world\textsuperscript{7,8}. The WHO estimates the global annual incidence of schizophrenia to range from 16-40/100,000/annum\textsuperscript{9} and studies have found a lifetime prevalence of schizophrenia of 4.0 per 100,000 persons\textsuperscript{10}. The lifetime prevalence of bipolar disorder has been estimated to be approximately 2,100 per 100,000 persons\textsuperscript{11}. Prevalence estimates of schizoaffective disorder have been challenged by shifting diagnostic criteria, though investigators in Finland have estimated that schizoaffective disorder occurs at a lifetime prevalence of 320 per 100,000 persons\textsuperscript{12–14}.

Mortality is high across bipolar disorder and schizophrenia as individuals with schizophrenia suffer from a death rate more than twice that of the general population\textsuperscript{15,16}, and individuals with bipolar disorder demonstrate a mortality rate 35\% greater than the general population\textsuperscript{17}. Patients with schizophrenia are estimated to commit suicide at a rate twelve times that of the general population and to suffer from increased mortality from general medical conditions, such as cardiovascular disease\textsuperscript{15,16}. Similarly, patients with bipolar disorder have been found to commit suicide at a rate more than ten times that of the general population\textsuperscript{18}. Direct costs of schizophrenia are conservatively estimated to account for 1.6\%-2.6\% of the total healthcare expenditure in Western countries\textsuperscript{19}. 
Psychotic Symptoms and Clinical Phenomenology

*The Diagnostic and Statistical Manual of Mental Disorders* defines schizophrenia by the presence of two or more of the following criteria over the majority of a one-month period with a significant decrease in level of functioning and impairment persistent for at least six months: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and diminished emotional expression or avolition (“negative symptoms”), and at least one of these must be amongst the first three symptoms\(^2\). Schizoaffective disorder is similarly defined by the latter criteria concurrent with a major mood episode (major depressive or manic), a major mood episode present for the majority of the duration of the illness, and at least two weeks in which delusions or hallucinations are present in the absence of mood symptoms\(^2\). Finally, bipolar disorder is defined by the experience of at least one episode of mania lasting at least one week or shorter in the event of hospitalization, or at least one major depressive episode lasting at least two weeks and an episode of hypomania lasting for a minimum of four days\(^2\). For the purposes of this investigation, bipolar patients were recruited only if they possessed a diagnosis of bipolar disorder with psychotic features. In this case, psychotic features, as defined by the *DSM* included: (1) hallucinations, perceptual experiences in the absence of external stimuli; or, (2) delusions, fixed beliefs despite contradicting evidence\(^{20,21}\).

Towards a Biologically Based Model of Psychotic Disorders

Despite the severe social and economic burden of disease, and with more than a century of research, the underlying pathophysiology of schizophrenia and other psychotic
disorders remains unclear, hindering the development of a rational treatment model. Historically, schizophrenia has classically been defined as a distinct clinical syndrome, as have schizoaffective disorder and bipolar disorder\textsuperscript{22,23}. However, genetic and genealogic data suggest that there is considerable overlap among these conditions, with interrelated heritability patterns and common risk genes\textsuperscript{24–26}. In addition, all three disorders share the phenotypic manifestation of psychosis, a disease presentation whose pathophysiology may offer clues to the underlying mechanisms of disease across these syndromes.

**Hippocampal Volumetric Changes Observed in Patients with Psychotic Disorders**

Structural MRI studies have the capacity to shed light on structural abnormalities underlying varied psychotic disorders (schizophrenia, bipolar disorder, schizoaffective disorder), and therefore can contribute to the development of a comprehensive biological model of psychotic disease. *In vivo* neuroimaging studies have identified the temporal lobe as a key area of alteration in schizophrenia and psychotic bipolar disorder\textsuperscript{27–30}. Volumetric alterations in the hippocampus have been characterized as a hallmark feature of schizophrenia, although alterations have also been observed in the parahippocampal gyrus and the entorhinal cortex\textsuperscript{29,31–33}. While this paper focuses on the MTL, other changes in neocortical regions have been described elsewhere as well\textsuperscript{34}. The MTL
alterations appear in first episode schizophrenia\(^1\) and in those at familial risk for this illness\(^32,36\), and may progress in severity over the course of illness for those with an existing diagnosis of schizophrenia\(^15,16\).

Hippocampal Role in Declarative Memory

Since the bilateral resection of Henry Molaison’s (“Patient H.M.”) hippocampi and the studies that subsequently ensued, the hippocampus has been recognized as the cerebral seat of memory\(^37\). However, Cohen and Squire’s\(^38\) work in the 1980’s revealed that the hippocampus is specifically involved in declarative memory, i.e., the summation of episodic and semantic memories. Animal studies, such as those that involve the DNMS task\(^2\), demonstrate that the hippocampus is not required for immediate memory\(^39\), while studies of H.M. suggest that the hippocampus is also unnecessary in the storage and retrieval of distant memories\(^37\). Instead, the hippocampus functions to accept memories encoded by the neocortex and temporarily held by the parahippocampus, comparing these with present and prior stimuli, contextualizing them, and weaving them into a larger

---

1 Studies evaluating structural alterations in Bipolar Disorder have been fewer in number and often underpowered\(^28,35\). Studies of larger sample size are needed to properly characterize structural brain changes across the entire psychotic spectrum.

2 The “Delayed Nonmatch to Sample” task presents subjects with a single stimulus termed the “sample.” The sample is then removed, and after a short time delay, the subject is presented concurrently with the “sample” and an alternative stimulus. The subject is then prompted to select the alternative stimulus, or the “nonmatch to sample.” Animals with hippocampal damage typically perform well on the DNMS task\(^39\).
network of memory organization\textsuperscript{39–41}. The hippocampus is also responsible for transitive inference, or the deduction of relations between two inputs that have not been explicitly compared, as well as for retrieval of memory traces based on partial inputs\textsuperscript{40,42}. Finally, the hippocampus is recognized for its unique role in constructing spatial maps and binding memories to a three dimensional representation of reality\textsuperscript{39}. In 1971, O’Keefe and Dostrovsky described hippocampal “place cells,” i.e., hippocampal pyramidal cells that increase their firing rate as rats traverse a particular location\textsuperscript{43}. Specifically, as the rats reached the precise physical location, increased cell firing rates were observed, even if one or two spatial cues had been removed or altered\textsuperscript{43,44}.

\textbf{Hippocampal Subfields and Proposed Individual Roles in Memory Formation and Re-activation}

Recent advances in imaging resolution have enabled a more nuanced study of the individual components of the hippocampus and their contribution to declarative memory. The hippocampus lies within the medial temporal lobe, is comprised of the cornu ammonis 1-3 (CA 1-3), dentate gyrus (DG), and subiculum, and is surrounded by the perirhinal, parahippocampal, and entorhinal cortex (EC)\textsuperscript{42,45}. The perirhinal and postrhinal cortices input polysensory information to the entorhinal cortex\textsuperscript{45}. From here, hippocampal circuitry is characterized by a unidirectional glutamate driven pathway, termed the “trisynaptic pathway”\textsuperscript{40,42,45} (Figure 1). Through this circuit, information which has entered the entorhinal cortex travels via the perforant pathway to the dentate gyrus\textsuperscript{40,42,45}. From the dentate gyrus, the information travels to the CA3 via the mossy...
fibers, and finally projects to the CA1 via the Schaffer Collaterals. Information then leaves the trisynaptic pathway and enters the subiculum and the deep layers of the entorhinal cortex, before projecting back to areas of the cortex from which the information originated.

This hippocampal loop may provide a means for memories to be encoded, and later recalled, modified, and re-encoded through processes that include consolidation, reconsolidation, and retrieval. It provides an opportunity for memory networks to be fluid, continually altered with new information and related inputs. It is theorized that each subfield of the hippocampus contributes differentially to this process. During the process of encoding, the dentate gyrus is thought to play a key role in pattern separation, whereby novel experiences are encoded as distinct representations apart from those of similar events. For example, in a recent study of mice lacking the N-methyl-D-aspartate (NMDA) receptor NR1 in the dentate gyrus granule cells, NR1 knockout mice were unable to distinguish between similar contexts and were found to demonstrate a freezing response both in rooms in which they had repeatedly received shocks and in rooms where no shock had been administered. By contrast, wild type mice demonstrated a freeze response only in the room in which a shock had been administered. Results of the study highlight the importance of glutamate signaling in the dentate gyrus for proper pattern separation.

While the dentate gyrus is thought to be involved in the process of “pattern separation,” the CA3, with its many recurrent synapses, has been theorized to be integral
to the process of “pattern completion.” During memory trace retrieval, CA3 retrieves and builds upon flexible memory traces via inferential reasoning, source memory, and association\textsuperscript{46}. In a study performed by Nakazawa\textsuperscript{48} and colleagues, mice lacking the NMDA receptor NR1 subunit in pyramidal CA3 cells were able to form and retrieve spatial memory without deficit when performing the Hidden Platform version of the Morris Water Maze Task\textsuperscript{3}. However, when three out of four of the extramaze cues were removed, control mice continued to seek escape by searching near the phantom platform, while knockout mice remained near their point of release at the center of the pool. In this “partial cue removal” task, control mice were able to utilize the remaining cues to retrieve the full memory of the task at hand while mice with altered glutamate signaling in the CA3 were unable to employ the single extramaze cue to generate a complete representation of the phantom platform task. In this way, the CA3 is integral to the process of pattern completion, generating or retrieving a complete memory trace from selective component inputs.

A Model for Psychosis Based on Alterations in Hippocampal Subfield Function

Patients with schizophrenia have long demonstrated impairments in declarative memory, ostensibly related to hippocampal dysfunction\textsuperscript{49,50}. It is hypothesized however, that...
that alterations in the hippocampi of patients with schizophrenia and other psychotic disorders may give rise to psychosis as well\textsuperscript{46}. Specifically, a reduction in glutamate signaling in the dentate gyrus and in its efferent projections to the cornu ammonis 3 (via the mossy fibers) would lead to diminished DG-mediated pattern separation, enhanced CA3-mediated pattern completion, and a reduced threshold for long-term potentiation in CA3. This lowered threshold for long-term potentiation in turn would evoke heightened neuronal excitability. The imbalance between pattern separation and pattern completion (with enhancement of pattern completion) would then foster increased illogical associations and false memories, some of which would be stored as psychotic content. As mentioned above, the hippocampus is also uniquely situated to generate multisensory spatial-bound representations.

In addition to cognitive theory, histologic and neurochemistry findings add substantial support for this model. Research suggests that glutamate signaling is significantly decreased in the dentate gyrus and the mossy fibers of individuals with schizophrenia. For example, reduced NMDAR1 mRNA is seen postmortem in the dentate gyrus of patients with schizophrenia as compared to normal controls\textsuperscript{51}. Reduced expression of mRNA encoding for non-NMDA glutamate receptors is likewise seen in several areas of the hippocampus, including the dentate gyrus, CA3, subiculum, and CA4\textsuperscript{52}. Decreases in mossy fiber synapses and a reduction in neurogenesis in the dentate gyrus have also been reported in individuals with schizophrenia\textsuperscript{53–55}. These findings may be more robust in individuals with predominantly positive symptom presentations\textsuperscript{54}; however, the research remains indeterminate\textsuperscript{55}. Finally, research has demonstrated that
decreased sensory input to a given site lowers the long term potentiation threshold, leading to increased neuronal excitability and greater long term potentiation with minimal input\textsuperscript{56–58}. This finding would support a model in which a decrease in signaling in the dentate gyrus and mossy fibers would induce heightened neuronal excitability in the CA3 and a resulting increase in pattern completion. In turn, the increase in pattern completion and decrease in pattern separation would result in false completion and the storage of memories with psychotic content. Given the unique capacity of the hippocampus and its place cells to generate spatially-bound representations, these false psychotic memories would be situated to be perceived as reality.

Studies of patients with schizophrenia have repeatedly demonstrated impaired connectivity between the frontal lobe and the medial temporal lobe\textsuperscript{1–4}. In turn, frontal lobe alterations in patients with schizophrenia have been associated with an impaired ability to distinguish between self-generated stimuli and external stimuli\textsuperscript{5}. In keeping with the proposed model, it may be posited that psychotic content is generated in the medial temporal lobe via the mechanisms described above, and due to alterations in the frontal lobe and impaired connectivity between the frontal and medial temporal lobes, individuals with psychotic disorders are unable to discriminate psychotic content as false and self-generated. This model of hippocampal alterations giving rise to psychosis is further supported by findings that patients with postictal psychosis in epilepsy demonstrate bitemporal and bifrontal hyperperfusion during episodes of psychosis\textsuperscript{59,60}. Functional neuroimaging of psychosis in schizophrenia have implicated these MTL regions as well\textsuperscript{3,61–67}. 

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Although theoretical, histologic and neurochemistry findings offer support for the proposed model, until recently, \textit{in vivo} analysis of the hippocampal subfields in individuals with psychotic disorders was not feasible. New advances in neuroimaging techniques, however, enable a detailed analysis of the hippocampal subfield volumes in individuals with a wide range of psychotic disorders. To date, no other large-scale study has examined the hippocampus and its hippocampal substructures \textit{in vivo} in individuals with disorders across the psychotic disorder spectrum.

\section*{Methods}

\textbf{Study participants}

This study included clinically stable probands\textsuperscript{4} with SZ (n=219), SZA (n=142), or BPP \textsuperscript{5} (n=188), as well as 337 healthy controls 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, and the Institute of Living/Yale University).

\textsuperscript{4} The term “probands” refers to patients with SZ, SZA, and/or BPP.

\textsuperscript{5} Patients with BPP have a history and diagnosis of bipolar disorder with psychotic features; however, this does not indicate that patients were actively psychotic at the time of testing. All patients (with BPP, SZ, and SZA) had a history of psychosis, though not all patients were psychotic at the time of testing.
Inclusion criteria were the following: (1) ages 15-65 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\textsuperscript{68}. Institutional review boards at each of the 6 sites approved the study, and all sites used identical diagnostic, clinical, and recruitment techniques. All participants provided written informed consent. All but 88 (SZ, n=17; SZA, n=19; BPP, n=52) patients were taking antipsychotics and 82 (SZ, n=13; SZA, n=16; BPP, n=53) were taking lithium. Antipsychotic dosing equivalents were computed using the method of Andreasen et al\textsuperscript{69}.

Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders\textsuperscript{70}. Symptom ratings were completed using the Positive and Negative Syndrome Scale (PANSS)\textsuperscript{71}, the Montgomery-Asberg Depression Rating Scale (MADRS)\textsuperscript{72}, and the Young Mania Rating Scale (YMRS)\textsuperscript{73}. Cognition was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS)\textsuperscript{74}. 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 were performed. 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 auto-reconstruction in FreeSurfer version 5.1 software. The skull stripped brains were checked for remaining dura or sinuses that could interfere with accurate segmentation. When non-brain tissue was found, trained raters blinded to clinical data edited images manually. All raters (I.M., N.T., A.F.) had intrarater reliabilities (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.

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6 MPRAGE scans were obtained following the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (http://www.loni.ucla.edu/ADNI) with the following parameters: TR=6.7 msec, TE= 3.1 msec, 8° flip angle, 256x240 matrix size, total scan duration=10:52.6 minutes, 170 sagittal slices, 1mm slice thickness, 1x1x1.2 mm3 voxel resolution.
Automated hippocampal subfield segmentation was carried out using a separate processing pipeline included in the FreeSurfer software package\textsuperscript{75}. The subfield regional volumes that are extracted include: CA1, CA2/3, CA4/DG, presubiculum, subiculum, hippocampal fissure, and fimbria\textsuperscript{76}. 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 utilizes prior distributions from hippocampal image data to generate predictions about where neuroanatomical labels typically occur throughout the image\textsuperscript{76}. Voxel measurements of the subfields were 0.5x0.5x0.5 mm\textsuperscript{31}.

**Statistical Analyses**

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 standard deviation\textsuperscript{77}. 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 and intracranial volume as covariates \textsuperscript{39}. If the resulting $P$ value of a composite structure was less than 0.05, subregions within the composite structure were tested, adjusting the number of regions within each composite structure with the Hochberg method\textsuperscript{78}. For regions showing a trending difference ($P<0.05$) at the proband level, a
contrast comparing HCs with each diagnostic group was run, adjusting for number of contrasts with the Hochberg method. Regions assessed bilaterally within the hippocampus include CA1, CA2/3, CA4/DG, presubiculum, and subiculum. The parahippocampal region included the parahippocampal gyrus and EC. As shown by Van Leemput et al, measurements of smaller subfields may be unreliable; therefore, we did not include the hippocampal fissure, fimbria, hippocampal tail, and regions where subfields are not discernable. Effect sizes (Cohen $d$) were calculated using pooled standard deviations and residualized means adjusted for covariates.

Partial Spearman rank correlations were used to investigate the relationships of symptom severity and cognition with hippocampal volumes, controlling for age, sex, intracranial volume, and site. Relationships with symptom severity were assessed using the PANSS. Measures used for analysis were PANSS Positive subscale, item 1 (delusions), and item 3 (hallucinations). Relationships with cognition were assessed using the $z$-scaled BACS composite and sum of list-learning tasks. A 1-way analysis of variance was used to test differences between HCs and probands in the BACS composite and list-learning tasks while controlling for age, sex, site, and intracranial volume.

**Results**

Our final sample included of 886 subjects (HC, $n=337$; SZ, $n=219$; SZA, $n=142$; BPP, $n=188$), consisting of 416 males (HC, $n=152$; SZ, $n=145$; SZA, $n=62$; BPP, $n=57$) and 470 females (HC, $n=185$; SZ, $n=74$; SZA, $n=80$; BPP, $n=131$). 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 a significant sex ($F=54.6; P<.001$), race ($F=48.1; P<.001$) and site effects ($F=62.1; P<0.001$); 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 gyral 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.
Table 1

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<td>3986.1</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>0.39***</td>
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<td></td>
<td>(23.9)</td>
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<td>(34.8)</td>
<td>(31.5)</td>
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<td>(29.1)</td>
<td>(26.3)</td>
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<tr>
<td>Entorhinal Cortex</td>
<td>1174.6</td>
<td>1140.8</td>
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<td></td>
<td>(11.4)</td>
<td>(13.8)</td>
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<td>(15.2)</td>
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<tr>
<td><strong>Right Hemisphere</strong></td>
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<tr>
<td>Hippocampus</td>
<td>4124.6</td>
<td>3955.5</td>
<td>3947.7</td>
<td>3995.6</td>
<td>&lt;0.001</td>
<td>0.33***</td>
<td>&lt;0.001</td>
<td>0.39***</td>
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<td>(23.8)</td>
<td>(28.9)</td>
<td>(34.6)</td>
<td>(31.4)</td>
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<td></td>
<td>2181.6</td>
<td>2096.8</td>
<td>2110.8</td>
<td>2130.2</td>
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<td>0.003</td>
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<td>(18.4)</td>
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<tr>
<td>Entorhinal Cortex</td>
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<td>1015.1</td>
<td>1023.3</td>
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<td>0.60</td>
<td>0.02</td>
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<tr>
<td></td>
<td>(11.4)</td>
<td>(13.9)</td>
<td>(16.6)</td>
<td>(15.3)</td>
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</table>

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 2**).

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 statistically significant volume reductions bilaterally in the CA1, CA2/3, CA4/DG, presubiculum, and subiculum. The most prominent reductions were in SZ bilaterally in CA2/3, subiculum,
and CA4/DG. Compared with HCs, the BPP group displayed bilateral volume reductions in CA2/3. The presubiculum was significant only on the left side. The CA4/DG and the subiculum were significant only on the right side.

Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>HC</th>
<th>SZ</th>
<th>SZA</th>
<th>BPP</th>
<th>HC vs Proband</th>
<th>HC vs SZ</th>
<th>HC vs SZA</th>
<th>HC vs BPP</th>
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<tr>
<td></td>
<td>Mean (SE), mm$^3$</td>
<td></td>
<td></td>
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<tr>
<td>CA1</td>
<td>319.59 (2.38)</td>
<td>311.06 (2.9)</td>
<td>308.3 (3.47)</td>
<td>316.88 (3.14)</td>
<td>0.15***</td>
<td>0.20**</td>
<td>0.26***</td>
<td>NS</td>
</tr>
<tr>
<td>CA2/3</td>
<td>956.46 (6.95)</td>
<td>916.21 (8.46)</td>
<td>924.29 (10.1)</td>
<td>936.88 (9.17)</td>
<td>0.22***</td>
<td>0.32***</td>
<td>0.26***</td>
<td>0.15*</td>
</tr>
<tr>
<td>CA4/DG</td>
<td>535.25 (3.79)</td>
<td>514.92 (4.62)</td>
<td>516.45 (5.53)</td>
<td>525.64 (5)</td>
<td>0.21***</td>
<td>0.29***</td>
<td>0.27**</td>
<td>NS</td>
</tr>
<tr>
<td>Presubiculum</td>
<td>463.6 (3.23)</td>
<td>452.61 (3.93)</td>
<td>449.79 (4.71)</td>
<td>451.06 (4.26)</td>
<td>0.19***</td>
<td>0.19</td>
<td>0.24*</td>
<td>0.21*</td>
</tr>
<tr>
<td>Subiculum</td>
<td>629.11 (4.06)</td>
<td>608.23 (4.95)</td>
<td>605.95 (5.93)</td>
<td>618.73 (5.37)</td>
<td>0.22***</td>
<td>0.28***</td>
<td>0.32***</td>
<td>NS</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>HC</th>
<th>SZ</th>
<th>SZA</th>
<th>BPP</th>
<th>HC vs Proband</th>
<th>HC vs SZ</th>
<th>HC vs SZA</th>
<th>HC vs BPP</th>
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<tr>
<td></td>
<td>Mean (SE), mm$^3$</td>
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</tr>
<tr>
<td>CA1</td>
<td>326.87 (2.28)</td>
<td>317.28 (2.78)</td>
<td>317.16 (3.33)</td>
<td>320.95 (3.01)</td>
<td>0.18***</td>
<td>0.23**</td>
<td>0.24*</td>
<td>NS</td>
</tr>
<tr>
<td>CA2/3</td>
<td>992.25 (6.61)</td>
<td>951.91 (8.05)</td>
<td>952.94 (9.64)</td>
<td>955.46 (8.73)</td>
<td>0.30***</td>
<td>0.34***</td>
<td>0.34***</td>
<td>0.31***</td>
</tr>
<tr>
<td>CA4/DG</td>
<td>552.27 (3.68)</td>
<td>530.83 (4.48)</td>
<td>530.51 (5.36)</td>
<td>534.05 (4.85)</td>
<td>0.28***</td>
<td>0.32***</td>
<td>0.33***</td>
<td>0.27***</td>
</tr>
<tr>
<td>Presubiculum</td>
<td>453.56 (3.2)</td>
<td>440.16 (3.9)</td>
<td>438.82 (4.67)</td>
<td>444.46 (4.23)</td>
<td>0.19***</td>
<td>0.23**</td>
<td>0.27**</td>
<td>NS</td>
</tr>
<tr>
<td>Subiculum</td>
<td>628.13 (3.93)</td>
<td>605.6 (4.78)</td>
<td>608.87 (5.72)</td>
<td>616.56 (5.18)</td>
<td>0.23***</td>
<td>0.32***</td>
<td>0.27**</td>
<td>0.16*</td>
</tr>
</tbody>
</table>

* p<0.05  
** p<0.01  
*** p <0.001

Clinical and BACS correlations

We did not find any correlations between chlorpromazine equivalent antipsychotic dosage and hippocampal subfield volumes ($r = -0.02$ to 0.007). A total of 495 probands (SZ, n=194; SZA, n=129; BPP, n=172) had imaging and PANSS data (Table 3). 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 ($r=-0.11$). The right hippocampus and subiculum were also negatively correlated with PANSS Positive subscale ($r= -0.12$ and $-0.13$, respectively). The right subiculum negatively correlated with delusions item scale score ($r=-0.12$).

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 ($P<0.001$) and BACS list-learning ($P<0.001$) scores. Positive significant correlations between hippocampal volumes, BACS composite score, and BACS list-learning score were in 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 $0.18$). 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 $0.14$).
Table 3

<table>
<thead>
<tr>
<th>Region</th>
<th>PANSS Positive</th>
<th>Item 1-Delusions</th>
<th>Item 3-Hallucinations</th>
<th>BACS Composite</th>
<th>BACS Verbal Memory</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
<td>r  p</td>
<td>r  p</td>
<td>r  p</td>
<td>r  p</td>
<td>r  p</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.16” 0.0021</td>
<td>-0.12” 0.031</td>
<td>-0.15” 0.0063</td>
<td>0.19”&lt;0.001</td>
<td>0.14” 0.010</td>
</tr>
<tr>
<td>CA1</td>
<td>NS  NS</td>
<td>NS  NS</td>
<td>NS  NS</td>
<td>0.10” 0.045</td>
<td>0.12” 0.035</td>
</tr>
<tr>
<td>CA2/3</td>
<td>NS  NS</td>
<td>NS  NS</td>
<td>-0.11” 0.030</td>
<td>0.16”&lt;0.0030</td>
<td>NS  NS</td>
</tr>
<tr>
<td>CA4/DG</td>
<td>-0.11” 0.049</td>
<td>NS  NS</td>
<td>-0.12” 0.026</td>
<td>0.15”&lt;0.0032</td>
<td>NS  NS</td>
</tr>
<tr>
<td>Presubiculum</td>
<td>-0.16” 0.0018</td>
<td>NS  NS</td>
<td>-0.13” 0.017</td>
<td>0.10” 0.023</td>
<td>NS  NS</td>
</tr>
<tr>
<td>Subiculum</td>
<td>-0.13” 0.013</td>
<td>NS  NS</td>
<td>-0.13” 0.021</td>
<td>0.16”&lt;0.0028</td>
<td>NS  NS</td>
</tr>
</tbody>
</table>

Discussion

This study is unique in numerous regards. First, this study is the first to examine hippocampal volume in a large sample size of patients across the psychotic spectrum. As a result of the patient populations studied, our findings are able to address alterations in patients not only with schizophrenia, but with schizoaffective disorder and bipolar disorder as well. Our analysis highlights unifying features of psychotic disorders as manifested across the range of relevant *DSM*-diagnoses. In addition, our study examines the individual hippocampal subfield volumes in patients with these disorders, advancing beyond previous spatial resolution limitations to further inform evolving models of the neuropathogenesis of psychosis.
Our study observed several conclusions about MTL involvement in the pathogenesis of psychotic disorders. First and foremost, volumetric alterations were consistently and uniquely observed in the hippocampi bilaterally across psychotic disorders, highlighting a possible contributing localization of psychosis. Notably, among those with bipolar disorder with psychotic features, only the hippocampus experienced volumetric changes, potentially contributing to the pathogenesis of psychotic derangements, whereas with schizophrenia and schizoaffective disorder, more widespread changes were observed across the medial temporal lobe. This finding strongly supports the model discussed earlier in which hippocampal alterations are involved not only in deficits in declarative memory, but also are integral to the pathogenesis of psychosis. These results suggest that psychosis is a derivative symptom of dysfunction in specific areas of the brain.

Focusing on specific subfields, the cornu ammonis 3 was noted to be consistently altered bilaterally across all the psychotic disorders studied, as was the right dentate gyrus. The specific pattern of alteration observed in this study, in which consistent alterations were observed in the cornu ammonis 3 and dentate gyrus across the psychotic spectrum, support the model postulated above. Decreased glutamate signaling in the dentate gyrus and mossy fibers leading to increased neuronal excitability in the cornu ammonis 3 with decreased pattern separation and increased pattern completion may lead to false completion of memories that are then stored with psychotic content. This psychotic content, which might ordinarily be recognized as aberrant internally-generated
thought content, may not be recognized as such by individuals with frontal lobe alterations. Prior research has suggested that individuals who suffer from schizophrenia have severe alterations in the frontal lobe and in connectivity between the frontal lobe and medial temporal lobe\(^1-4\). These alterations may cause an inability to distinguish between internally generated content and external stimuli. Further research should investigate the possibility of an interaction effect between frontal lobe subregions and hippocampal subfield volume alterations in psychotic disorders.

Some prior work has suggested that individuals with schizophrenia may experience lateralized changes in the hippocampus with more severe alterations in the left hemisphere\(^3^4\). Our finding of bilateral alterations in the hippocampi across probands does not lend support to this previous finding. However, laterality was observed with regard to the alterations in the dentate gyrus in individuals with bipolar disorder with psychotic features. Specifically, we noted statistically significant volume reductions in the right dentate gyri of individuals with BPP, but did not observe alterations in the left dentate gyri of BPP patients. The significance of this finding is not fully understand, but may point to a different role of right and left dentate gyri in the production of psychosis.

Though less robust than findings in the CA3 and DG, alterations in the right subiculum were also noted across the psychotic disorders studied. The significance of this finding is not entirely understood, as the subiculum's role has not been fully elucidated. However, alterations in the subiculum may be implicated in failure of dopamine-mediated gating of information flow from the prefrontal cortex to the
hippocampus. This dysregulation may contribute to the previously mentioned inability of patients with schizophrenia to accurately distinguish internal generated thought content as such.

In contrast to alterations noted in the psychotic disorders studied, alterations in the entorhinal cortex and the parahippocampal gyrus were noted only in patients with schizophrenia and schizoaffective disorder, but not in those with bipolar disorder. This finding suggests that alterations in the parahippocampal gyrus and entorhinal cortex may contribute to the development of psychosis or the cognitive deficits present in patients with these diseases, but that such alterations are not necessary for the generation of psychosis.

In addition, we noted a weak negative correlation between bilateral hippocampal volume and psychotic symptoms. Although the weakness of this finding may detract from the previously elucidated model, the probands in this study were primarily receiving appropriate pharmacotherapy for their psychotic symptoms. As a result, few of the studied probands were experiencing active psychotic symptoms at the time of the study, potentially confounding any observable effects. This finding, coupled with changes in hippocampal volume across the psychotic disorders studied, may suggest that the mechanism of antipsychotics targets mechanisms downstream from observable hippocampal change.
Aside from these psychotic changes noted in the probands, widespread hippocampal subfield volume alterations were associated with deficits in cognition (as assessed by the BACS composite score). These findings are consistent with the extensive literature noting that hippocampal volumes are closely related to overall declarative memory function.

**Limitations and Directions for Future Research**

This study and its limitations suggest a number of possible additional lines of fruitful inquiry. First, our study population was comprised only of individuals with psychosis and healthy controls. By design, we were thus unable to compare hippocampal volumes in patients with bipolar disorder with psychosis to those without associated psychosis. Distinct findings of CA3 and DG alterations in patient with psychosis as compared to those without psychosis would lend significant support to the proposed model. As noted earlier, the patients recruited for this study had already initiated pharmacotherapy. Though our analysis did not show an effect of antipsychotic dosages on hippocampal volumes, the use of chlorpromazine equivalents is an imperfect measure. This analysis did not include duration of psychosis, which can impact brain volumes. Future analyses should incorporate duration of illness as a covariate.

Finally, an additionally potentially interesting line of inquiry may involve the study of the interaction between frontal lobe subregion alterations and hippocampal subfield volume alterations, as well as additional relevant circuitry in the study of these
psychotic disorders. As mentioned above, alteration of the hippocampal subfields in concert with frontal lobe dysfunction may uniquely interact to generate the experience of psychosis. Positive findings from such an inquiry might have implications not only for schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, but may illuminate the mechanism of postictal psychosis as well.

**Conclusion**

In *Madness and Civilization*, Michel Foucault shared what was at the time a groundbreaking hypothesis that madness was ultimately defined subjectively by civilization\(^8\). Severe psychiatric illness has been thought to be defined subjectively by civilization, and more recently has been defined descriptively with clinically based guidelines. This study is part of a contemporary approach that seeks to develop mechanistic biomarkers that allow for the identification, characterization, and treatment of psychiatric disorders. Through demonstrating unique and consistent brain alterations across psychotic disorders, this study suggests that madness is not in fact a subjective function but rather an organic, biologic process with a discernible etiology and clearly diagnosable neurologic findings. Future research in a similar vein would not only have the impact of further reducing inconsistent, erroneous, and stigmatizing psychiatric diagnoses, it would also likely serve to advance the field of psychiatry towards rational therapeutic models in which specific neurobiological alterations become the defined targets for pharmacologic intervention.
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Appendix

Figures

Figure 1 The Trisynaptic Pathway

The "Trisynaptic Pathway" is a unidirectional glutamate-mediated pathway, which courses from the entorhinal cortex to the dentate gyrus, from the dentate gyrus to the cornu ammonis 3, and from the cornu ammonis 3 to the cornu ammonis 1. The dentate gyrus has traditionally been associated with the function of pattern separation, while the cornu ammonis 3 has been associated with pattern completion.
Figure 2 Hippocampal Subfields

Reproduced with the permission of JAMA Psychiatry. (A) FreeSurfer segmentation and location of
different subfields within the hippocampus. CA indicates cornu ammonis; DG, dentate gyrus. Effect sizes per group according to the Cohen $d$ color scale are shown for healthy controls (HCs) vs. probands (B), HCs vs. patients with schizophrenia (SZ) (C), HCs vs. patients with schizoaffective disorder (SZA) (D), and HCs vs. patients with psychotic bipolar disorder (BPP) (E).
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