Archival Report

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In Vivo Hippocampal Subfield Volumes in Schizophrenia and Bipolar Disorder

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ABSTRACT

BACKGROUND: Hippocampal dysfunction and volume reductions have been reported in patients with schizophrenia and bipolar disorder. The hippocampus consists of anatomically distinct subfields. We investigated to determine whether in vivo volumes of hippocampal subfields differ between clinical groups and healthy control subjects.

METHODS: Clinical examination and magnetic resonance imaging were performed in 702 subjects (patients with schizophrenia spectrum [$n = 210$; mean age, 32.0 ± 9.3 (SD) years; 59% male], patients with bipolar spectrum [$n = 192$; mean age, 35.5 ± 11.5 years; 40% male] and healthy control subjects [$n = 300$; mean age, 35.3 ± 9.9 years; 53% male]). Hippocampal subfield volumes were estimated with FreeSurfer. General linear models were used to explore diagnostic differences in hippocampal subfield volumes, covarying for age, intracranial volume, and medication. Post hoc analyses of associations to psychosis symptoms (Positive and Negative Syndrome Scale) and cognitive function (verbal memory [California Verbal Learning Test, second edition] and IQ [Wechsler Abbreviated Scale of Intelligence]) were performed.

RESULTS: Patient groups had smaller cornu ammonis (CA) subfields CA2/3 (left, $p = 7.2 \times 10^{-6}$; right, $p = 2.3 \times 10^{-6}$), CA4/dentate gyrus (left, $p = 1.4 \times 10^{-5}$; right, $p = 2.3 \times 10^{-6}$), subiculum (left, $p = 3.7 \times 10^{-6}$; right, $p = 2.8 \times 10^{-8}$), and right CA1 ($p = .006$) volumes than healthy control subjects, but smaller presubiculum volumes were found only in patients with schizophrenia (left, $p = 6.7 \times 10^{-5}$; right, $p = 1.6 \times 10^{-7}$). Patients with schizophrenia had smaller subiculum (left, $p = .035$; right, $p = .031$) and right presubiculum ($p = .002$) volumes than patients with bipolar disorder. Smaller subiculum volumes were related to poorer verbal memory in patients with bipolar disorder and healthy control subjects and to negative symptoms in patients with schizophrenia.

CONCLUSIONS: Hippocampal subfield volume reductions are found in patients with schizophrenia and bipolar disorder. The magnitude of reduction is greater in patients with schizophrenia, particularly in the hippocampal outflow regions presubiculum and subiculum.

Keywords: Hippocampus, MRI, Neuroanatomy, Psychosis, Subiculum, Verbal memory

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Schizophrenia and bipolar disorder have overlapping clinical characteristics (1), brain morphologic abnormalities (2), and genetic risk factors (3,4). Several lines of evidence suggest that the two disorders may represent two entities along a continuum of psychosis spectrum disorders (5). The pathophysiologic mechanisms of schizophrenia and bipolar disorder are unknown, but hippocampal dysfunction has been reported in both disorders (6,7). The hippocampus is a limbic structure located in the medial temporal lobe. It is involved in verbal memory functions and other complex behaviors, including stress responses, emotions, sensorimotor integrations, and goal-directed activity (8), all of which may be disrupted in schizophrenia and bipolar disorder.

Neuroanatomic in vivo magnetic resonance imaging (MRI) studies of patients with schizophrenia and bipolar disorder have demonstrated smaller hippocampal volumes in both disorders but with greater heterogeneity of findings in bipolar disorder (2,9–11) The hippocampus is not a uniform structure and consists of subfields with distinct morphology: the cornu ammonis (CA) subfields CA1–4, the dentate gyrus (DG), the fimbria, and the adjacent subiculum and presubiculum (8,12). Postmortem studies have demonstrated smaller pyramidal neuron cell bodies (13,14), reduced dendritic spine density (15), and reduced interneuron density and number (16–18) in the hippocampi of patients with schizophrenia and bipolar disorder. The postmortem cellular findings differ among subfields, with CA4 showing more prominent pyramidal soma reduction than CA1 in patients with schizophrenia (16) and CA3 showing decreased number of mossy fiber synapses in patients with schizophrenia (15) as well as a significant reduction of somatostatin-positive neurons in CA1 and parvalbumin-positive neurons in CA1 and CA4 in patients with bipolar disorder (17). Although postmortem hippocampal neuronal abnormalities are present in both patients with

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schizophrenia and patients with bipolar disorder, there is evidence of diagnostically specific differences in presubiculum—patients with schizophrenia show reduced somatostatin-positive neuron density compared with patients with bipolar disorder (18).

Connectivity disruptions in local and external hippocampal circuits may be important to the formation of psychotic symptoms and thought content (7). The hippocampal subfields are classically described to be connected in a one-way trisynaptic circuit, in which DG granular neurons connect via mossy fibers with CA3 pyramidal neurons that project via Schaffer collaterals to CA1 and to subiculum (7,12), but the connections between the hippocampal subfields are more complex (19). The DG receives input from the entorhinal cortex, whereas subiculum represents the main hippocampal outflow to the entorhinal cortex and other brain regions (8,12). The ventral/anterior hippocampus is important to affective regulation, stress responses, and emotions, and the posterior parts are involved in cognitive functions, in particular, visuospatial orientation and memory processing (20). Animal models of psychosis have demonstrated hippocampal hyperactivity leading to dopamine increase and lack of dopamine regulations in the ventral hippocampus (21); this dysregulation has been related to deficits in normal ignorance of non-important stimuli, a disruption that may underlie delusions and hallucinations (21). Reduced glutaminergic signaling in the DG has been associated with diminished pattern separation, which, in combination with increased CA3 associational activity and accelerated pattern completion, may cause delusions and thought disorders (22). If alterations in hippocampal subfield volumes differ between schizophrenia and bipolar disorder, this could point toward neurobiological mechanisms underlying the distinct clinical features of the two disorders.

Advances in computational MRI postprocessing methods allow automated segmentation of the hippocampal subfields (Figure 1) (23). With the use of this method, a negative statistical correlation between current positive psychotic symptoms and CA1–3 volume was reported in patients with schizophrenia (24), smaller CA4/DG and fimbria volumes compared with control subjects have been demonstrated in patients with bipolar II disorder (25), and reduced subiculum volumes have been associated with impaired verbal declarative memory in persons with a familial risk for schizophrenia (26). It is unknown to which extent in vivo hippocampal subfield volumes differ between schizophrenia and bipolar disorder.

The aim of the present study was to identify diagnostic differences in in vivo hippocampal subfield volumes in a large sample of patients with schizophrenia, patients with bipolar disorder, and healthy control subjects. We hypothesized that patients would have smaller hippocampal subfield volumes than healthy control subjects and that patients with schizophrenia would have smaller volumes than patients with bipolar disorder. We conducted post hoc analyses of associations between selected subfields and psychosis symptoms and cognitive function and hypothesized smaller volumes to correlate with poorer cognitive function and greater severity of psychosis symptoms.

METHODS AND MATERIALS

Subjects

The subject sample ($N = 702$) consisted of patients with a DSM-IV diagnosis within the schizophrenia spectrum ($n = 210$; schizophrenia [DSM-IV 295.1, 295.3, 295.6, 295.9; $n = 161$], schizophreniform disorder [DSM-IV 295.4; $n = 21$], or schizoaffective disorder [DSM-IV 295.7; $n = 28$]), patients with a DSM-IV diagnosis within the bipolar spectrum ($n = 192$; bipolar I disorder [DSM-IV 296.0-7; $n = 117$], bipolar II disorder [DSM-IV 296.89; $n = 66$], or bipolar disorder not otherwise specified [DSM-IV 296.80; $n = 9$]), and healthy control subjects ($n = 300$) from the ongoing multicenter Thematically Organized Psychosis Study at the University of Oslo and collaborator hospitals in Oslo, Norway.

Patients were included from four major psychiatric hospitals and their outpatient clinics that together cover most of the population in Oslo. The inclusion criteria were age 18–65 years old, no head trauma leading to loss of consciousness, and absence of previous or current somatic illness that might affect brain morphology. Healthy control subjects were randomly selected from the national population register. The

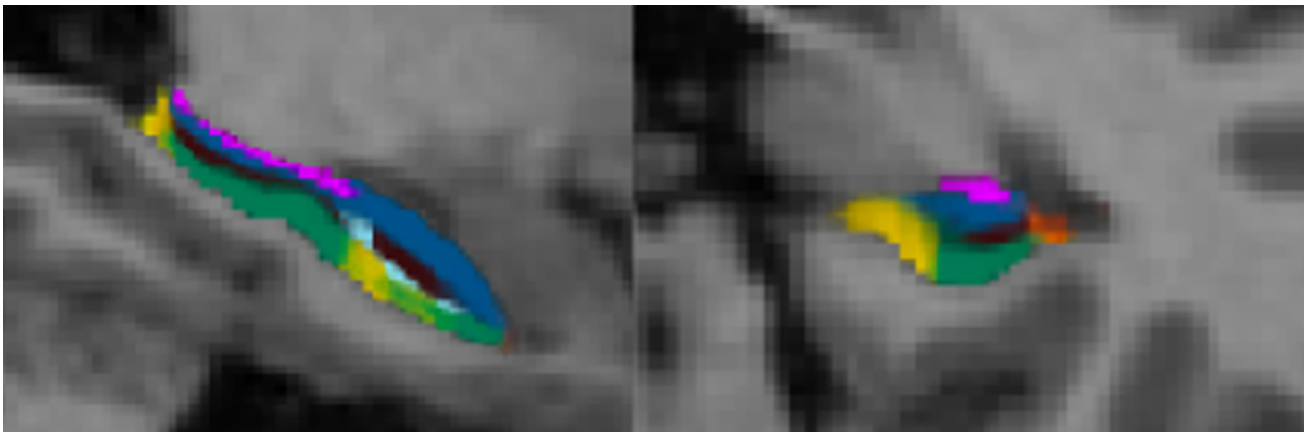

Figure 1. Hippocampal subfield segmentation. Sagittal (left) and coronal (right) views. Color code: red, CA1; blue, CA2/3; dark brown, CA4/dentate gyrus; purple, fimbria; orange, presubiculum; green, subiculum; light blue, hippocampal fissure; light yellow, "remaining" hippocampus. CA, cornu ammonis.