Title

In Vivo Hippocampal Subfield Volumes in Schizophrenia and Bipolar Disorder

Journal

Biological Psychiatry, 77(6)

ISSN

0006-3223

Authors

Haukvik, Unn K
Westlye, Lars T
Mørch-Johnsen, Lynn
et al.

Publication Date

2015-03-01

DOI

10.1016/j.biopsych.2014.06.020

Peer reviewed

Archival Report

Biological Psychiatry

In Vivo Hippocampal Subfield Volumes in Schizophrenia and Bipolar Disorder

Unn K. Haukvik, Lars T. Westlye, Lynn Mørch-Johnsen, Kjetil N. Jørgensen, Elisabeth H. Lange, Anders M. Dale, Ingrid Melle, Ole A. Andreassen, and Ingrid Agartz

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

http://dx.doi.org/10.1016/j.biopsych.2014.06.020

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

ISSN: 0006-3223

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

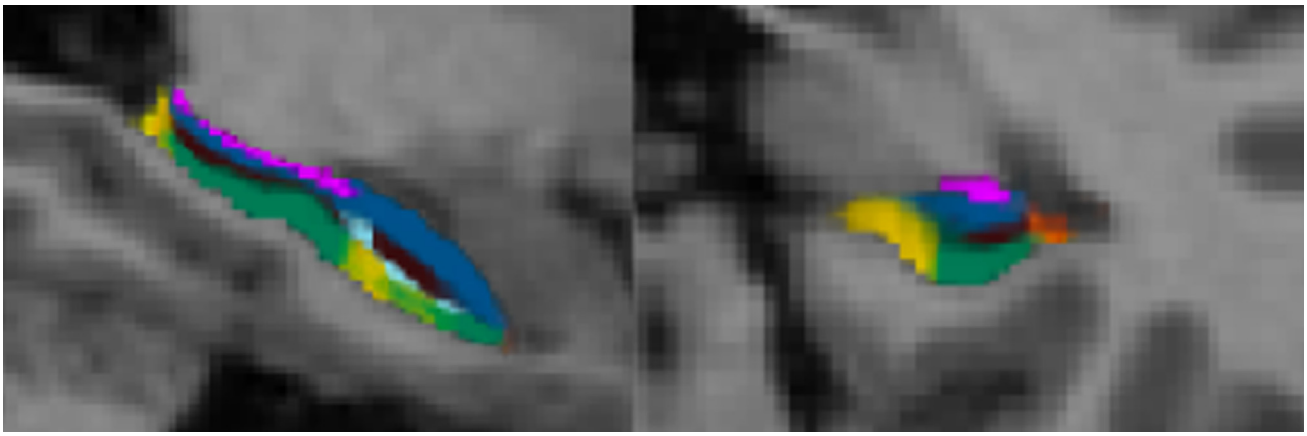

Figure 1. Hippocampal subfield segmentation. Sagittal (left) and coronal (right) views. Color code: red, CA1; blue, CA2/3; dark brown, CA4/dentate gyrus; purple, fimbria; orange, presubiculum; green, subiculum; light blue, hippocampal fissure; light yellow, "remaining" hippocampus. CA, cornu ammonis.

control subjects were resident in the same catchment area and were within the same age range as the patients.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and was conducted in accordance with the Helsinki Declaration. After complete description of the study to the subjects, written informed consent was obtained from all participating subjects.

Clinical Assessments

All patients underwent thorough clinical investigation by specially trained psychologists and physicians. Clinical diagnoses were assessed using the Structured Clinical Interview for DSM module A–E (27), with an overall agreement for diagnostic categories of 82%, $\kappa = .77$ (95% confidence interval = .60–.94). Psychosocial function was assessed with the Global Assessment of Function scale, split version. Affective state was assessed with the Young Mania Rating Scale and the Calgary Depression Scale for Schizophrenia, and current psychotic symptoms were rated by the use of the Positive and Negative Syndrome Scale (PANSS) (28), with high intraclass coefficients (29). Patients with bipolar disorder were classified as having psychotic or nonpsychotic bipolar disorder based on the presence of either a current psychotic episode (defined as a score of ≥4 on any one of the PANSS items P1, P3, P5, P6, G9) or a history of psychosis based on information retrieved from the B-module in the Structured Clinical Interview for DSM interview as well as medical records.

Healthy control subjects were interviewed for symptoms of severe mental illness by trained clinical psychologists and examined with the Primary Care Evaluation of Mental Disorders (30) to ensure no current or previous psychiatric disorders. Control subjects with current or previous somatic illness or substance abuse disorder including alcohol overuse that could affect brain morphology were excluded.

Neurocognitive Assessment

Trained psychologists performed the neurocognitive assessment (1). Based on the literature (8,19,26,31–33), we used the delayed verbal recall subtests of the California Verbal Learning Test, second edition (34) because delayed recall has previously been associated with the subfields we selected for the neurocognitive analyses. General cognitive functioning was estimated with the Wechsler Abbreviated Scale of Intelligence full-scale IQ (35). Higher scores correspond to better neurocognitive functioning for all tests.

MRI Acquisition and Postprocessing

All participants underwent MRI scanning on the same 1.5-T Siemens MAGNETOM Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. Two sagittal T1-weighted magnetization prepared rapid acquisition gradient-echo volumes were acquired with the Siemens tfl3d1_ns pulse sequence (echo time = 3.93 msec; repetition time = 2730 msec; inversion time = 1000 msec; flip angle = 7°; field of view = 24 cm; voxel size = 1.33 × .94 × 1 mm^3; number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal-to-noise ratio. There was no major scanner upgrade during the study period, and patients and control subjects were scanned interchangeably to avoid the possibility for across-time scanner drifting to confound diagnostic differences. A neuroradiologist evaluated all scans, and 12 subjects with scans showing minor brain pathology were excluded from the study, leaving 702 participants.

FreeSurfer software (version 5.2.0) (http://surfer.nmr.mgh.harvard.edu/) was used to obtain volumes of the hippocampal subfields (Figure 1), total hippocampal formation volume, and intracranial volume (ICV) (36). Processing includes motion correction and averaging (37) of multiple volumetric T1-weighted images (when more than one is available); removal of nonbrain tissue using a hybrid watershed/surface deformation procedure (38); automated Talairach transformation; and segmentation of the subcortical white matter and deep gray matter volumetric structures by combining information on image intensity, probabilistic atlas location, and local spatial relationships between structures to assign a neuroanatomic label automatically to each voxel in the MRI volume (39,40). The hippocampal subfield segmentation is based on a Bayesian modeling approach and manual delineations of each hippocampal subfield. A region of interest around the hippocampal formation (94 × 66 × 144 voxels) is automatically assigned to each image using an affine mutual information–based registration technique by first aligning the whole-brain template and then the region of interest template only (23). The hippocampal subfield volumes obtained with this method were compared with manual hippocampal subfield tracings and were shown to be most reliable for the larger subfields CA2/3, CA4/DG, and subiculum, with acceptable reliability for CA1, presubiculum, and fimbria (23). Hence we chose to include the subfields CA1, CA2/3, subiculum, presubiculum, CA4-DG, and fimbria in the statistical analyses.

The MRI postprocessing procedures were fully automated without manual editing. All segmented scans were visually inspected following standard procedures. Six subjects were excluded because of scan segmentation errors.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp, Armonk, New York). Demographic and clinical variables were evaluated by analysis of variance and χ^2 analysis between diagnostic groups. All statistical tests were two-tailed. Hippocampal subfield volume differences between groups were tested using analysis of covariance with the subfield as the dependent variable, diagnosis as fixed factor, and age and ICV as covariates. Effects of sex were ruled out by including sex as a covariate in this model, with no changes in significance threshold for any of the subfields or diagnostic groups. Hence the sex variable was left out of the final statistical model. Standardized residuals and Cook's distance were estimated, and the data were reanalyzed after exclusion of all subjects with residual values >2.5 or <−2.5 for each separate subfield. Bonferroni correction was applied to the between-group comparisons to account for multiple testing ($n = 6$ subfields) and then within each subfield test to adjust for multiple pair-wise

test (n = 3, patients with schizophrenia vs. control subjects, patients with bipolar disorder vs. control subjects, and patients with schizophrenia vs. patients with bipolar disorder). Diagnostic differences in total hippocampal formation volumes were studied using the same model, with the hippocampal formation as the dependent variable. In concordance with previous studies by our group, we performed subgroup analyses on patients within the bipolar spectrum [psychotic vs. nonpsychotic bipolar disorder (41) and bipolar I vs. bipolar II disorder (2)].

The subfield analyses were repeated with total hippocampal formation volume (for each hemisphere) replacing ICV as covariate to investigate the anatomic specificity of the effects. Finally, we included the diagnosis × total hippocampal formation interaction term (with the total left and right hippocampal formation for the left and right hemisphere subfields, respectively) together with age, diagnosis, ICV, and total hippocampal formation with each of the hippocampal subfields as dependent variables in six analyses for each hemisphere.

To account for possible confounding effects of medication, we calculated defined daily dosage (DDD) of current lithium, antiepileptic, and antipsychotic medication in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd). Linear regression analyses were conducted to test for effects of first-generation and second-generation antipsychotic medication, antiepileptics, and lithium on hippocampal subfield volumes. Medication was not associated with any of the hippocampal subfield volumes within any of the patient groups. Second-generation antipsychotic medication was associated with total hippocampal formation volumes and included as a covariate in the statistical analyses of the total hippocampal volumes.

Post hoc analyses of associations between selected subfields and psychosis symptoms (PANSS positive and negative subscales), verbal memory (California Verbal Learning Test long and short delay free and cued recall, z scores), and general cognitive performance (Wechsler Abbreviated Scale of Intelligence) were performed in a subset of participants for cognitive analyses (n = 603; 177 patients with schizophrenia, 165 patients with bipolar disorder, 261 control subjects), and for symptoms analyses (n = 172; 97 patients with schizophrenia, 75 patients with bipolar disorder) (Tables S1 and S2 in Supplement 1). We tested for associations with the subfields that showed significantly different volumes between patients with schizophrenia and bipolar disorder (subiculum and presubiculum, left and right hemisphere combined), and verbal memory tests were selected because they have previously demonstrated a relation to the subicular area (8,19,26,31–33). We used nonparametric Spearman rank correlation with relative subiculum volume (subfield divided by ICV) to correct for differences in head size. Because of significant group differences in symptom and cognitive scores (Table 1; Tables S1 and S2 in Supplement 1), the analyses were stratified by diagnostic groups. Given the a priori hypothesis, all post hoc tests were one-tailed.

RESULTS

Demographic and Clinical Variables

Demographic and clinical variables are presented in Table 1.

Hippocampal Subfield Volume Differences Between Diagnostic Groups

Volume differences between groups (Table 2) were found in hippocampal subfields CA2/3, CA4/DG, presubiculum, and subiculum

Table 1. Demographic and Clinical Characteristics

	Schizophrenia Subjects (n = 210)		Bipolar Disorder Subjects (n = 192)		Control Subjects (n = 300)		p Value χ^2
	Number	%	Number	%	Number	%	
Sex (M/F)	125/85	59/41	77/115	40/61	158/142	53/47	4.2×10^{-4}
Handedness (R/L/A) (n = 181/169/265)	159/22/0	88/12/0	147/20/2	87/12/1	243/19/3	92/7/1	NS
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	ANOVA
Age (Years)	32.0 (9.3)	18–63	35.1 (11.5)	18–65	35.3 (9.9)	18–73	4.7×10^{-4}
Years of Education	12.8 (2.5)	7–23	13.5 (2.3)	9–20	14.2 (2.3)	9–20	1.5×10^{-8}
WASI IQ (n = 177/165/261)	103.0 (14.6)	66–136	109.1 (12.0)	77–138	114.4 (12.8)	78–135	$<5.0 \times 10^{-6}$
YMRS	4.5 (5.0)	0–23	3.7 (4.9)	0–28			NS
CDSS	5.8 (4.4)	0–17	5.0 (4.9)	0–23			NS
GAF Symptom	42 (11)	9–81	57 (11)	28–84			7.1×10^{-30}
GAF Function	44 (10)	14–81	53 (12)	28–82			2.7×10^{-16}
PANSS Positive	14.9 (5.4)	7–29	10.0 (3.6)	7–25			4.4×10^{-22}
PANSS Negative	15.5 (6.6)	7–39	10.1 (3.6)	7–25			4.1×10^{-20}
Age at Illness Onset	23.8 (7.5)	7–51	27.3 (10.1)	7–63			1.1×10^{-4}
Medication (DDD) (n = SCZ/BD)							
Antipsychotics (n = 187/103)	1.4 (.8)	.1–5.5	.9 (.7)	.1–3.9			NA
Antiepileptics (n = 43/87)	.5 (.4)	.0–1.3	.7 (.5)	.0–2.0			NA
Lithium (n = 2/33)	.5 (.0)	.5–.5	1.1 (.4)	.1–1.8			NA

ANOVA, analysis of variance; BD, bipolar disorder; CDSS, Calgary Depression Scale for Schizophrenia; DDD, defined daily dosage; GAF, Global Assessment of Function split version; M/F, male/female; NA, not applicable; NS, not significant; PANSS, Positive and Negative Syndrome Scale; R/L/A, right/left/ambidextrous; SCZ, schizophrenia; WASI, Wechsler Abbreviated Scale of Intelligence; YMRS, Young Mania Rating Scale.

Table 2. Mean Hippocampal Subfield Volumes (mm^3), SD, and Range Stratified by Diagnostic Groups

	Schizophrenia Subjects (n = 210)		Bipolar Disorder Subjects (n = 192)		Healthy Control Subjects (n = 300)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Left						
Presubiculum	455 (59)	326–622	463 (58)	301–628	478 (59)	2892–5520
CA1	321 (42)	206–462	322 (45)	235–453	331 (43)	234–486
CA2/3	969 (136)	630–1426	981 (128)	668–1342	1029 (136)	667–1401
Fimbria	73 (23)	19–135	72 (23)	16–152	76 (23)	25–185
Subiculum	629 (78)	426–823	642 (80)	458–924	666 (75)	463–774
CA4/DG	542 (74)	367–774	548 (70)	366–758	574 (72)	365–774
Right						
Presubiculum	430 (56)	268–624	443 (55)	328–596	456 (57)	327–642
CA1	333 (45)	206–469	334 (44)	220–457	349 (47)	234–460
CA2/3	1019 (142)	648–1444	1026 (128)	617–1360	1079 (140)	687–1588
Fimbria	64 (21)	12–148	62 (21)	20–123	65 (23)	14–187
Subiculum	628 (75)	399–838	640 (75)	461–854	669 (79)	461–1021
CA4/DG	565 (76)	351–789	571 (72)	355–761	600 (77)	372–857

CA, cornu ammonis; DG, dentate gyrus.

bilaterally and right CA1 when age and ICV were accounted for; patients with schizophrenia or bipolar disorder had smaller volumes than healthy control subjects for all subfields except the presubiculum, where only patients with schizophrenia had smaller volumes (Table 3). Both patient groups showed smaller right and left total hippocampal volumes than healthy control subjects (Table 3). Patients with bipolar disorder showed intermediate volumes relative to patients with schizophrenia and healthy control subjects for all subfields except the fimbria (Table 2); the difference reached statistical significance for the right presubiculum, the right and left subiculum, and the hippocampal formation (Table 3) as well as a trend level significance for the left presubiculum volume ($t = -2.16$, $p = .09$). Subgroup analyses revealed no differences between patients with psychotic versus nonpsychotic bipolar disorder or between patients with bipolar I versus bipolar II disorder. To account for potential confounding effects of duration of illness, the analyses were rerun with duration of illness as a covariate. Duration of illness was not related to any of the hippocampal subfields. Including duration of illness as a covariate in the analysis of covariance did not affect the results except for the right CA1, where patients with bipolar disorder did not have smaller volumes than healthy control subjects when duration of illness was accounted for.

When covarying for total hippocampal formation volume (left and right total hippocampal volume for the left and right hemisphere subfields, respectively), there was an association between diagnosis and left CA1 volume [$F_{2,699} = 7.15$, $p = .001$]; patients with schizophrenia had significantly larger CA1 volume ($t = 3.79$, $p = .001$) than healthy control subjects. This finding remained significant when ICV was

Table 3. Statistical Comparisons of Hippocampal Subfield Volumes Between Groups

	All Groups		Schizophrenia vs. Control Subjects			Bipolar Disorder vs. Control Subjects			Schizophrenia vs. Bipolar Disorder Subjects		
	$F_{2,699}$	p Adjusted	t	B (SE)	p Adjusted	t	B (SE)	p Adjusted	t	B (SE)	p Adjusted
Left											
Presubiculum	9.12	7.2×10^{-4}	−4.3	−158 (37)	6.7×10^{-5}			NS			NS
CA1	1.79	.617			NS			NS			NS
CA2/3	13.95	7.2×10^{-6}	−5.12	−424 (83)	1.2×10^{-6}	−3.23	−272 (84)	.004			NS
Fimbria	.847	1			NS			NS			NS
Subiculum	14.61	3.7×10^{-6}	−5.39	−256 (48)	2.9×10^{-7}	−2.54	−123 (48)	.034	−2.53	−133 (52)	.035
CA4/DG	13.22	1.4×10^{-5}	−4.95	−226 (46)	2.8×10^{-6}	−3.26	−152 (47)	.003			NS
Hippocampal formation	23.77	6.0×10^{-10}	−6.83	−225 (33)	5.7×10^{-11}	−3.60	−122 (34)	.001	−2.83	−133 (36)	.014
Right											
Presubiculum	15.25	2.0×10^{-6}	−5.50	−185 (34)	1.6×10^{-7}			NS	−3.36	−125 (37)	.002
CA1	7.45	.006	−3.47	−105 (30)	.002	−2.97	−92 (31)	.009			NS
CA2/3	15.07	2.3×10^{-6}	−5.25	−437 (83)	6.2×10^{-7}	−3.58	−305 (85)	.001			NS
Fimbria	.845	1			NS			NS			NS
Subiculum	19.71	2.8×10^{-8}	−6.22	−291 (47)	2.6×10^{-9}	−3.31	−158 (48)	.003	−2.57	−133 (52)	.031
CA4/DG	15.10	2.3×10^{-6}	−5.31	−250 (47)	4.5×10^{-7}	−3.43	−165 (48)	.002			NS
Hippocampal formation	29.32	3.5×10^{-12}	−7.57	−243 (33)	3.5×10^{-13}	−4.07	−133 (33)	1.6×10^{-4}	−3.10	−109 (35)	.006

Analyses of covariance with age and intracranial volume included in the model. All p values are adjusted for multiple tests with Bonferroni correction.
CA, cornu ammonis; DG, dentate gyrus; NS, not significant.

included as an additional covariate in the model ($t = 3.46$, $p = .006$) and when defined daily dosage of second-generation antipsychotic medication was included in this model ($t = 2.65$, $p = .048$). For all other subfields, there were no significant volume differences between patients with schizophrenia and patients with bipolar disorder and healthy control subjects. When the diagnosis × total hippocampal formation volume interaction term was included in the model, no main effects of diagnosis or interaction effects were found for any of the subfields.

Associations with Psychosis Symptoms and Cognitive Functioning

Verbal retrieval was positively related to subiculum volume in patients with bipolar disorder (short delay cued recall $r_S = .18$, $p < .05$; long delay cued recall $r_S = .18$, $p < .05$; long delay free recall $r_S = .12$, $p < .05$) and healthy control subjects (short delay free recall $r_S = .13$, $p < .05$; short delay cued recall $r_S = .11$, $p < .05$; long delay cued recall $r_S = .12$, $p < .05$) but showed no relationship in patients with schizophrenia (Figure S1 in Supplement 1). There were no associations between Wechsler Abbreviated Scale of Intelligence scores and subiculum volume. In patients with schizophrenia, PANSS negative symptoms were positively related to subiculum volume ($r_S = -.14$, $p < .05$). No other associations between subiculum volume and PANSS positive or negative scores were found. No associations between presubiculum volume and cognitive functioning or psychosis symptoms were found.

DISCUSSION

The main findings in this study were smaller in vivo volumes of the hippocampal subfields CA2/3, CA4/DG, subiculum, and right CA1 in patients with schizophrenia and patients with bipolar disorder compared with healthy control subjects, with distinctly smaller subiculum and presubiculum volumes in patients with schizophrenia compared with patients with bipolar disorder.

Subiculum and presubiculum constitute the outflow parts of the hippocampal neuronal circuitry (8) and receive the major output from CA1 (19,42), a subfield that has been linked to several aspects of psychosis pathology (24,43,44). It has been speculated that the subiculum amplifies hippocampal output, with extensive neuronal bursting, regular, theta-modulated, and fast spiking in response to input from CA1 (19). A more recent study (45) found glutamate hypermetabolism to be related to specific volume reductions in subiculum and CA1 of at-risk subjects who progressed to psychosis. Previous studies have reported subicular shape deformations in both patients with schizophrenia (46) and patients with major depressive disorder (47) compared with healthy controls. A stereologic post mortem study reported reduced density of gamma-aminobutyric acidergic somatostatin-positive neurons (of importance to synchronized network activity) in the presubiculum of patients with schizophrenia but not in patients with bipolar I disorder (18). The observed volumetric reduction in subiculum and presubiculum in the present study may represent an in vivo correlate of cellular abnormalities that could be more pronounced in schizophrenia than in bipolar disorder.

With regard to subicular function, findings from animal models suggest a dorsal-ventral segregation. The ventral subiculum appears to be involved in hypothalamic-pituitary-adrenal axis regulation (19), which has been shown to be altered in both patients with schizophrenia (48) and patients with bipolar disorder (49). The dorsal subiculum is important to information processing including memory functions (19), which are more severely impaired in patients with schizophrenia than patients with bipolar disorder (1,50). We found smaller subiculum volume to be related to poorer immediate and delayed verbal recall in patients with bipolar disorder and healthy control subjects. Reduced subiculum volume has been related to impaired immediate verbal recall in subjects with a familial risk for schizophrenia (26) and to delayed verbal recall in patients with Alzheimer's disease (32). Functional MRI studies of healthy subjects demonstrated specific associations between subiculum and memory retrieval, whereas CA2/3 activation was related to memory encoding (31,33). We did not find an association between verbal memory and subiculum volume in patients with schizophrenia, but we found smaller subiculum volume to correlate with increased severity of negative symptoms. A recent functional MRI resting state study reported negative symptoms in patients with schizophrenia to be inversely related to cognitive functioning in relation to hippocampal activation (51). We can speculate that a higher load of negative symptoms may confound possible associations between memory retrieval and subiculum volume in patients with schizophrenia. Nevertheless, the subiculum volume reductions appear to have functional consequences in both patients with schizophrenia and patients with bipolar disorder, and further studies exploring the underlying pathomechanisms are warranted.

We found volumetric reductions in all hippocampal subfields except the fimbria. Our findings are in line with a study using ultra-high-field MRI (7T) reporting a trend toward lower contrast of the dentate granule cell layer (a site of neuron proliferation and maturation) in the DG of patients with schizophrenia (52). This trend may reflect altered intracellular and extracellular water as a response to abnormal neuronal density, organization, and architecture (52). Postmortem studies have reported reduced neural stem cell proliferation in the DG of patients with schizophrenia (53) and decreased number of oligodendrocytes in CA4 (54); this could contribute to reduced myelination of the axon and impaired connectivity to CA3 (54). The CA3 projects to the CA1 (7). Unexpectedly, we found larger CA1 volumes in patients with schizophrenia when we covaried for total hippocampal volume. The findings appear contradictory to a more recent study that reported specific psychosis-related volume reductions in CA1 and subiculum in a cohort of 25 subjects at risk for psychosis (45). We included a much larger cohort with patients with an established diagnosis of schizophrenia or bipolar disorder, and the results are not directly comparable. Perhaps more important, the automated FreeSurfer hippocampal subfield algorithm we used has been suggested to underestimate CA1 volume (32,55). The CA1 is one of the largest hippocampal subfields (56), but the current FreeSurfer method (23) estimates it as one of the smallest relative to the other subfields within the hippocampus (Table 2) (26,32). Although a recent study demonstrated CA1 volumes obtained with FreeSurfer to correlate with CA1 cellular density in epilepsy (55), the CA1 results in the present study must be interpreted with caution.

The present study has some limitations. First, despite controlling for effects of current medication use, we did not have reliable data on cumulative medication and could not rule out possible confounding effects of medication. Second, the use of Bonferroni correction may be overly conservative because the hippocampal subfield volumes are not independent, and type II errors might have occurred. Third, we used MRI scans obtained on a 1.5-T scanner, which may have decreased sensitivity to disease-related biological variability compared with data obtained from higher field magnets that may allow for signal-to-noise ratio. It has been noted that the FreeSurfer hippocampal subfield algorithm appears to underestimate CA1 volumes at the expense of a relative enlargement of subiculum in the hippocampal head where the boundary between the two subfields is difficult to delineate; however, this appears to be a systematic misclassification (32,55) that would affect the relative volume differences between the subfields but not putative case-control differences within or across subfields. Strengths of our study include the large sample size; thorough clinical characterization of participating subjects; interrater reliability testing on clinical instruments; Structured Clinical Interview for DSM–verified diagnoses obtained by specially trained psychiatrists, clinical psychologists, or physicians; and use of the same MRI scanner with neither software nor hardware upgrades during the study period.

In conclusion, although hippocampal subfield volume reductions are found in both patients with schizophrenia and patients with bipolar disorder, the magnitude of reduction is greater in patients with schizophrenia, particularly in the hippocampal outflow regions presubiculum and subiculum. Further studies exploring the pathophysiologic mechanisms that underlie the different associations between the subicular volume reductions and functional outcome in schizophrenia and bipolar disorder are warranted.

ACKNOWLEDGMENT AND DISCLOSURES

This work was supported by the Research Council of Norway Grant Nos. 190311/V50, 167153/V50, and 204966/F20; the South Eastern Norway Regional Health Authority Grant Nos. 2008011, 2009037, and 2011096; and the K.G. Jebsen Foundation. The funding organizations had no further role in study design; in the collection, analysis, or interpretation of data; in the writing of the article; or in the decision to submit the article for publication.

AMD is a founder and holds equity in CorTechs Labs and serves on the Scientific Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. OAA has received speaker's honorarium from Eli Lilly Company, Lundbeck, and GlaxoSmithKline in the last 2 years. UKH, LTW, LM-J, KNJ, EHL, IM, and IA report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Norwegian Centre for Mental Disorders Research K.G. Jebsen Centre for Psychosis Research (UKH, LM-J, KNJ, EHL, IM, OAA, IA), Institute of Clinical Medicine, University of, Oslo; Department of Psychology (LTW), University of Oslo; Norwegian Centre for Mental Disorders Research K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction (LTW, IM, OAA), Oslo University Hospital, Oslo, Norway; Department of Psychiatric Research (UKH, LM-J, KNJ, HL, IA), Diakonhjemmet Hospital, Oslo, Norway; Department of Neurosciences (AMD), University of California, San Diego, School of Medicine, La Jolla, California; and Department of Radiology (AMD), University of California, San Diego, School of Medicine, La Jolla, California.

Address correspondence to Unn K. Haukvik, M.D., Ph.D., Institute of Clinical Medicine, University of Oslo, P.O. Box 1039 Blindern 0315 Oslo, Norway; E-mail: unn.haukvik@medisin.uio.no.

Received Sep 18, 2013; revised May 30, 2014; accepted Jun 22, 2014.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2014.06.020.

REFERENCES

1. Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Faerden A, *et al*. (2011): Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. Schizophr Bull 37:73–83.
2. Rimol LM, Hartberg CB, Nesvag R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, *et al*. (2010): Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry 68:41–50.
3. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, *et al*. (2013): Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genet 9:e1003455.
4. Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, *et al*. (2009): Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. Lancet 373: 234–239.
5. Craddock N, O'Donovan MC, Owen MJ (2009): Psychosis genetics: Modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. Schizophr Bull 35:482–490.
6. Frey BN, Andreazza AC, Nery FG, Martins MR, Quevedo J, Soares JC, *et al*. (2007): The role of hippocampus in the pathophysiology of bipolar disorder. Behav Pharmacol 18:419–430.
7. Tamminga CA, Stan AD, Wagner AD (2010): The hippocampal formation in schizophrenia. Am J Psychiatry 167:1178–1193.
8. Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA (2011): A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat Rev Neurosci 12:585–601.
9. Adriano F, Caltagirone C, Spalletta G (2012): Hippocampal volume reduction in first-episode and chronic schizophrenia: A review and meta-analysis. Neuroscientist 18:180–200.
10. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, *et al*. (2011): Structural magnetic resonance imaging in bipolar disorder: An international collaborative mega-analysis of individual adult patient data. Biol Psychiatry 69:326–335.
11. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ (2012): Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev 36: 1342–1356.
12. Gilbert PE, Brushfield AM (2009): The role of the CA3 hippocampal subregion in spatial memory: A process oriented behavioral assessment. Prog Neuropsychopharmacol Biol Psychiatry 33:774–781.
13. Harrison PJ (2004): The hippocampus in schizophrenia: A review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology (Berl) 174:151–162.
14. Liu L, Schulz SC, Lee S, Reutiman TJ, Fatemi SH (2007): Hippocampal CA1 pyramidal cell size is reduced in bipolar disorder. Cell Mol Neurobiol 27:351–358.
15. Kolomeets NS, Orlovskaya DD, Uranova NA (2007): Decreased numerical density of CA3 hippocampal mossy fiber synapses in schizophrenia. Synapse 61:615–621.
16. Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H, *et al*. (2011): Hippocampal interneurons are abnormal in schizophrenia. Schizophr Res 131:165–173.
17. Konradi C, Zimmerman EI, Yang CK, Lohmann KM, Gresch P, Pantazopoulos H, *et al*. (2011): Hippocampal interneurons in bipolar disorder. Arch Gen Psychiatry 68:340–350.
18. Wang AY, Lohmann KM, Yang CK, Zimmerman EI, Pantazopoulos H, Herring N, *et al*. (2011): Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. Acta Neuropathol 122:615–626.

19. O'Mara SM, Sanchez-Vives MV, Brotons-Mas JR, O'Hare E (2009): Roles for the subiculum in spatial information processing, memory, motivation and the temporal control of behaviour. Prog Neuropsychopharmacol Biol Psychiatry 33:782–790.
20. Fanselow MS, Dong HW (2010): Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65:7–19.
21. Lodge DJ, Grace AA (2011): Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. Trends Pharmacol Sci 32:507–513.
22. Tamminga CA, Southcott S, Sacco C, Wagner AD, Ghose S (2012): Glutamate dysfunction in hippocampus: Relevance of dentate gyrus and CA3 signaling. Schizophr Bull 38:927–935.
23. Van Leemput K, Bakkour A, Benner T, Wiggins G, Wald LL, Augustinack J, *et al*. (2009): Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. Hippocampus 19:549–557.
24. Kuhn S, Musso F, Mobascher A, Warbrick T, Winterer G, Gallinat J (2012): Hippocampal subfields predict positive symptoms in schizophrenia: First evidence from brain morphometry. Transl Psychiatry 2: e127.
25. Elvsashagen T, Westlye LT, Boen E, Hol PK, Andersson S, Andreassen OA, *et al*. (2013): Evidence for reduced dentate gyrus and fimbria volume in bipolar II disorder. Bipolar Disord 15:167–176.
26. Francis AN, Seidman LJ, Tandon N, Shenton ME, Thermenos HW, Mesholam-Gately RI, *et al*. (2013): Reduced subicular subdivisions of the hippocampal formation and verbal declarative memory impairments in young relatives at risk for schizophrenia. Schizophr Res 151:154–157.
27. Spitzer RL, Williams JB, Gibbon M, First MB (1988): In: Structured Clinical Interview for DSM-III-R—Patient version. New York: Biometrics Research Department, New York State Psychiatric Institute.
28. Kay SR, Fiszbein A, Opler LA (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13: 261–276.
29. Engh JA, Friis S, Birkenaes AB, Jonsdottir H, Klungsoyr O, Ringen PA, *et al*. (2010): Delusions are associated with poor cognitive insight in schizophrenia. Schizophr Bull 36:830–835.
30. Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV 3rd, Hahn SR, *et al*. (1994): Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 272: 1749–1756.
31. Eldridge LL, Engel SA, Zeineh MM, Bookheimer SY, Knowlton BJ (2005): A dissociation of encoding and retrieval processes in the human hippocampus. J Neurosci 25:3280–3286.
32. Lim HK, Hong SC, Jung WS, Ahn KJ, Won WY, Hahn C, *et al*. (2013): Automated segmentation of hippocampal subfields in drug-naive patients with Alzheimer disease. AJNR Am J Neuroradiol 34:747–751.
33. Zeineh MM, Engel SA, Thompson PM, Bookheimer SY (2003): Dynamics of the hippocampus during encoding and retrieval of face-name pairs. Science 299:577–580.
34. Delis D, Kramer J, Kaplan E, Ober BA (2004): In: California Verbal Learning Test–Second Edition (CVLT-II). Norwegian Manual Supplement. Stockholm, Sweden: Pearson Assessment.
35. Wechsler D (2007): In: Wechsler Abbreviated Scale Of Intelligence (WASI). Norwegian Manual Supplement. Stockholm, Sweden: Harcourt Assessement.
36. Fischl B (2012): FreeSurfer. Neuroimage 62:774–781.
37. Reuter M, Rosas HD, Fischl B (2010): Highly accurate inverse consistent registration: A robust approach. Neuroimage 53:1181–1196.
38. Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, *et al*. (2004): A hybrid approach to the skull stripping problem in MRI. Neuroimage 22:1060–1075.
39. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al*. (2002): Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.
40. Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, *et al*. (2004): Sequence-independent segmentation of magnetic resonance images. Neuroimage 23(suppl 1):S69–S84.
41. Haukvik UK, McNeil T, Lange EH, Melle I, Dale AM, Andreassen OA, Agartz I (2014): Pre- and perinatal hypoxia associated with hippocampus/amygdala volume in bipolar disorder. Psychol Med 44: 975–985.
42. Benes FM (1999): Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. Biol Psychiatry 46:589–599.
43. Zierhut KC, Grassmann R, Kaufmann J, Steiner J, Bogerts B, Schiltz K (2013): Hippocampal CA1 deformity is related to symptom severity and antipsychotic dosage in schizophrenia. Brain 136:804–814.
44. Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, *et al*. (2009): Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. Arch Gen Psychiatry 66:938–946.
45. Schobel SA, Chaudhury NH, Khan UA, Paniagua B, Styner MA, Asllani I, *et al*. (2013): Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. Neuron 78:81–93.
46. Narr KL, Thompson PM, Szeszko P, Robinson D, Jang S, Woods RP, *et al*. (2004): Regional specificity of hippocampal volume reductions in first-episode schizophrenia. Neuroimage 21:1563–1575.
47. Cole J, Toga AW, Hojatkashani C, Thompson P, Costafreda SG, Cleare AJ, *et al*. (2010): Subregional hippocampal deformations in major depressive disorder. J Affect Disord 126:272–277.
48. Guest PC, Martins-de-Souza D, Vanattou-Saifoudine N, Harris LW, Bahn S (2011): Abnormalities in metabolism and hypothalamic-pituitary-adrenal axis function in schizophrenia. Int Rev Neurobiol 101:145–168.
49. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH (2004): Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry 184:496–502.
50. Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, *et al*. (2010): Specific and generalized neuropsychological deficits: A comparison of patients with various first-episode psychosis presentations. Am J Psychiatry 167:78–85.
51. Tregellas JR, Smucny J, Harris JG, Olincy A, Maharajh K, Kronberg E, *et al*. (2014): Intrinsic hippocampal activity as a biomarker for cognition and symptoms in schizophrenia. Am J Psychiatry 171: 549–556.
52. Kirov II, Hardy CJ, Matsuda K, Messinger J, Cankurtaran CZ, Warren M, *et al*. (2013): In vivo 7 Tesla imaging of the dentate granule cell layer in schizophrenia. Schizophr Res 147:362–367.
53. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, *et al*. (2006): Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11:514–522.
54. Schmitt A, Steyskal C, Bernstein HG, Schneider-Axmann T, Parlapani E, Schaeffer EL, *et al*. (2009): Stereologic investigation of the posterior part of the hippocampus in schizophrenia. Acta Neuropathol 117:395–407.
55. Schoene-Bake JC, Keller SS, Niehusmann P, Volmering E, Elger C, Deppe M, *et al*. (2014): In vivo mapping of hippocampal subfields in mesial temporal lobe epilepsy: Relation to histopathology [published online ahead of print Mar 17]. Hum Brain Mapp.
56. Duvernoy HM, Cattin F, Fatterpekar G, Th Naidich, Ch Raybaud, Risold PY, Salvolini U, Scarabino T (2005): In: The Human Hippocampus, Functional Anatomy, Vascularization and Serial Section with MRI. New York: Springer-Verlag.