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Altered Sex Differences in Hippocampal Subfield Volumes in Schizophrenia

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***Background and Hypothesis*: The hippocampus is a heterogenous brain structure that differs between the sexes and has been implicated in the pathophysiology of psychiatric illnesses. Here, we explored sex and diagnostic group differences in hippocampal subfield volumes, in individuals with schizophrenia spectrum disorder (SZ), bipolar disorders (BD), and healthy controls (CTL). *Study Design*: One thousand and five hundred and twenty-one participants underwent T1-weighted magnetic resonance imaging (SZ, $n = 452$, mean age 30.7 ± 9.2 [SD] years, males 59.1%; BD, $n = 316$, 33.7 ± 11.4, 41.5%; CTL, $n = 753$, 34.1 ± 9.1, 55.6%). Total hippocampal, subfield, and intracranial volumes were estimated with Freesurfer (v6.0.0). Analysis of covariance and multiple regression models were fitted to examine sex-by-diagnostic (sub)group interactions in volume. In SZ and BD, separately, associations between volumes and clinical as well as cognitive measures were examined between the sexes using regression models. *Study Results*: Significant sex-by-group interactions were found for the total hippocampus, dentate gyrus, molecular layer, presubiculum, fimbria, hippocampal-amygdaloid transition area, and CA4, indicating a larger volumetric deficit in male patients relative to female patients when compared with same-sex CTL. Subgroup analyses revealed that this interaction was driven by males with schizophrenia. Effect sizes were overall small (partial $\eta < 0.02$). We found no significant sex differences in the associations between hippocampal volumes and clinical or cognitive measures in SZ and BD. *Conclusions*: Using a well-powered sample, our findings indicate that the pattern of morphological sex differences in hippocampal subfields is altered in individuals with schizophrenia relative to CTL, due to higher volumetric deficits in males.**

Key words: hippocampus/neuroimaging/schizophrenia/bipolar disorders/sex differences

Introduction

Schizophrenia is a severe, multifactorial brain disorder with prominent sex differences in prevalence and presentation.[1] Relative to females, males have a 40% higher likelihood of developing schizophrenia and tend to suffer from more severe forms of the illness, including worse long-term outcomes and more pronounced and persistent negative symptoms.[1] Sex differences in the prevalence and presentation of bipolar disorders (BD) have also been reported, but a clear consensus is lacking.[2] Despite reported sex differences in disease manifestation, it remains unknown whether and how these sex differences are reflected in the brain. Acquiring such knowledge would constitute a critical step toward mechanistic models explaining sex differences in disease susceptibility.

One brain structure that seems to differ between the sexes and has been implicated in the pathophysiology of both schizophrenia and BD is the hippocampus.[3] Located in the medial temporal lobe, the hippocampus is a geminate limbic brain structure with a critical role in learning,[4] memory formation,[5] and mood regulation.[6] These hippocampal-dependent functions differ between the sexes[7] and are affected in schizophrenia and BD. For instance, using functional magnetic resonance imaging (MRI), lower hippocampal activation during encoding and recognition tasks has been associated with alterations in declarative memory performance in schizophrenia.[8,9] Similarly, structural MRI studies have shown smaller hippocampal volumes in both schizophrenia and

BD,[10,11] with greater volumetric deficits in schizophrenia.[12] Hippocampal volume alterations have also been associated with cognitive impairment,[13,14] and thus appear functionally relevant.[15] However, sex differences in these associations have scarcely been studied, as sex is frequently used as a covariate and not as a discovery variable.[16,17]

The hippocampus is, however, not a uniform structure; rather it consists of heterogeneous subfields which serve distinct functions. Using a combination of ultra-high-resolution ex vivo MRI data and conventional in vivo MRI scans, Iglesias and colleagues created a probabilistic labeling algorithm. This method segments 12 hippocampal subfields, namely the parasubiculum, presubiculum, subiculum, cornu ammonis (CA)1, CA3, CA4, granule cells in the molecular layer of the dentate gyrus (GC-ML-DG), hippocampal-amygdaloid transition area (HATA), fimbria, molecular layer, hippocampal fissure, and hippocampal tail.[18] Functional separations of hippocampal subfields have been proposed, particularly in the context of declarative memory. For instance, DG and CA3 are thought to play a crucial role in pattern separation, the flexible distinction between multiple, highly similar memories.[19] Similarly, mechanisms in CA3, CA1, and subiculum may be critical for pattern completion, the retrieval of full memories from incomplete input. Deficits in these subfields have been proposed to result in spurious or false memory associations, creating a susceptibility to psychosis.[19]

Meta-analyses in schizophrenia and BD suggest lower volumes in all hippocampal subfields, predominantly in schizophrenia, with the largest effects in the CA1, CA3, CA4, GC-ML-DG, and subiculum.[20] A recent large-scale collaborative study in BD found similarly smaller volumes in nine of 12 hippocampal subfields, excluding the fimbria, fissure, and parasubiculum, in individuals with BD relative to healthy controls (CTL).[21] Directly comparing both disorders, the left CA2 and right subiculum were smaller in schizophrenia than in BD, suggesting differential patterns of volumetric deficits depending on the diagnosis.[20]

Although diagnostic group differences in hippocampal subfield volume have been extensively demonstrated, sex differences in hippocampal volumes are still debated. A recent study in over 1,500 healthy adults revealed region-specific sex differences in hippocampal subfield volumes, with larger volumes in males relative to females, most prominently in the fimbria and parasubiculum.[22] Similar studies in schizophrenia and BD are currently lacking. While emerging evidence suggests that lower hippocampal volumes are only present in males and absent in females with schizophrenia,[23,24] subfield-specific sex differences in schizophrenia are yet to be reported. Investigating sex differences in hippocampal subfield alterations in schizophrenia and BD may advance our understanding of the pathophysiology of these disorders and their relation to biological sex.

Here, we studied sex differences in hippocampal subfield volumes in a large sample of individuals with schizophrenia spectrum disorders (SZ) and BD and CTL. We examined the associations between medication use, symptom profiles as well as cognitive measures on hippocampal volumes by sex and diagnostic groups. Due to a lack of consistent evidence on sex differences in hippocampal volumes in schizophrenia and BD, the analyses were exploratory by nature.

Methods

Participants

The sample of 768 individuals with SZ and BD, and 753 CTL is part of the ongoing Thematically Organized-Psychosis study, Oslo, Norway. Individuals with SZ and BD were recruited from in- and outpatient psychiatric units covering specific catchment areas in the greater Oslo area. CTL were recruited from the national population register in the same catchment area. All participants provided written informed consent. The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Inspectorate and carried out in accordance with the Declaration of Helsinki. For details on inclusion criteria, see supplementary note 1.

Clinical Assessment

Clinical characterization was conducted by trained health personnel. Clinical diagnoses were established according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder IV axis 1 disorder, module A-E.[25] The Positive and Negative Syndrome Scale (PANSS)[26] was used to assess the presence and severity of psychotic symptoms, and the Inventory for Depressive Symptomatology (IDS)[27] and the Young Mania Rating Scale (YMRS)[28] to evaluate affective symptoms. General functioning in all participants was measured with the Global Assessment of Function (GAF) scale, split version[29] (details see supplementary note 2).

Clinical diagnoses were: (1) SZ, n = 452: Schizophrenia [SCZ, n = 245], schizophreniform [n = 31], schizoaffective [SCZ-AF, n = 59], other psychotic disorders [n = 117], (2) BD, n = 316: Bipolar I [n = 188], bipolar II [n = 113], bipolar not otherwise specified [n = 15].

Cognitive Assessment

Clinical psychologists and trained personnel administered cognitive assessments of the clinical groups and CTL, respectively. Between 2004 and 2019, the cognitive assessment was performed using 2 different cognitive test batteries. Seven hundred and twenty-nine participants were evaluated with battery 1, a standardized battery described in detail elsewhere.[30] Starting from 2012, participants (n = 722) were assessed using a licensed translated

Table 1. Overview of Cognitive Domains and Corresponding Tests, Stratified by Diagnostic Group and Sex

		BD			SZ		
		Female	Male	*P*	Female	Male	*P*
N	Battery	173	126		172	250	
Cognitive measures, z-scores							
Verbal learning		0.16 ± 0.95	−0.45 ± 1.31	**<0.001**	−0.62 ± 1.25	−0.97 ± 1.22	**0.005**
CVLT, list A total correct	1	0.20 ± 0.94	−0.48 ± 1.38	**<0.001**	−0.49 ± 1.13	−0.92 ± 1.20	**0.004**
HVLT-R, immediate recall	2	0.08 ± 0.97	−0.38 ± 1.18	**0.037**	−0.83 ± 1.41	−1.05 ± 1.27	0.306
Verbal memory		0.11 ± 0.94	−0.57 ± 1.37	**<0.001**	−0.77 ± 1.34	−0.93 ± 1.32	0.244
CVLT, long delay free recall	1	0.12 ± 0.96	−0.65 ± 1.45	**<0.001**	−0.55 ± 1.20	−0.87 ± 1.27	**0.042**
HVLT-R, delayed recall	2	0.07 ± 0.90	−0.42 ± 1.16	**0.022**	−1.21 ± 1.51	−1.05 ± 1.41	0.540
Processing speed		−0.44 ± 1.15	−0.90 ± 1.11	**0.001**	−0.97 ± 1.16	−1.39 ± 1.21	**<0.001**
Digit Symbol Coding Test from WAIS-III	1	−0.55 ± 1.20	−0.89 ± 1.12	**0.044**	−0.99 ± 1.10	−1.29 ± 1.19	**0.038**
Brief Assessment of Cognition in Schizophrenia	2	−0.23 ± 1.02	−0.93 ± 1.12	**0.002**	−0.93 ± 1.27	−1.56 ± 1.23	**0.002**
Working memory		−0.51 ± 0.95	−0.54 ± 0.94	0.787	−0.82 ± 0.99	−0.77 ± 1.01	0.625
Letter-Number Sequencing Test from WAIS-III	1	−0.64 ± 0.98	−0.65 ± 0.93	0.951	−0.89 ± 0.99	−0.80 ± 1.03	0.517
Letter-Number Sequencing Test from the MCCB	2	−0.28 ± 0.86	−0.35 ± 0.95	0.687	−0.69 ± 0.99	−0.71 ± 0.97	0.946

Mean ± standard deviation. Abbreviation: BD, bipolar disorders, SZ, schizophrenia spectrum disorders, N, sample size; CVLT, California verbal learning test; HVLT-R, Hopkins verbal learning test revised; WAIS, Wechsler adult intelligence scale; MCCB, MATRICS consensus cognitive battery. Kruskal–Wallis tests were used to compare cognitive scores between females and male by diagnostic group. Significant group differences are highlighted in bold.

version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB).[31] In the current study, we focused on four cognitive domains, that have been linked to hippocampal functioning,[13,14] may vary between the sexes[30,32,33] and may be impaired in schizophrenia and BD[34]: (1) *processing speed*, (2) *working memory*, (3) *verbal learning, and (4) verbal memory* (for details see supplementary note 3). The tests included in battery 1 and 2 are detailed in table 1. A total of 67 participants did not have cognitive data. Current intelligence quotient was assessed using the Wechsler Abbreviated Scale of Intelligence (4 subtests).

To merge SZ and BD test scores from both batteries for each cognitive domain, we computed z-scores for both sexes combined based on the performance of the CTL group. Z-scores were calculated using the following formula:

$$z = (x - \mu)/\sigma$$

where X is the raw cognitive score, μ is the mean and σ is standard deviation of the CTL group. Combined z-scores for each cognitive domain and separate z-scores per tests, stratified by sex and diagnostic group, are highlighted in table 1. Raw scores for each cognitive test are summarized in supplementary table S1, stratified by sex and diagnostic group, including values from CTL.

Medication Use

In the clinical groups, current use of the following medication was recorded and converted into defined daily dose (DDD)[35]: Antipsychotics, antidepressants, and antiepileptics. In individuals with BD, lithium user status (yes/no) and serum concentration were also assessed (details published elsewhere[36]).

Neuroimaging Data Acquisition

T1-weighted images were acquired either at 1.5T (2004–2009, $n = 745$) or at 3T (2011–2019, $n = 776$). At 1.5T, images were acquired on a Siemens Magnetom Sonata scanner. At 3T, participants were scanned either on General Electric Signa HDxt scanner ($n = 438$) or a General Electric Discovery 750 scanner ($n = 338$). For details about the MRI acquisition parameters, see supplementary note 4.

Neuroimaging Data Processing

The FreeSurfer software package (v6.0.0) was used to process T1-weighted images to extract volume estimates for left and right hippocampal total and subfield volumes as well as intracranial volume (ICV); estimated based on the Talairach transform. The automated segmentation of the hippocampus is based on a probabilistic atlas, and segmentation quality was visually inspected. If necessary, manual editing of the surface reconstruction was performed by trained assistants following standard FreeSurfer procedures.[37] No individuals were excluded based on the inspection of the hippocampal segmentation. We used ComBat to remove unwanted variation associated with scanner while preserving biological associations in the data[38,39] (see supplementary note 5, figure S1–S2).

Statistical Analysis

All statistical tests were conducted in R, v4.2.2. Model formulas in R are specified in the text (1-9). Main effects of the interaction terms are automatically included in the model. Continuous variables in interaction terms were standardized (subtracting the mean and dividing by the SD) before the regression analysis. All analyses included combined hippocampal volumes (left + right) as dependent variables (DV). Results from the main analyses for the left and right hippocampal subfields are reported in supplementary table S2. To account for multiple comparisons, false discovery rate (FDR) correction[40] was applied across all hippocampal volumes (total + subfield volumes) for each set of analyses testing a hypothesis. The sets of FDR corrections are reflected in the corresponding results tables.

Sex and Diagnostic Group Differences in Hippocampal Volume

To examine sex-by-diagnostic group differences in hippocampal volumes, we used analysis of covariance (ANCOVA, type III, *car* package). Total hippocampal volume and each subfield volume were entered as DV in separate models, which included diagnostic group-by-sex interaction as a fixed factor and age, age^2, and ICV as covariates:

$$DV \sim Age + Age^2 + ICV + Group * Sex \quad (1)$$

Post-hoc Tukey tests were performed to contrast volume differences between females vs. males, females vs. females, and males vs. males for each diagnostic group. Sex-adjusted case–control differences in hippocampal volumes were also assessed in additional models, correcting for sex, age, age^2, and ICV:

$$DV \sim Age + Age^2 + ICV + Sex + Group \quad (2)$$

To explore the absolute differences in hippocampal volumes by sex and diagnostic group, we re-ran the main analyses without adjustment for ICV:

$$DV \sim Age + Age^2 + Group * Sex \quad (3)$$

Effect sizes were calculated as partial eta-squared (partial η^2) based on the F-statistic.

To further evaluate hippocampal volume differences between diagnostic groups by age, we fitted regression models (*lm* function) with total hippocampal and subfield volumes as DV and group-by-age interaction, group-by-age^2 interaction, sex, and ICV as independent variables:

$$DV \sim Group * Age + Group * Age^2 + Sex + ICV \quad (4)$$

Additional regression models were fitted to further examine sex-by-diagnostic subgroup differences (ie, bipolar I, bipolar II, SCZ-AF, SCZ, and other psychotic disorders, relative to CTL) in total hippocampal and subfield volumes, adjusting for age, age^2, and ICV:

$$DV \sim Subgroups * Sex + Age + Age^2 + ICV \quad (5)$$

Effect sizes for regression results were calculated as Cohen's d based on the *t*-statistic (see supplementary note 6 for additional considerations).

Sex-Specific Associations Between Medication, Clinical Measures, and Hippocampal Volumes

To test if putative associations between medication use (antipsychotics, antidepressants, and antiepileptics) and hippocampal volumes (DV) differed between the sexes, additional regression models were fitted using an interaction term (sex-by-DDD) in SZ and BD separately:

$$DV \sim DDD * Sex + Age + Age^2 + ICV \quad (6)$$

In BD, we further explored the effects of lithium use status (yes/no) and serum concentration levels, on hippocampal volumes, in separate regression models.

Sex-Specific Associations Between Clinical Measures and Hippocampal Volumes

The aforementioned model specifications were used to examine the associations between hippocampal volumes and psychotic symptoms (PANSS, , negative/positive- subscale) in SZ, affective symptoms (YMRS and IDS) in BD, age of onset, duration of illness, and general functioning (GAF symptoms/function) between the sexes:

$$DV \sim Clinical\ Measure * Sex + Age + Age^2 + ICV \quad (7)$$

As both age of onset (BD $r = 0.58$, SZ $r = 0.66$) and duration of illness (BD $r = 0.66$, SZ $r = 0.62$) had high Pearson correlations with age, these linear models were only adjusted for ICV, whereas the other models were adjusted for age, age^2, and ICV.

Sex-Specific Associations Between Cognitive Measures and Hippocampal Volumes

To investigate associations between cognitive measures (verbal learning, verbal memory, processing speed, and working memory) and hippocampal volumes between females and males, regression models with a sex-by-cognitive measure interaction term were fitted. These

models were adjusted for age, age^2, ICV, and years of education:

$$\text{DV} \sim \text{Cognitive Measure} * \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} + \text{Education} \quad (8)$$

The sex-adjusted main effects of medication, clinical measures as well as cognitive measures on hippocampal volumes were tested in separate models, covarying for the beforementioned covariates and sex:

$$\text{DV} \sim \text{Measure-of-Interest} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (9)$$

Results

Demographic and Clinical Variables

Sample demographics and clinical characteristics, stratified by sex and diagnostic group, are summarized in table 2, and supplementary note 7. Cognitive measures, stratified by diagnostic group and sex, are displayed in table 1 and supplementary table S1, and described in supplementary note 8.

Sex and Diagnostic Group Differences in Hippocampal Volumes

Including a sex-by-diagnostic group interaction term, total hippocampal, CA1, CA4, GC-ML-DG, HATA, and molecular layer volumes were significantly smaller in individuals with SZ and BD relative to CTL (model1, see Table 3, figure 1). All hippocampal volumes were smaller in SZ and BD relative to CTL, when not accounting for potential sex-by-diagnostic group interactions (model2, see supplementary table S3).

We found significant main effects of sex for the total hippocampus and for 10 of the 12 hippocampal subfields, not including CA3 and CA4 (model1). Significant sex-by-group interactions were found for the total hippocampus, CA4, fimbria, GC-ML-DG, HATA, presubiculum, and molecular layer (model1). Effect sizes were overall small (partial $\eta^2 \leq 0.018$). When not adjusting for ICV, we found significant sex-by-group interactions for total hippocampus volume and GC-ML-DG after FDR correction (model 3, see supplementary table S4). Post-hoc Tukey tests revealed higher volumes in males than females in the CTL group in most subfields, but not in BD or SZ (details for subfields, see supplementary table S5).

Age and age^2 showed a significant main effect on all volumes, except the presubiculum and parasubiculum, based on the ANCOVA models with sex-by-group interactions (model 4).

The diagnostic subgroup analysis revealed significant sex-by-group effects for GC-ML-DG, molecular layer, fimbria, CA4, and total hippocampus volumes in schizophrenia only (model 5, figure 2, supplementary table S6). In detail, females with schizophrenia showed higher volumes in these subfields than males with schizophrenia relative to CTL, where volumes were higher in males than in females.

Sex-Specific Associations Between Medication Use and Hippocampal Volumes

After FDR correction, we found no significant main effects or sex-by-medication interaction effects between DDD measures, lithium use, and hippocampal volumes in SZ and BD (model 6 and 9, see supplementary table S7).

Sex-Specific Associations Between Clinical Characteristics and Hippocampal Volumes

We found a significant main effect for the association between fissure volumes and age of onset ($t = 4.149$, $P = 4.32\text{e-}05$, $P_{FDR} = .007$) as well as duration of illness ($t = 3.713$, $P = 2.43\text{e-}04$, $P_{FDR} = .025$) in BD (model 7). Similarly, in SZ, we also found a significant association between age of onset and duration of illness and fissure volume. Only the association with duration of illness was significant after FDR correction ($t = 4.432$, $P = 1.18\text{e-}05$, $P_{FDR} = .004$). No other main or interaction effects survived FDR correction (model 7 and 9). All associations are detailed in supplementary table S8.

Sex-Specific Associations Between Cognitive Measures and Hippocampal Volumes

We found no significant associations between cognitive measures (z-scores) and hippocampal volumes in SZ and BD, after FDR correction (model 8 and 9, see supplementary table S9).

Discussion

Using a well-powered sample, our findings indicate that the pattern of morphological sex differences in hippocampal subfields is altered in individuals with schizophrenia relative to CTL, due to higher volumetric deficits in males.

Alterations in hippocampal morphology in psychiatric illnesses have been widely reported, both on a macro- and microscopic level. Here, we found significantly lower total hippocampal, CA1, CA4, GC-ML-DG, molecular layer, and HATA volumes in individuals with SZ and BD relative to CTL, when accounting for sex-by-diagnostic group interactions and ICV. When not adjusting for this interaction, all 12 hippocampal subfields were smaller in SZ and BD relative to CTL, which is in line with previous results.[20] When not accounting for ICV, significant sex-by-group interactions for total hippocampus volume and the GC-ML-DG remained after FDR correction. Effect sizes were overall small.

Table 2. Demographics and Clinical Measures of the Study Sample

	CTL			BD			SZ			Dx Differences	
	Female *N* = 334	**Male** N = 419	***P***	**Female** *N* = 185	**Male** *N* = 131	***P***	**Female** *N* = 185	**Male** *N* = 267	***P***	**Female** ***P***	**Male** ***P***
Age at Scan (years)	33.4 [26.3, 40.5]	33.1 [27.7, 40.2]	.864	30.3 [24.4, 41.0]	32.1 [25.5, 40.7]	.317	29.0 [23.9, 38.4]	28.2 [23.2, 34.9]	.243	**.004**	**<.001**
Education (years)	15.0 [12.0, 16.0]	15.0 [12.0, 17.0]	.663	15.0 [12.3, 16.5]	14.5 [13.0, 16.0]	.823	13.0 [12.0, 16.0]	13.0 [12.0, 15.0]	.323	**<.001**	**<.001**
BMI (kg/m^2)	23.3 [21.4, 26.3]	24.7 [23.2, 27.3]	**<.001**	24.0 [21.8, 27.2]	26.0 [22.9, 28.1]	**.004**	23.9 [21.6, 27.2]	25.8 [23.1, 29.3]	**<.001**	.271	**.029**
IQ	112.0 [107.0, 119.0]	115.0 [108.8, 120.0]	**.006**	108.0 [101.0, 116.0]	109.0 [103.0, 117.0]	.347	104.0 [95.0, 112.0]	107.0 [94.3, 114.0]	.283	**<.001**	**<.001**
Age of Onset (years)				18.0 [15.0, 23.0]	19.0 [16.0, 26.8]	**.018**	22.0 [18.0, 27.5]	22.0 [19.0, 27.0]	.489	**<.001**	**.003**
DOI (years)				11.0 [6.4, 17.9]	9.8 [5.4, 16.8]	.203	5.7 [2.3, 11.5]	4.4 [1.6, 9.1]	**.011**	**<.001**	**<.001**
GAF, symptom				60.0 [51.0, 67.0]	60.0 [52.0, 65.0]	.932	45.0 [38.0, 55.0]	41.0 [37.0, 51.0]	**.025**	**<.001**	**<.001**
GAF, function				56.5 [48.0, 65.0]	54.0 [47.0, 67.0]	.654	45.0 [40.0, 55.0]	44.0 [38.0, 52.0]	**.044**	**<.001**	**<.001**
PANSS, total				43.0 [37.0, 49.0]	43.0 [38.3, 50.0]	.333	54.5 [44.0, 66.3]	60.0 [51.0, 71.0]	**<.001**	**<.001**	**<.001**
PANSS, negative				9.0 [7.0, 11.0]	10.0 [8.0, 12.0]	**.008**	12.0 [9.0, 17.0]	15.0 [11.0, 20.0]	**<.001**	**<.001**	**<.001**
PANSS, positive				9.0 [7.0, 10.0]	9.0 [7.0, 11.0]	.569	13.0 [9.0, 16.0]	14.0 [11.0, 17.0]	**.019**	**<.001**	**<.001**
YMRS				2.0 [0.0, 4.8]	2.0 [0.0, 4.0]	.964	1.0 [0.0, 5.0]	2.5 [0.0, 8.0]	**.021**	.611	.054
IDS				16.0 [9.0, 26.0]	13.0 [7.0, 20.3]	**.014**	15.0 [7.0, 25.0]	15.0 [7.0, 25.0]	.699	.180	.154
AP, user *N* (%)				113 (61.7)	96 (73.3)	**.044**	171 (92.4)	259 (97.0)	**.046**	**<.001**	**<.001**
DDD				0.5 [0.3, 1.0]	0.9 [0.5, 1.3]	**.007**	1.0 [0.7, 1.8]	1.2 [0.8, 1.8]	.296	**<.001**	**<.001**
AD, user *N* (%)				77 (41.6)	34 (26.0)	**.006**	65 (35.1)	74 (27.7)	.115	**<.001**	**<.001**
DDD				1.0 [1.0, 2.0]	1.5 [1.0, 2.0]	.265	1.0 [1.0, 1.6]	1.5 [1.0, 2.0]	.113	.695	.828
Lithium, user *N* (%)				35 (18.9)	20 (15.3)	.488	6 (3.2)	5 (1.9)	.536	**<.001**	**<.001**
DDD				1.0 [1.0, 1.3]	1.0 [0.8, 1.4]	.918	0.6 [0.5, 0.8]	0.8 [0.5, 1.0]	.400	**.002**	.121
AE, user *N* (%)				71 (38.4)	44 (33.6)	.451	29 (15.7)	29 (10.9)	.173	**<.001**	**<.001**
DDD				0.7 [0.3, 1.0]	0.8 [0.6, 1.1]	.150	0.7 [0.6, 0.8]	0.7 [0.5, 0.9]	.660	0.924	.242
ICV (liter)	1.5 [1.4, 1.5]	1.6 [1.5, 1.7]	**<.001**	1.5 [1.4, 1.6]	1.7 [1.6, 1.8]	**<.001**	1.5 [1.4, 1.5]	1.6 [1.5, 1.8]	**<.001**	0.072	.117

*Non-normal continuous data in median [Interquartile range] and categorical data as number %. Abbreviations: CTL, healthy controls; BD, bipolar disorders; SZ, schizophrenia disorders; N, number; R, right; L, left; A, ambidextrous; M, missing; y, year; BMI, body mass index; IQ, intelligence quotient; DOI, duration of illness; GAF, global assessment of functioning; PANSS, positive and negative syndrome scale; YMRS, young mania rating scale; IDS, inventory for depressive symptomatology; AP, antipsychotics; DDD, defined daily dose; AD, antidepressants; AE, antiepileptics; ICV, intracranial volume; Dx, Diagnosis. Chi^2 test for categorial data and Kruskal-Wallis test for continuous data were used to test for group differences in demographic and clinical measures. Significant results are highlighted in bold.

While diagnostic group differences in hippocampal subfield volumes have been extensively demonstrated, sex differences in hippocampal volumes are still debated. In CTL, region-specific sex differences in hippocampal subfield volumes have been demonstrated, with larger volumes in males relative to females, most prominently in the fimbria and parasubiculum.[22] Our post-hoc Tukey pair-wise comparison revealed significantly higher volumes in healthy males relative to healthy females for the total hippocampus, parasubiculum, presubiculum, CA1,

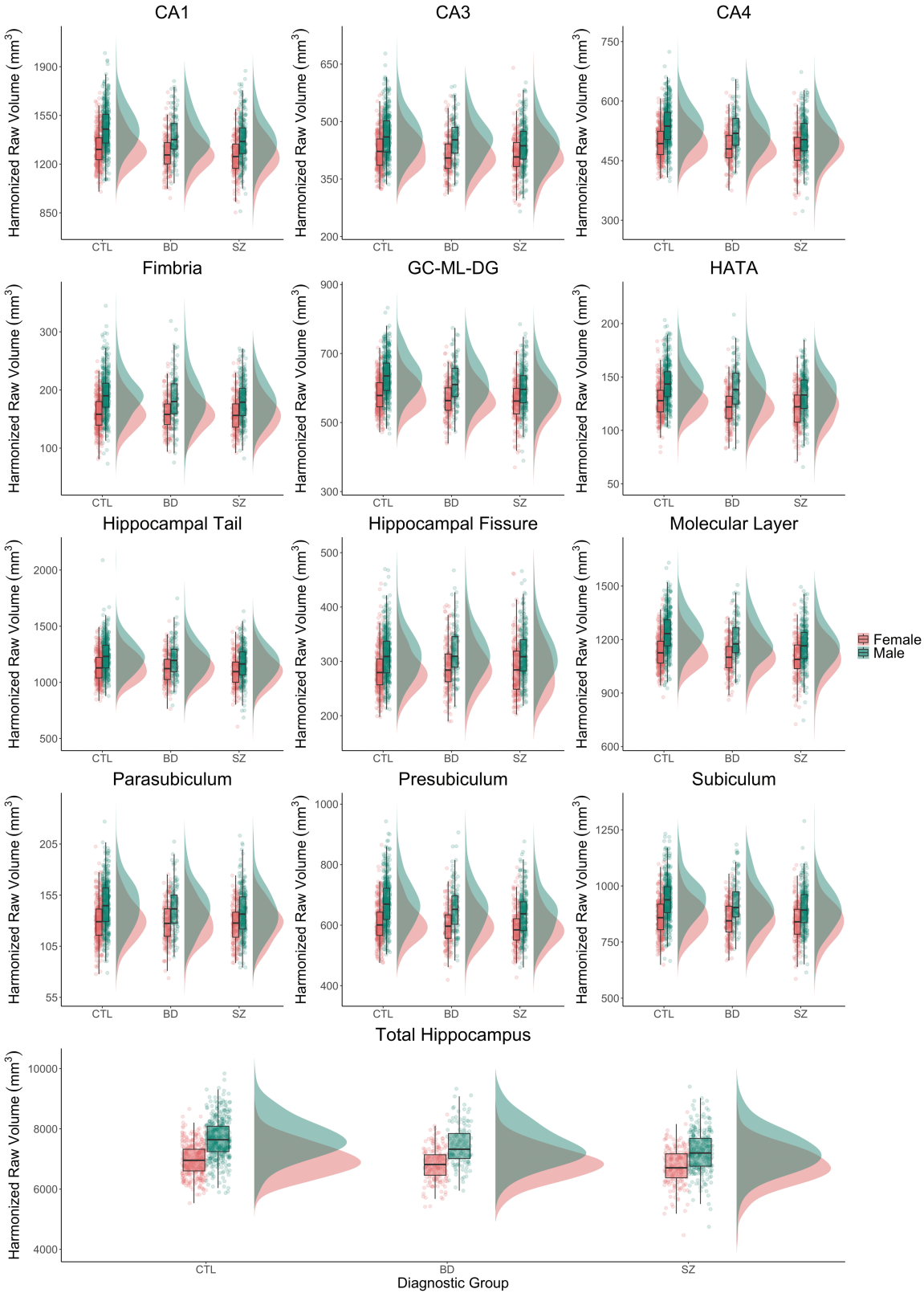

Fig. 1. Hippocampal volumes stratified by diagnostic group and sex. ComBat-harmonized volumetric data is displayed as raincloud plots, which combines boxplots, unadjusted raw data points (scatterplot), and the distributions of the data (histogram) using split-half violins. CTL, healthy controls, BD, bipolar disorders, SZ, schizophrenia spectrum disorders; CA, cornu ammonis; GC-ML-DG, granule cells in the molecular layer of the dentate gyrus; HATA, hippocampal-amygdaloid transition area.

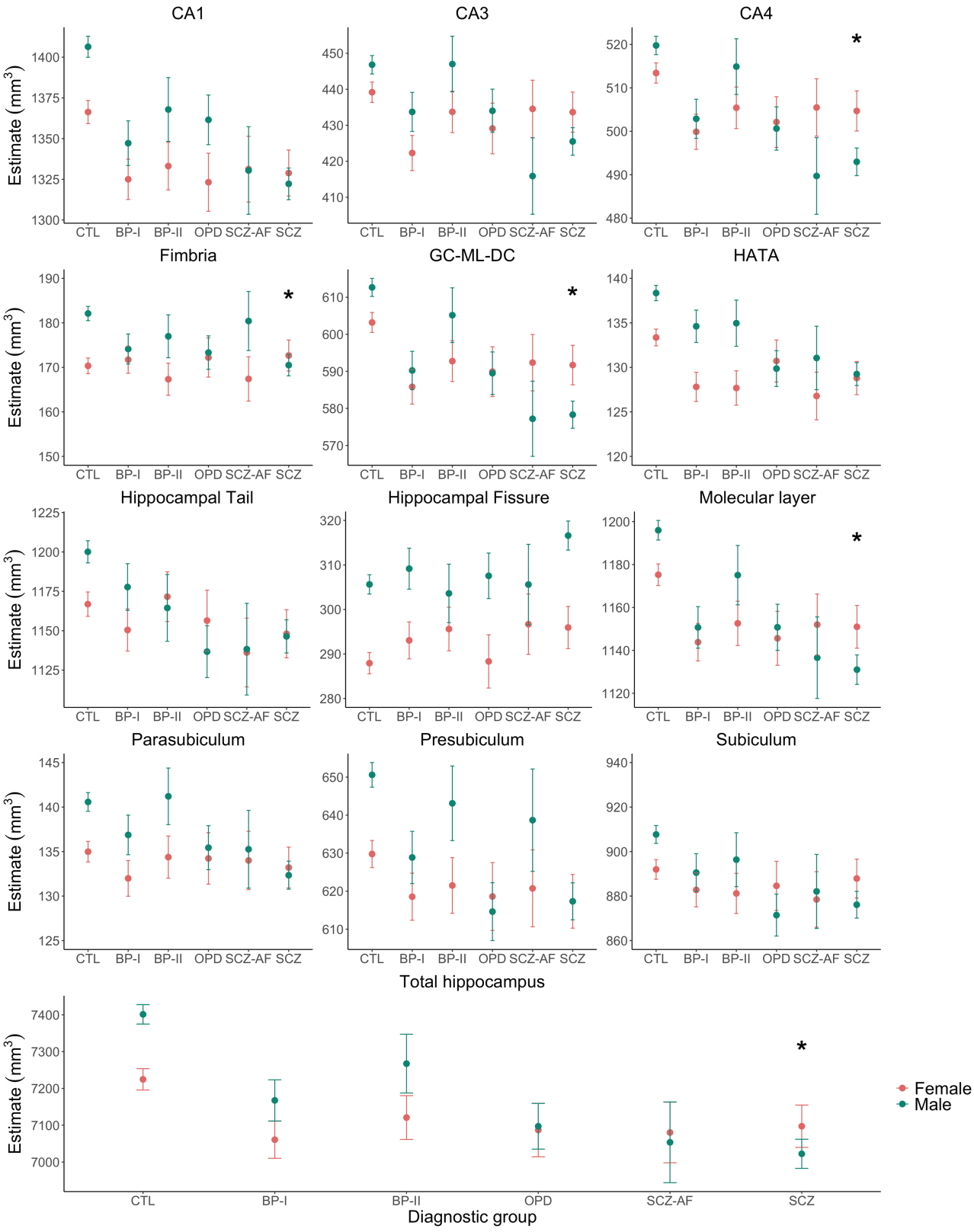

Fig. 2. Estimates of total hippocampus and subfield volumes stratified by diagnostic subgroup and sex. The model is adjusted for age, age^2, and intracranial volume. Estimates are displayed with upper and lower confidence intervals. Stars represent significant group difference relative to healthy controls (CTL), after false discovery rate correction. Significance codes: $P < .01$ "*." Abbreviation: BP, bipolar; SCZ, schizophrenia; SCZ-AF, schizoaffective disorder, OPD, other psychotic disorders; CA, cornu ammonis; GC-ML-DG, granule cells in the molecular layer of the dentate gyrus; HATA, hippocampal-amygdaloid transition area.

molecular layer, HATA, fimbria, hippocampal tail, and fissure, after adjustment for ICV. We found no evidence for larger volumes in healthy female CTL as compared to males for any of the subfields. Although the mechanisms behind larger hippocampal volumes in human males compared to females are currently unclear, animal work suggests sex and sex hormone differences in hippocampus structure and plasticity that may contribute to the observed volumetric sex difference.[7] However, it should be noted that sex differences in neuroanatomical structure may be dependent on ICV estimation[41] and choice of statistical method for adjusting for ICV.[42–44] Here, we estimated ICV as estimated total ICV via Freesurfer v6.0.0 and used the ANCOVA method, which has been shown to more effectively remove ICV-related variation than the proportions method.[42]

While we found higher volumes for most subfields in healthy males relative to females, this sex difference was largely absent or even reversed in individuals with SZ and BD. Directly comparing SZ and BD, we found lower total hippocampal, GC-ML-DG, and HATA volumes in males with SZ relative to males with BD before FDR correction (see supplementary table S5). No differences were found between females with BD and SZ. This finding is

Table 3. Sex, Diagnostic Group, and Sex-by-Diagnostic Group Effects on Total Hippocampal and Subfield Volumes Assessed Using Analysis of Covariance

Subfield	Variable	F-value	partial η^2	*P*-value	P_{FDR}-value
CA1	Diagnostic group	8.575	0.011	**1.98e-04**	**.001**
	Sex	16.114	0.011	**6.26e-05**	**.000**
	Group-by-sex interaction	2.334	0.003	.097	.119
CA3	Diagnostic group	3.098	0.004	**.045**	.066
	Sex	3.704	0.002	.054	.071
	Group-by-sex interaction	3.126	0.004	**.044**	.066
CA4	Diagnostic group	5.237	0.007	**.005**	**.012**
	Sex	3.853	0.003	.050	.069
	Group-by-sex interaction	4.944	0.006	**.007**	**.016**
Fimbria	Diagnostic group	0.103	1.36e-04	.902	.902
	Sex	23.009	0.015	**1.77e-06**	**3.45e-05**
	Group-by-sex interaction	3.914	0.005	**.020**	**.033**
GC-ML-DG	Diagnostic group	6.666	0.009	**.001**	**.005**
	Sex	6.455	0.004	**.011**	**.021**
	Group-by-sex interaction	5.866	0.008	**.003**	**.008**
HATA	Diagnostic group	8.937	0.012	**1.39e-04**	**.001**
	Sex	15.237	0.010	**9.90e-05**	**.001**
	Group-by-sex interaction	4.012	0.005	**.018**	**.031**
Hippocampal tail	Diagnostic group	1.584	0.002	.205	.229
	Sex	9.354	0.006	**.002**	**.006**
	Group-by-sex interaction	2.298	0.003	.101	.119
Hippocampal fissure	Diagnostic group	1.899	0.003	.150	.172
	Sex	28.125	0.018	**1.31e-07**	**5.09e-06**
	Group-by-sex interaction	0.188	2.49e-04	.828	.850
Molecular layer	Diagnostic group	8.118	0.011	**3.11e-04**	**.001**
	Sex	8.679	0.006	**.003**	**.008**
	Group-by-sex interaction	4.749	0.006	**.009**	**.018**
Parasubiculum	Diagnostic group	0.696	0.001	.499	.526
	Sex	11.692	0.008	**.001**	**.003**
	Group-by-sex interaction	2.921	0.004	.054	.071
Presubiculum	Diagnostic group	2.561	0.003	.078	.098
	Sex	17.224	0.011	**3.51e-05**	**3.42e-04**
	Group-by-sex interaction	4.092	0.005	**.017**	**.030**
Subiculum	Diagnostic group	1.169	0.002	.311	.337
	Sex	6.708	0.004	**.010**	**.019**
	Group-by-sex interaction	3.266	0.004	**.038**	.060
Hippocampus	Diagnostic group	6.608	0.009	**.001**	**.005**
	Sex	19.027	0.012	**1.38e-05**	**1.79e-04**
	Group-by-sex interaction	6.114	0.008	**.002**	**.006**

Note The statistical results are based on analysis of covariance (adjusted for age, age^2, and intracranial volume). Significant results are highlighted in bold. Abbreviation: CA, cornu ammonis; GC-ML-DG, granule cells in the molecular layer of the dentate gyrus; HATA, hippocampal-amygdaloid transition area; FDR, false discovery rate. FDR-correction was applied across all volumes and tests listed in this table.

in line with previous studies showing greater magnitudes of hippocampal subfield volume reductions in schizophrenia than in BD.[12,45] However, our results suggest that this differential pattern of volume deficits is not just dependent on diagnosis but also on sex.

In a previous study using the same study sample, we found no significant group-by-sex interaction for bilateral total amygdala volume and amygdala nuclei volumes,[36] suggesting that sex-by-diagnostic group differences may be specific to the hippocampus within the amygdala-hippocampus formation. The diagnostic subgroup analysis revealed significant sex-by-group effect on hippocampal volume in schizophrenia only, particularly for the GC-ML-DG, molecular layer, fimbria, CA4, and total hippocampus. In these subfields, volumes were significantly lower in males with schizophrenia as compared with CTL, but not in females with schizophrenia. This finding is in line with previous studies, showing lower total hippocampal or medial temporal lobe volume in males with schizophrenia, but not in females with schizophrenia relative to same-sex CTL.[46,47]

Our findings suggest that this male-specific deficit in total hippocampal volume may be driven by lower volumes in the CA4, GC-ML-DG, molecular layer, and fimbria. The CA4 is considered a starting point for axonal fibers of the fornix, and fornix fibers traverse through the fimbria, which connects the hippocampus with several cortical and subcortical regions. As the hippocampus and fornix are anatomically tightly connected, lower CA4 and fimbria volume may contribute to impaired fornix integrity, as reported in schizophrenia.[48] Interestingly, impaired fornix-hippocampus integrity has previously been linked both to early psychosis[49] and cognitive disturbances and memory function in schizophrenia.[50] Furthermore, the molecular layer has also been linked to memory function.[51] Based on these previous findings, one might speculate that the observed male-specific volume reductions in the CA4, GC-ML-DG, fimbria, and molecular layer in schizophrenia could be linked to cognitive impairments, which have been shown to be more pronounced in males than females with schizophrenia.[33] Even though we found sex differences in SZ on verbal learning, verbal memory, and processing speed tasks, where females outperformed males, we did not find any significant interaction effects between cognitive measures and volumes in the aforementioned subfields by sex. Similarly, none of the observed main effects of cognitive measures on subfield-specific volumes survived FDR correction. This finding is not in line with previous results.[13,52,53] However, previous studies have either focused on a few cognitive tests,[13,52] not multiple domains, or have studied the whole hippocampus and not hippocampal subfields,[53] reducing the number of multiple comparisons. Furthermore, while we selected tasks that have previously been linked to hippocampal volumes and have been shown to be impaired in SZ and BD, these cognitive tasks are not specific to the hippocampus; but also rely on other brain regions such as the dorsolateral prefrontal cortex.[54] More research, including cognitive batteries particularly sensitive to hippocampal functioning,[7] may elucidate the relationship between cognitive functioning, hippocampal morphology, and sex in SZ and BD. However, it should be noted that sex differences in structure may not translate to or cause sex differences in cognition. It could be equally possible that sex differences in structure prevent sex differences in behavior by compensating for sex differences in physiological conditions such as sex hormone levels.[55]

Although medication, including antipsychotics,[56] antidepressants,[57] and lithium[58] have been associated with hippocampal volumes, we found no association between current use of psychotropic drugs or mood stabilizers and volumes in SZ and BD after FDR-correction. However, as medication effects might depend on the specific types of drugs and duration of exposure which may not necessarily be linear, the use of defined daily dose alone to address this confound has limitations. Similarly, we found no associations between most clinical measures and hippocampal volumes after FDR correction. The lack of an association between psychotic symptoms and volumes in SZ may result from the relatively small variation in psychotic symptoms in our sample. It may also relate to issues such as variability of symptom states over time, or currently unknown confounders. We did, however, find a significant main effect of age of onset and duration of illness on hippocampal fissure volume in BD and SZ, suggesting a positive association. The hippocampal fissure does not represent hippocampal tissue, but rather a cerebral spinal fluid cleft that forms during early brain development.[59] The presence of enlarged hippocampal fissures has been shown in first-episode individuals with schizophrenia, and may be a sign of disrupted hippocampal development in schizophrenia.[60]

A major strength of the current study is the large sample size with a balanced sex distribution, and detailed clinical and cognitive assessment of individuals with SZ and BD. This allowed for a comprehensive study of sex differences in hippocampal subfield volumes in SZ, BD, and CTL, currently unmatched in the literature. However, the cross-sectional nature of the data precludes causal inferences, and longitudinal studies are needed to determine the timing of changes in hippocampal subfields by diagnostic group and sex. Furthermore, automated hippocampal subfield segmentation using MRI is challenging. The segmentation method used here is based on ultra-high-resolution ex vivo MRI data which allows for the precise delineation of hippocampal subfields to determine tissue priors.[18] In the current study, however, subfields are probabilistically labeled based on conventional MRI data with 1 mm isotropic resolution. As such, the volumes of subfields contained within the interior of the hippocampal formation must be interpreted with caution, and a replication of our results using high-resolution MRI data is warranted. Furthermore, the reliability of automated volumetry is

inversely associated with volume size.[61] The volumes of smaller hippocampal subfields, such as the hippocampal fissure, fimbria, parasubiculum, and HATA, may thus be less reliable. In addition, although automated volumetry has been shown to be generally reliable in multicenter MRI studies,[61] and we successfully harmonized volumes and ICV across scanners using ComBat, residual effects of scanner may still be present. Besides the effect of sex, we also found significant main effects of age and age^2 on all volumes, except the presubiculum and parasubiculum. This finding is partly in line with a study in CTL, reporting age-related volume changes in all subfields, except in the subiculum complex (subiculum proper, presubiculum, and parasubiculum).[60,62] However, before FDR correction, we found a significant age-by-diagnostic group interaction for individuals with SZ relative to CTL in the presubiculum and parasubiculum, potentially suggesting abnormal aging processes in these subfields in SZ.

In summary, the pattern of morphological sex differences in the hippocampus appears to be altered in individuals with schizophrenia relative to CTL, due to higher volumetric deficits in males. Our findings highlight that sex should be considered when studying individuals with psychiatric illnesses, not just as a covariate, which might mask potential sex differences, but as a discovery variable.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflict of Interest

For work unrelated to the content of this manuscript, OAA and IA received speaker's honorarium from Lundbeck. OAA also received speaker's honorarium from Sunovion and Janssen, and works as a consultant for Cortechs.ai. The other authors report no biomedical financial interests or potential conflicts of interest.

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