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In Vivo Amygdala Nuclei Volumes in Schizophrenia and Bipolar Disorders

Claudia Barth*[,1,2], Stener Nerland[1,2], Ann-Marie G. de Lange[1,3,4], Laura A. Wortinger[1,2], Eva Hilland[1], Ole A. Andreassen[1,5], Kjetil N. Jørgensen[1,2], and Ingrid Agartz[1,2,6]

[1]Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Section Vinderen, P.O. Box 85, N-0319 Oslo, Norway; [2]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway; [3]Department of Psychiatry, University of Oxford, Oxford, UK; [4]Department of Psychology, University of Oslo, Oslo, Norway; [5]Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; [6]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

*To whom correspondence should be addressed; tel: +47 22 02 99 67, fax: +47 22 02 99 01, e-mail: claudia.barth@medisin.uio.no

Abnormalities in amygdala volume are well-established in schizophrenia and commonly reported in bipolar disorders. However, the specificity of volumetric differences in individual amygdala nuclei is largely unknown. Patients with schizophrenia disorders (SCZ, *N* = 452, mean age 30.7 ± 9.2 [SD] years, females 44.4%), bipolar disorders (BP, *N* = 316, 33.7 ± 11.4, 58.5%), and healthy controls (*N* = 753, 34.1 ± 9.1, 40.9%) underwent T1-weighted magnetic resonance imaging. Total amygdala, nuclei, and intracranial volume (ICV) were estimated with Freesurfer (v6.0.0). Analysis of covariance and multiple linear regression models, adjusting for age, age², ICV, and sex, were fitted to examine diagnostic group and subgroup differences in volume, respectively. Bilateral total amygdala and all nuclei volumes, except the medial and central nuclei, were significantly smaller in patients relative to controls. The largest effect sizes were found for the basal nucleus, accessory basal nucleus, and cortico-amygdaloid transition area (partial $\eta^2 > 0.02$). The diagnostic subgroup analysis showed that reductions in amygdala nuclei volume were most widespread in schizophrenia, with the lateral, cortical, paralaminar, and central nuclei being solely reduced in this disorder. The right accessory basal nucleus was marginally smaller in SCZ relative to BP ($t = 2.32$, $P = .05$). Our study is the first to demonstrate distinct patterns of amygdala nuclei volume reductions in a well-powered sample of patients with schizophrenia and bipolar disorders. Volume differences in the basolateral complex (lateral, basal, and accessory basal nuclei), an integral part of the threat processing circuitry, were most prominent in schizophrenia.

Key words: amygdala/neuroimaging/schizophrenia/bipolar disorder/schizoaffective disorder/other psychotic disorders

Introduction

Schizophrenia and bipolar disorders are severe mental health disorders with shared pathophysiological traits along a psychosis continuum.[1] Although the neural substrates of the 2 disorders are still largely unknown, structural brain abnormalities in amygdala volume have been reported in both.[2,3] The amygdala is an almond-shaped brain structure located in the mesiotemporal region of the temporal lobe, adjacent to the hippocampus.[4] It is involved in a broad range of complex behaviors, including emotion and threat processing, and the regulation of adaptive behavioral responses,[4] known to be affected in schizophrenia[5] and bipolar disorders.[6] Using functional magnetic resonance imaging (MRI), studies on schizophrenia have shown reduced amygdala activation in response to aversive emotional stimuli[7] as well as during facial emotion recognition and evaluation tasks.[8,9] Similarly, abnormal amygdala activity has been observed during emotional processing tasks in patients with bipolar disorders.[10]

On a structural level, there is considerable uncertainty about the specificity and magnitude of volumetric differences in the amygdala in schizophrenia and bipolar disorders. In schizophrenia, whole amygdala volumes showed statistically significant reductions in 3 large-scale meta-analyses, with low to moderate effect sizes ($d \approx 0.2$).[2,3,11] In bipolar disorders, less pronounced volumetric reductions have been shown,[12] with considerable heterogeneity between studies.[13] This discrepancy in findings may stem from phenotypic heterogeneity, such as differences in disease severity and duration, medication history, and comorbidities. Particularly, medication may impact amygdala volume. For instance, lower left

amygdala volumes were found in non-lithium-treated patients but not in lithium-treated patients,[14] and this effect may be dependent on the duration of lithium exposure.[15] Differences in neuroimaging data acquisition, amygdala segmentation methods, and analysis approaches, eg, shape vs volume measures,[16,17] can further affect study outcomes.

The amygdala is not a uniform structure; it rather consists of heterogeneous nuclei with distinct functional correlates.[18] Using ultra-high-resolution ex vivo MRI data, Saygin et al were able to probabilistically label 9 nuclei boundaries, namely the lateral, basal, central, medial, cortical, paralaminar, and accessory basal nuclei, the cortico-amygdaloid transition area, and the anterior amygdaloid area.[19] Based on animal studies, each nucleus seems to serve specific functions. The lateral nucleus is the main entry point for sensory information to the amygdala[20]: it receives sensory afferent input from the cortex and thalamus and integrates this information before relaying it to other nuclei. Together with the basal nucleus, the lateral nucleus is an integral part of the threat processing circuitry,[21] and postmortem studies indicate that both nuclei may be affected in schizophrenia.[22–24]

Recent in vivo studies replicated smaller lateral and basal nuclei volumes in first-episode psychosis relative to controls,[16] in schizophrenia relative to healthy individuals,[25] and in bipolar patients with psychotic features.[17] Volume reductions in the lateral nucleus have also been detected in clinical high-risk individuals.[16] Another study in patients with bipolar disorders found significantly smaller volumes in a number of nuclei relative to controls but no reductions in the lateral nucleus.[26] These findings indicate that reduced lateral nucleus volume may be associated with psychosis risk, particularly in schizophrenia. Other nuclei may also be reduced in schizophrenia[17,25]; however, findings are rather sparse. To our knowledge, no study has systematically investigated amygdala nuclei differences in schizophrenia and bipolar disorders, including schizoaffective disorder, schizophrenia, and other psychotic disorders (OPD), as well as bipolar I and II disorders, in a well-powered sample. This is a research gap as a better understanding of how in vivo amygdala nuclei volumes differ in patients with schizophrenia and bipolar disorders may enable more precise and mechanistic theories of amygdala dysfunction in the development of psychosis.

The amygdala is often studied together with the hippocampus[15,25,27] as both structures are tightly and reciprocally connected.[28] Abnormalities in the amygdala–hippocampus complex have been implicated in schizophrenia[2] and bipolar disorders.[13] However, differences in total amygdala and hippocampal volume are rarely directly compared, and it is unclear whether amygdala volume is distinctly or similarly altered relative to hippocampal volume in patients with schizophrenia and bipolar disorders relative to controls.

Here, we examined diagnostic group differences in amygdala nuclei volumes in 768 patients with schizophrenia and bipolar disorders and 753 healthy controls. Based on previous studies, we expected the strongest volume reductions in patients with schizophrenia, most prominently in the lateral and basal nuclei. We further investigated whether differences in total amygdala volume were comparable to differences in hippocampal volume between diagnostic groups. In exploratory analyses, we also studied potential sources of heterogeneity in volumetric indices based on sex,[29] antipsychotic and mood stabilizing medication,[14] and psychotic as well as affective symptoms.

Methods

Participants

A sample of 753 controls and 768 patients was drawn from the ongoing Thematically-Organized-Psychosis study cohort (October 2002–January 2018; supplementary materials). Patients were recruited from inpatient and outpatient psychiatric units covering catchment areas in the Oslo region. Healthy controls were randomly drawn from the Norwegian national population register in the same catchment areas. All participants gave written informed consent to participate. The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Inspectorate and carried out in accordance with the Helsinki Declaration.

Clinical Assessment

Clinical diagnoses were established according to the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) axis 1 disorder (SCID-I), module A–E.[30] Healthy controls were evaluated with the Primary Care Evaluation of Mental Disorders (Prime-MD) to rule out current or previous psychiatric disorders.[31] Presence and severity of psychotic symptoms of patients were assessed using the Positive and Negative Syndrome Scale.[32] Affective state was evaluated using the Young Mania Rating Scale (YMRS)[33] and the Inventory for Depressive Symptomatology (IDS).[34] Global Assessment of Function (GAF) scale, split version, was administered to measure general functioning level.[35] Clinical characterization was conducted by trained psychologists or psychiatrists.

Based on DSM-IV criteria, the patient sample was diagnosed as follows: (1) *broad schizophrenia spectrum* (SCZ; N = 452): schizophrenia [DSM-IV 295.1, 295.3, 295.6, 295.9; N = 245], schizophreniform [DSM-IV 295.4; N = 31], schizoaffective [DSM-IV 295.7; N = 59], other psychotic disorders [OPD, DSM-IV 297.1, 298.8, 298.9; N = 117], (2) *bipolar spectrum* (BP, N = 316): bipolar I [DSM-IV 296.0–7; N = 188], bipolar II [DSM-IV 296.89; N = 113], and bipolar not otherwise specified [DSM-IV 296.8; N = 15]. The

majority of the bipolar patients were investigated in their euthymic phase (87.3%, ie, YMRS < 8 and IDS ≤ 13[36]).

Medication

Current use of medication among patients, including antipsychotics, antidepressants, and antiepileptics, was recorded and converted into defined daily dose (DDD).[37] We further assessed lithium user status und serum concentration in BP (for details, see supplementary material).

MRI Data Acquisition and Processing

Participants underwent T1-weighted structural imaging either at 1.5T (2004–2009, $N = 745$) or at 3T (2011–present, $N = 776$) scanner (for details, see supplementary material). The 1.5T sample was acquired on a Siemens Magnetom Sonata scanner (voxel size = 1.33 × 0.94 × 1 mm). At 3T, volumes were acquired on a General Electric Signa HDxt scanner (voxel size = 1 × 1 × 1.2 mm) and a Discovery 750 scanner (voxel size = 1 × 1 × 1 mm), respectively.

T1-weighted MRI volumes were processed in FreeSurfer (v6.0.0) using the standard cross-sectional processing stream to obtain volumes of the bilateral hippocampus, amygdala, amygdala nuclei, and intracranial volume (ICV; estimate based on the Talairach transform). The automated segmentation of the amygdala is based on a probabilistic atlas, created with ultra-high-resolution ex vivo MRI data (~0.1–0.15 mm isotropic) and includes 9 subdivisions.[19] ComBat harmonization was performed on amygdala volumes, hippocampal volumes, and ICV to remove unwanted variation associated with scanner whilst preserving biological associations in the data.[38,39] Empirical Bayes was used to leverage information across volumes, and with age, sex, and diagnostic group as biological variables of interest. Across diagnostic groups, amygdala volumes are visualized before (supplementary figure S1) and after ComBat harmonization (supplementary figure S2).

Statistical Analyses

To assess diagnostic group differences in bilateral total amygdala and nuclei volumes, we performed analysis of covariance (ANCOVA) with volume as dependent variable, diagnostic group and sex as fixed factors, and age, age^2, and ICV as covariates. Age^2 was added to more accurately model the effect of age, which may have a nonlinear relationship with volume.[40] Levene's tests (volume–diagnostic group) were performed to test whether the key assumption of ANCOVAs—homogeneity of variance—is met. No violations were detected. To test whether results replicated between scanners, we reran the ANCOVA to assess diagnostic group differences in total amygdala and nuclei volume for the 1.5T ($N = 745$), 3T-HDxt ($N = 438$), and 3T-MR750 ($N = 337$) samples separately. Post hoc Tukey tests were performed to contrast volume differences between control vs BP, control vs SCZ, BP vs SCZ, and females vs males. Effect sizes were calculated as partial eta-squared based on F-statistic. To further explore amygdala volume differences between diagnostic groups, across age and sex, we fitted separate multiple linear models with bilateral total amygdala volumes as dependent variable and either group-by-age interaction, group-by-age^2 interaction, sex, and ICV or group-by-sex interaction, age, age^2, and ICV as independent variables, respectively. As associations between brain size and IQ have previously been reported,[41] we also ran regression models, including IQ as an additional covariate.

Multiple linear regression models were also fitted to assess diagnostic subgroup differences in total amygdala and nuclei volume, adjusting for age, age^2, ICV, and sex. As we found amygdala alterations with bilateral effects (see table 2), we combined left and right volumes in the diagnostic subgroup analyses to avoid unnecessary multiple comparisons.

We also evaluated total amygdala volume differences in bipolar I and II patients as well as in bipolar patients with and without psychotic features in additional linear models. The presence of psychotic features was defined based on DSM-IV diagnoses (ie, 296.44, 296.54, 296.04, and 296.64) and a history of psychotic episodes. Diagnostic plots revealed one influential outlier (male bipolar I patient, Cook's distance > 0.5), which was removed from further analysis. Effect sizes for multiple linear regression results were calculated as Cohen's d based on t-statistic.

We further examined whether amygdala volume was similarly or differently affected compared to hippocampal volume between diagnostic groups by calculating pairwise group differences between amygdala and hippocampus volume based on z tests for correlated samples (for details, see supplementary material).

To test for the potentially confounding effect of medication on amygdala volumes (dependent variable), additional multiple linear regression models were fitted for each diagnostic group separately. In both SCZ and BP, the effects of antipsychotics, antidepressants, and antiepileptics, measured as DDD (independent variable), were assessed. In BP, we further explored the effects of lithium, measured as lithium use status and serum concentration levels, on amygdala volumes. The models were adjusted for age, age^2, ICV, and sex.

To examine the association between amygdala volumes and psychotic symptoms (PANSS subscales in SCZ), affective symptoms (YMRS and IDS in BP), duration of illness and general functioning (GAF symptoms/function), additional multiple linear regression models were fitted, adjusted for age, age^2, ICV, and sex.

False discovery rate (FDR) correction was applied to account for multiple comparisons across all volumes tested. All statistical tests were conducted in R (v3.5.2).

Results

Demographic and Clinical Variables

Sample demographics and clinical characteristics are reported in table 1. Characteristics of the diagnostic subgroups are summarized in supplementary table S1.

Amygdala Nuclei Volume Differences Between Diagnostic Groups

Total amygdala and all nuclei volumes, except the medial and central nuclei, were significantly lower in SCZ and BP relative to controls (figure 1; table 2; see supplementary table S2 for results across scanners). The largest effects sizes were found for the basal nucleus, accessory basal nucleus, and cortico-amygdaloid transition area. Post hoc Tukey tests revealed significant differences between healthy controls and BP for the bilateral whole amygdala, basal nucleus, accessory basal nucleus, anterior amygdaloid area, cortico-amygdaloid transition area as well as left paralaminar nucleus (supplementary table S3). Right accessory basal nucleus volume was lower in SCZ relative to BP (beta = 4.63, SE = 1.99, t = 2.32, P = .053).

Based on the ANCOVA models, we further found a significant effect of sex for all amygdala volumes. Across diagnostic groups, males had higher volumes relative to females (figure 1; supplementary table S3). We found no significant group-by-sex interaction for bilateral total amygdala volumes. Similar to sex, age and age^2 showed a significant main effect on all volumes, except the left medial and right paralaminar nucleus, based on the ANCOVA models. We did not find, however, significant group-by-age and group-by-age^2 interactions for amygdala volumes in the linear regression models. In addition, no significant associations between IQ and amygdala volumes were found across diagnostic groups.

Table 1. Sample demographics and clinical measures in patients with schizophrenia and bipolar disorders relative to controls

	CTL	BP	SCZ	*P*-value	Test
	N = 753	*N* = 316	*N* = 452		
Sex, male *N* (%)	419 (55.6)	131 (41.5)	267 (59.1)	**<.001**	χ2
Handedness, *N* (R/L/A/M)	655/73/4/21	250/35/3/28	372/43/2/35	**.001**	FET
Age at scan (years)	33.2 [27.0, 40.4]	30.8 [24.6, 40.9]	28.5 [23.4, 36.5]	**<.001**	KW
Education (years)	15.0 [12.0, 16.0]	15.0 [12.5, 16.0]	13.0 [12.0, 15.0]	**<.001**	KW
IQ	114.0 [108.0, 120.0]	109.0 [102.0, 117.0]	105.5 [95.0, 114.0]	**<.001**	KW
BMI (kg/m^2)	24.4 [22.3, 26.8]	24.7 [22.2, 27.6]	25.0 [22.3, 29.0]	**.038**	KW
ICV (l)	1.5 [1.5, 1.7]	1.5 [1.5, 1.7]	1.6 [1.4, 1.7]	.677	KW
Age of onset (years)		19.0 [15.0, 25.0]	22.0 [19.0, 27.0]	**<.001**	KW
DUP (weeks)		3.0 [1.0, 25.0]	30.0 [4.0, 104.0]	**<.001**	KW
GAF, symptom		60.0 [51.8, 66.0]	42.0 [38.0, 53.0]	**<.001**	KW
GAF, function		55.0 [48.0, 65.5]	45.0 [38.0, 53.0]	**<.001**	KW
PANSS, total		43.0 [38.0, 49.0]	58.0 [48.0, 69.0]	**<.001**	KW
Negative		9.0 [7.0, 11.0]	13.0 [10.0, 19.0]	**<.001**	KW
Positive		9.0 [7.0, 10.5]	13.0 [10.0, 17.0]	**<.001**	KW
YMRS		2.0 [0.0, 4.0]	2.0 [0.0, 8.0]	.196	KW
IDS		15.0 [8.0, 24.0]	15.0 [7.0, 25.0]	.794	KW
Medication (DDD)					
Antipsychotics (AP)		0.7 [0.4, 1.0]	1.1 [0.8, 1.8]	**<.001**	KW
AP status, users *N* (%)		209 (66.6)	430 (95.1)	**<.001**	χ2
Antidepressants (AD)		1.0 [1.0, 2.0]	1.1 [1.0, 2.0]	.982	KW
AD status, users *N* (%)		111 (35.1)	139 (30.8)	**<.001**	χ2
Antiepileptics (AE)		0.7 [0.4, 1.0]	0.7 [0.5, 0.8]	.545	KW
AE status, users *N* (%)		115 (36.4)	58 (12.8)	**<.001**	χ2
Lithium, serum level, mmol/l		0.6 [0.5, 0.7]	0.5 [0.4, 0.7]	.174	KW
Status, users *N* (%)		55 (17.4)	11 (2.4)	**<.001**	χ2
Psychotic features, yes *N* (%)		191 (60.4)			
Scanner (Sequence), *N* (%)				**<.001**	χ2
1.5-T, Siemens MS, MPRAGE	270 (35.9)	184 (58.2)	291 (64.4)		
3-T, GE HDxt, FSPGR	281 (37.3)	57 (18.0)	100 (22.1)		
3-T, GE D750, BRAVO	202 (26.8)	75 (23.7)	61 (13.5)		

Note: Nonnormal distributed data in median [interquartile range]. Medication status at the time of assessment is defined as: yes (user) and no (non-user). Significant results are highlighted in bold.
CTL, healthy controls; BP, bipolar disorders; SCZ, schizophrenia disorders, *N*, number; R, right; L, left; A, ambidextrous; M, missing; y, year; BMI, body mass index; ICV, intracranial volume; DUP, duration of untreated psychosis; GAF, global assessment of functioning; PANSS, positive and negative syndrome scale; YMRS, young mania rating scale; IDS, inventory for depressive symptomatology; DDD, defined daily dose; KW, Kruskal–Wallis; FET, Fisher's exact test; GE, General Electric; MS, Magnetom Sonata; D750, Discovery 750.

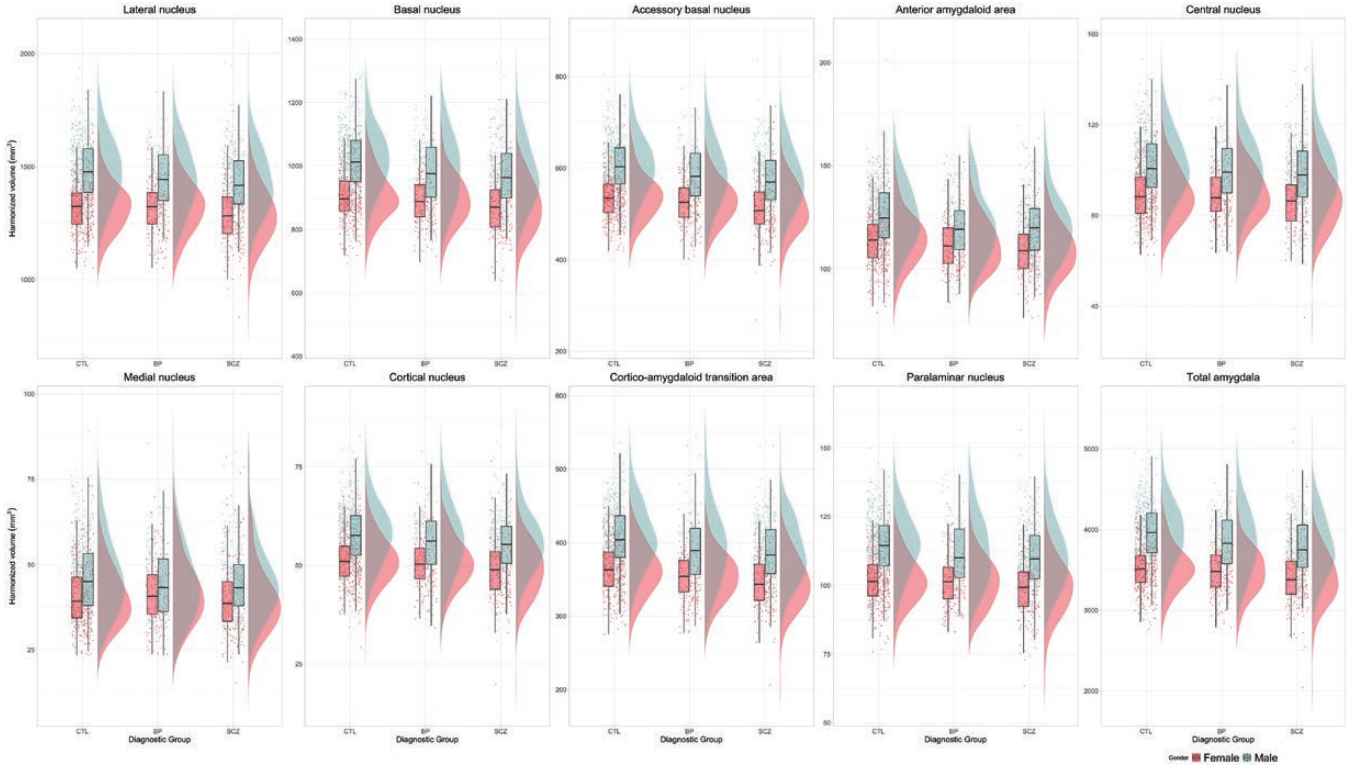

Fig. 1. Amygdala volumes stratified by diagnostic group and sex. ComBat-harmonized volumetric data is displayed as raincloud plots, which combines boxplots, raw data points (scatterplot), and the distributions of the data (histogram) using split-half violins. Volumes are presented as sex-disaggregated data (females = red, males = blue) in line with the "sex-as-a-biological-variable" National Institute of Health initiative. CTL = healthy controls, BP = bipolar disorders, SCZ = schizophrenia disorders.

The diagnostic subgroup analysis revealed nuclei-specific volume reduction, with schizophrenia showing the most widespread effects (figure 2; supplementary table S4). All nuclei, except the bilateral medial nucleus, were significantly smaller in patients with schizophrenia relative to healthy controls. While the basal nucleus, accessory basal nucleus, anterior amygdaloid area, and cortico-amygdaloid transition area were smaller in bipolar I, lower nuclei volumes in bipolar II were restricted to the basal nucleus and the cortico-amygdaloid transition area. In OPD, we identified nuclei-specific volume reductions largely overlapping with bipolar I: accessory basal nucleus, anterior amygdaloid area, and cortico-amygdaloid transition area. We did not find a significant difference in total amygdala volume either between bipolar I and II patients (beta = 1.86, SE = 31.65, t = 0.06, P = .953) or between bipolar patients with (N = 191) and without psychotic features (N = 124, beta = 12.16, SE = 30.61, t = 0.40, P = .691).

Relative to hippocampal volume, amygdala volume was significantly less reduced in patients compared to healthy controls, while the difference between SCZ and BP was not significant (table 3). Mean hippocampal volume (mm^3) for each of the groups was as follows: control 7358.44 ± 695.10 (SD), BP 7081.31 ± 661.10, and SCZ 7034.74 ± 693.42.

There were no significant associations between antipsychotic, antidepressant, and antiepileptic medication use (DDD) and bilateral total amygdala and nuclei volumes in SCZ and BP. In patients with BP, we also found no significant associations with lithium use status or serum concentration, surviving correction for multiple comparisons (see supplementary material).

Bilateral total amygdala and nuclei volumes were not associated with psychotic symptoms in SCZ and affective symptoms in BP. Furthermore, no significant associations were found between either general functioning or duration of illness and bilateral amygdala volumes in any of the patient groups after FDR correction (see supplementary material).

Discussion

In the current study, total amygdala and all nuclei volumes, except the medial and central nuclei, were smaller in patients with schizophrenia and bipolar disorders relative to controls. The largest effect sizes were found for the basal nucleus, accessory basal nucleus, and cortico-amygdaloid transition area (partial $\eta^2 > 0.02$; table 2). The diagnostic subgroup analysis showed that total amygdala volume was significantly smaller in schizophrenia, bipolar I, and OPD but not in schizoaffective disorder and bipolar II

Table 2. Results of the analysis of covariance of amygdala nuclei in patients with schizophrenia and bipolar disorders relative to healthy controls.

Volume (mm^3)	Side	CTL	BP	SCZ	*F*-value	partial η^2	*P*-value	$P\text{-value}_{FDR}$
Lateral nucleus	R	714.94 ± 2.14 [710.75, 719.14]	706.99 ± 3.30 [700.52, 713.46]	699.73 ± 2.78 [694.27, 705.18]	9.505	0.012	**7.91e-05**	**1.32e-04**
	L	684.87 ± 2.06 [680.84, 688.90]	678.24 ± 3.17 [672.02, 684.46]	671.65 ± 2.67 [666.40, 676.89]	7.732	0.010	**4.56e-04**	**6.52e-04**
Basal nucleus	R	489.77 ± 1.50 [486.83, 492.72]	479.46 ± 2.31 [474.92, 484.00]	474.10 ± 1.95 [470.27, 477.92]	21.520	0.028	**6.09e-10**	**3.05e-09**
	L	469.75 ± 1.44 [466.92, 472.57]	460.57 ± 2.22 [456.21, 464.93]	455.85 ± 1.88 [452.17, 459.53]	18.330	0.024	**1.36e-08**	**3.89e-08**
Accessory basal nucleus	R	292.30 ± 0.99 [290.37, 294.23]	286.19 ± 1.52 [283.21, 289.17]	281.56 ± 1.28 [279.05, 284.07]	22.606	0.029	**2.12e-10**	**1.41e-09**
	L	277.65 ± 0.97 [275.74, 279.56]	270.97 ± 1.50 [268.03, 273.91]	268.04 ± 1.27 [265.56, 270.52]	19.589	0.025	**3.99e-09**	**1.42e-08**
Anterior amygdaloid area	R	63.13 ± 0.28 [62.59, 63.67]	61.43 ± 0.43 [60.60, 62.27]	60.59 ± 0.36 [59.88, 61.29]	16.751	0.022	**6.38e-08**	**1.42e-07**
	L	56.56 ± 0.25 [56.06, 57.05]	55.17 ± 0.39 [54.40, 55.93]	54.74 ± 0.33 [54.10, 55.39]	10.765	0.014	**2.28e-05**	**4.56e-05**
Central nucleus	R	49.61 ± 0.26 [49.11, 50.12]	49.31 ± 0.39 [48.54, 50.09]	48.61 ± 0.33 [47.96, 49.26]	2.872	0.004	0.057	0.067
	L	45.96 ± 0.25 [45.47, 46.45]	45.47 ± 0.38 [44.71, 46.22]	45.21 ± 0.32 [44.58, 45.85]	1.787	0.002	0.168	0.186
Medial nucleus	R	22.42 ± 0.22 [21.99, 22.85]	22.68 ± 0.34 [22.01, 23.35]	22.41 ± 0.29 [21.84, 22.97]	0.235	3.11e-04	0.790	0.790
	L	21.04 ± 0.21 [20.62, 21.45]	20.72 ± 0.33 [20.08, 21.36]	20.66 ± 0.28 [20.12, 21.19]	0.711	0.001	0.492	0.517
Cortical nucleus	R	28.12 ± 0.14 [27.85, 28.39]	27.81 ± 0.21 [27.39, 28.22]	27.27 ± 0.18 [26.92, 27.62]	6.973	0.009	**0.001**	**0.001**
	L	26.28 ± 0.15 [25.99, 26.57]	25.65 ± 0.23 [25.20, 26.10]	25.52 ± 0.19 [25.14, 25.90]	5.672	0.007	**0.004**	**0.004**
Cortico-amygdaloid transition area	R	196.46 ± 0.67 [195.14, 197.78]	191.17 ± 1.04 [189.13, 193.20]	188.38 ± 0.87 [186.66, 190.10]	28.405	0.036	**7.76e-13**	**1.55e-11**
	L	188.75 ± 0.65 [187.48, 190.03]	183.38 ± 1.00 [181.41, 185.35]	181.22 ± 0.85 [179.56, 182.88]	27.120	0.035	**2.68e-12**	**2.68e-11**
Paralaminar nucleus	R	54.47 ± 0.18 [54.13, 54.82]	53.81 ± 0.27 [53.28, 54.34]	53.30 ± 0.23 [52.85, 53.74]	8.582	0.011	**1.97e-04**	**3.03e-04**
	L	53.57 ± 0.17 [53.24, 53.91]	52.78 ± 0.26 [52.26, 53.30]	52.38 ± 0.22 [51.95, 52.82]	9.531	0.012	**7.70e-05**	**1.32e-04**
Whole amygdala	R	1911.09 ± 5.45 [1900.40, 1921.78]	1878.90 ± 8.41 [1862.41, 1895.40]	1856.01 ± 7.09 [1842.11, 1869.91]	19.523	0.025	**4.25e-09**	**1.42e-08**
	L	1824.25 ± 5.23 [1813.98, 1834.51]	1793.00 ± 8.07 [1777.17, 1808.84]	1775.49 ± 6.81 [1762.14, 1788.84]	16.971	0.022	**5.14e-08**	**1.28e-07**

Note: Estimated marginal means ± SE [CI]. The statistical results are based on analysis of covariance (adjusted for age, age^2, intracranial volume, and sex). Significant results are highlighted in bold.
CTL, controls, BP, bipolar disorders; SCZ, schizophrenia disorders; R, right; L, left; FDR, false discovery rate.

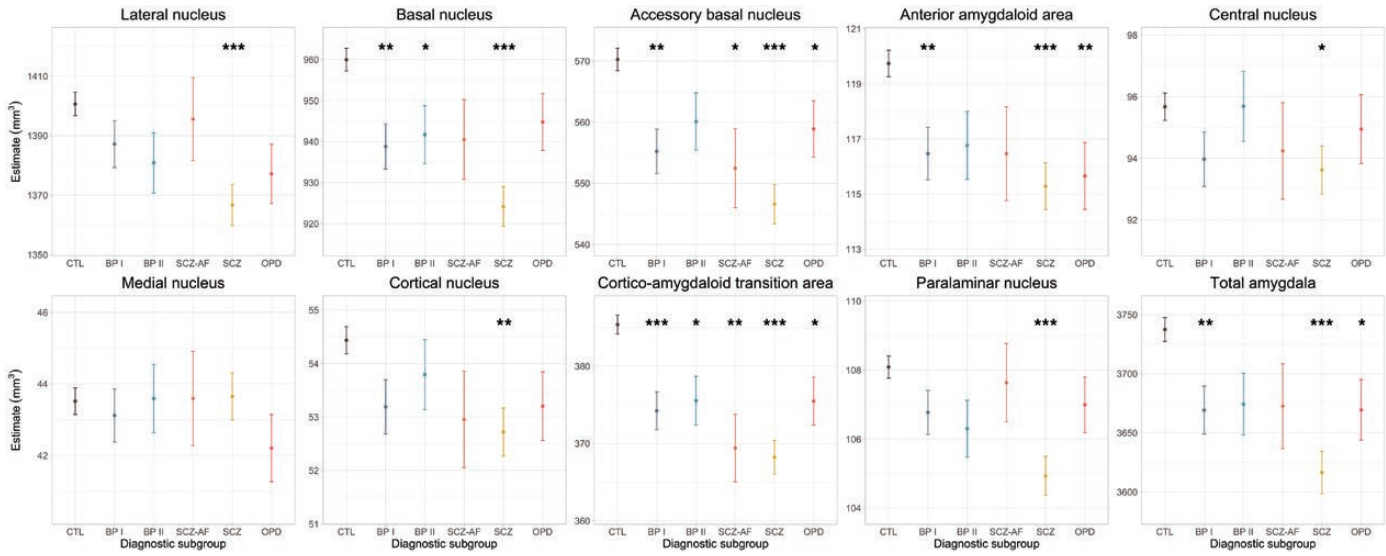

Fig. 2. Estimates of amygdala volumes stratified by diagnostic subgroup. Estimates are displayed with upper and lower CIs, adjusted for age, age^2, intracranial volume, and sex. Stars represent significant group difference relative to healthy controls (CTL) after family-wise-error correction. Significance codes: ***$P < .0001$; **$P < .001$; *$P > .01$. BP = bipolar, SCZ = schizophrenia, SCZ-AF = schizoaffective disorder, OPD = other psychotic disorders.

Table 3. Pair-wise group differences between amygdala and hippocampus volume based on *Z* tests

Comparison	Amygdala β ± SE	Hippocampus β ± SE	*Z*-score	*P*-value	FDR-corrected *P*
SCZ vs CTL	−104.83 ± 16.95	−266.66 ± 30.65	−7.11	**1.21e-12**	**3.62e-12**
BP vs CTL	−60.75 ± 19.04	−153.48 ± 33.78	−3.60	**1.22e-04**	**4.80e-04**
SCZ vs BP	−35.31 ± 20.19	−86.47 ± 38.07	−1.76	0.078	0.078

Note: Significant results are highlighted in bold.
CTL, healthy controls; BP, bipolar disorders; SCZ, schizophrenia disorders; FDR, false discovery rate.

(supplementary table S4). Reductions in amygdala nuclei volume were most pronounced in schizophrenia: all nuclei, except the medial nucleus, were significantly smaller in patients relative to healthy controls, indicating a more widespread change in amygdala morphology than previously thought.

In schizophrenia, previous postmortem studies found lower mean total neuron number in the lateral nucleus,[23] and changes in nuclear area, nucleolar volume,[22] and oligodendrocyte density[42] in the basolateral complex, consisting of the lateral, basal, and accessory basal nuclei. These findings seem to be corroborated by recent in vivo studies showing smaller nuclei volumes, predominantly, in the basal and lateral nuclei[16] or the right basolateral complex.[25] The lateral nucleus plays a key role in fear-related responses,[21] and lower volume as well as neuroarchitectural changes in this subregion has been suggested as a putative biomarker for psychosis risk.[16,22,23] Here, the lateral nucleus was significantly smaller in schizophrenia but not in any other diagnostic subgroup, indicating that the lateral nucleus may be particularly implicated in schizophrenia.

However, next to the lateral nucleus, the cortical, paralaminar, and central nuclei were also solely reduced in schizophrenia. The cortical nucleus is a major target of olfactory projections,[43] and the presence of olfactory deficits is well established in schizophrenia.[44] It is possible that volume reductions in the cortical nucleus may contribute to this dysfunction. However, we did not find significant volume differences in the medial nucleus between diagnostic groups, a nucleus, which also receives major inputs from the olfactory bulb.[45] The paralaminar nucleus projects to the central nucleus, which is believed to be an important output region for the expression of innate emotional and associated physiological responses[45] and receives inputs from the hippocampus.[46] The latter afferents are considered to be involved in contextual fear learning.[47] Together with volume reductions in major input regions, such as the lateral nucleus, our findings suggest that both the evaluation of emotional stimuli (input) and the subsequent response (output) are particularly impaired in patients with schizophrenia. In addition, contrary to previous reports, malformations in a network of nuclei rather than volume reductions in selected nuclei,

such as the lateral nucleus, seem to contribute to emotional processing deficits in schizophrenia.

While the lateral nucleus, as part of the basolateral complex, was only reduced in schizophrenia, lower basal and accessory basal nuclei volumes were found across diagnostic subgroups. Basal nucleus volume was significantly lower in bipolar I and II and in schizophrenia; accessory basal nuclei volume was reduced in all diagnostic subgroups, except bipolar II. Both nuclei play a crucial role in integrating, coordinating, and processing of external sensory information.[43,48] For instance, studies suggest that the basal nucleus decodes emotionally relevant information together with higher-order brain areas[49] to subsequently guide goal-directed behaviors via connections to striatal brain regions.[45,50] Based on these findings, malformations in basolateral complex may contribute to maladaptive emotional processing and subsequent deficits of adaptive behavior across the schizophrenia–bipolar spectrum. Directly comparing patients with bipolar disorders to patients with schizophrenia disorders, we found lower right accessory basal nucleus volume in schizophrenia disorders. One might speculate that exacerbated volume reductions in right accessory basal nucleus, next to other nuclei, may give rise to the more severely disturbed emotion processing in schizophrenia disorders relative to bipolar disorders.[51,52]

Across all diagnostic subgroups, the cortico-amygdaloid transition area, which is expected to play a crucial role in social communication,[48,53] was consistently smaller relative to controls. Preliminary evidence suggests that the cortico-amygdaloid transition area participates in the assessment of negative emotions,[54] and volume reductions in this subregion may contribute to the deficits in facial emotion interpretation and social skills observed across the schizophrenia–bipolar spectrum.

The anterior amygdaloid area was also significantly smaller across multiple diagnostic subgroups, namely in schizophrenia, bipolar I, and OPD relative to controls. In patients with bipolar disorders, one previous study reported reduced right anterior amygdaloid area volume.[26] However, little is known about the connections and functions of the anterior amygdaloid area, making inferences about its implication in these disorders challenging.

Across the bipolar disorder spectrum, fewer amygdala nuclei showed volume reductions in bipolar II than bipolar I when compared to healthy controls. While total amygdala volume as well as basal nucleus, accessory basal nucleus, anterior amygdaloid area, and cortico-amygdaloid transition area volume were significantly lower in bipolar I patients, volume reductions in bipolar II were limited to the basal nucleus and cortico-amygdaloid transition area. Although amygdala volume differences in bipolar disorders relative to healthy controls have been debated,[55] our finding is in line with reports from the ENIGMA bipolar disorder working group showing lower amygdala volume in bipolar I but not bipolar II[13]. More pronounced nuclei volume reductions in bipolar I, similar to schizophrenia, may relate to its symptomatology of pronounced manic episodes and psychotic features, while bipolar II has been linked to a higher rate of depressive episodes (for details, see[56]). However, we did not find significant total amygdala volume differences either between bipolar I and II patients or between bipolar patients with and without psychotic symptoms. The lack of detectable amygdala volume differences between bipolar I (82.4% psychotic) and II (24.0% psychotic) reflects findings from genetic studies, which were also unable to show significant genetic patterns that differentiate these subtypes.[57] Although different relative to controls, amygdala morphology appears similar between bipolar I and II and is likely due to shared genetic underpinnings. Further studies are needed to test whether abnormalities in amygdala structure as well as function may contribute to the distinct clinical manifestation of bipolar subtypes.

Similar to bipolar II, patients with schizoaffective disorder showed volume reductions in only a few amygdala nuclei relative to controls: the accessory basal nucleus and the cortico-amygdaloid transition area. The absence of pronounced volume difference might be due to the limited sample size (N = 59) or its intermediate phenotype between bipolar disorders and schizophrenia. Due to its intermediate status, the validity and nosology of schizoaffective disorder is highly debated,[58,59] and, therefore, these results need to be interpreted with caution.

The amygdala receives polymodal sensory information from several sources, with particularly strong and reciprocal projections from the hippocampus.[28,43] Here, we found that total amygdala volume was significantly less reduced than total hippocampus volume in patients compared to healthy controls, while the difference between schizophrenia and bipolar disorders was not significant (table 3). Efferents from the basolateral complex to the hippocampus and other brain regions are believed to be glutamatergic,[60] and idiopathic psychoses, including schizophrenia and mood disorders with psychotic features, may arise from abnormal glutamatergic neurotransmission in the hippocampus.[61] Abnormalities in amygdala morphology and projections to the hippocampus might exacerbate hippocampal dysfunction, reflected in greater volume reductions detected by MRI. However, due to reciprocal projections, the effect could also be reversed: higher hippocampal volume reductions may lead to morphological abnormalities in the amygdala. Future studies may examine whether lower nuclei volumes are associated with decreased connectivity between the amygdala and the hippocampus as well as other brain regions important for emotional processing in schizophrenia and bipolar disorders.

We found a significant effect of sex for all amygdala nuclei volumes, with higher volumes in males relative to females, after correcting for ICV (supplementary table S3). This finding is in line with results from a recent

cohort study, including 2838 healthy adults.[29] However, we did not find a sex-by-diagnostic group interaction, indicating that the effect of sex may be uniform across diagnostic groups. Furthermore, we found no significant group-by-age and group-by-age^2 interactions, indicating similar aging trajectories of amygdala volume in patients and controls. Whether subcortical volumes show normal or accelerated aging trajectories in patients with schizophrenia–bipolar spectrum disorders relative to controls is currently unknown and warrants further research using longitudinal designs.

Although medication, including antidepressants and lithium, have been shown to increase amygdala volume,[14,62] we found no association between exposure to psychotropic drugs or mood stabilizers and volume in schizophrenia and bipolar disorders. However, putative medication effects are likely multifactorial and driven by overall medication history and duration of exposure. Longitudinal studies are needed to shed light on the neuroplastic effects of specific medications on amygdala volume in psychotic disorders. Furthermore, amygdala volume was not significantly associated with any measure of symptom severity, including psychotic symptoms in schizophrenia disorders and affective symptoms in bipolar disorders. These results are in line with previous reports not showing any associations between amygdala volume and symptom measures.[63–65] The lack of significant associations between morphology and proxies of burden of illness is unclear but may relate to diagnostic issues, such as marked heterogeneity among psychotic disorders, imprecise measurement tools, variability of symptom states over time, or currently unknown confounders.

The major strength of the current study is the large sample size with a largely balanced sex distribution and detailed assessment of clinical characteristics of patients with schizophrenia and bipolar disorders. However, the cross-sectional nature of the presented data does not enable causal inference, and longitudinal studies are needed to determine the timing of morphologically changes in amygdala nuclei in patients. Furthermore, as the amygdala is a small subcortical structure, parsing this region into nuclei using MRI is challenging. The method deployed here is the first to use ultra-high-resolution ex vivo MRI data,[19] which implies high sensitivity to detect nuclei-specific structural abnormalities in the amygdala. However, the internal boundaries between the nuclei are probabilistically labeled based on the ex vivo training data, and the reliability of automatic volumetry is inversely associated with volume size.[66] The volumes of amygdala nuclei must thus be interpreted with caution, in particular of smaller structures, such as the medial, cortical, and central nucleus. In addition, although automatic volumetry has been shown to be generally reliable in multicenter MRI studies,[66] and we successfully harmonized volumes and ICV across scanners using ComBat (see supplementary figures S1 and S2), residual effects of scanner may still be present.

In summary, our study is the first to highlight distinct patterns of amygdala nuclei volume reductions in a well-powered sample of patients with schizophrenia and bipolar disorders. Further research is needed to replicate our findings, parse out the clinical significance of amygdala nuclei reductions, and assess the propensity of nuclei-specific malformations to serve as putative biomarkers to distinguish between psychiatric disorders.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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