Hippocampal subfield alterations in schizophrenia and major depressive disorder: a systematic review and network meta-analysis of anatomic MRI studies

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Background: Hippocampal disturbances are important in the pathophysiology of both schizophrenia and major depressive disorder (MDD). Imaging studies have shown selective volume deficits across hippocampal subfields in both disorders. We aimed to investigate whether these volumetric alterations in hippocampal subfields are shared or divergent across disorders. **Methods:** We searched PubMed and Embase from database inception to May 8, 2021. We identified MRI studies in patients with schizophrenia, MDD or both, in which hippocampal subfield volumes were measured. We excluded nonoriginal, animal or postmortem studies, and studies that used other imaging modalities or overlapping data. We conducted a network meta-analysis to estimate and contrast alterations in subfield volumes in the 2 disorders. **Results:** We identified 45 studies that met the initial criteria for systematic review, of which 15 were eligible for network meta-analysis. Compared to healthy controls, patients with schizophrenia had reduced volumes in the bilateral cornu ammonis (CA) 1, granule cell layer of the dentate gyrus, subiculum, parasubiculum, molecular layer, hippocampal tail and hippocampus–amygdala transition area (HATA); in the left CA4 and presubiculum; and in the right fimbria. Patients with MDD had decreased volumes in the left CA3 and CA4 and increased volumes in the right HATA compared to healthy controls. The bilateral parasubiculum and right HATA were smaller in patients with schizophrenia than in patients with MDD. **Limitations:** We did not investigate medication effects because of limited information. Study heterogeneity was noteworthy in direct comparisons between patients with MDD and healthy controls. **Conclusion:** The volumes of multiple hippocampal subfields are selectively altered in patients with schizophrenia and MDD, with overlap and differentiation in subfield alterations across disorders. Rigorous head-to-head studies are needed to validate our findings.

Introduction

Schizophrenia and major depressive disorder (MDD) are common psychiatric illnesses with overlaps in pathogenesis, symptom presentation and neurobiological features. Epidemiological evidence suggests that both disorders are associated with prenatal maternal adversity, which is a well-established risk factor for pathogenesis.[1,2] Large-scale genome-wide association meta-analysis has shown that biological etiology is partially shared in schizophrenia and MDD.[3] Clinically, up to 80% of patients with schizophrenia experience depressive episodes in the early stages of illness,[4] and people with depression or anxiety disorders may have psychotic symptoms.[5] Impulsivity and anhedonia can also be observed in both disorders.[6,7] Neurobiological data further reveal a relationship between symptom severity and oxytocin in both disorders,[8,9] as well as a genetic correlation between them.[10] Overlaps in structural brain alterations have also been found in schizophrenia and MDD,[11] including reductions in hippocampal volume.[12,13] Because the hippocampus consists of several subfields that relate to cognitive and affective disturbances, abnormalities in its subregions are worthy of investigation. Subfield-level comparisons of volumetric alterations in schizophrenia and MDD would help us to better understand the pathophysiology of both disorders.

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Hippocampal subfields are histologically and functionally distinct, including the cornu ammonis (CA) 1 to 4, the dentate gyrus and the subiculum.[14] MRI-based segmentation methods in FreeSurfer software (surfer.nmr.mgh.harvard.edu) provide automatic volume measurement of hippocampal subfields with high accuracy.[15] These methods have shown favourable performance and have been used widely. For example, FreeSurfer 6.0, employing the atlas of Iglesias and colleagues,[15] measures the CA1, CA2/3 and CA4 comparably to histological examinations;[16] it also yields higher reproducibility and traces more quickly than manual segmentation.[17]

Previous MRI studies in schizophrenia and MDD have found selective volume deficits in hippocampal subfields, but the subregions involved have varied across reports. Generally, volume reduction has been identified in the whole hippocampus, CA1, CA2/3, CA4/dentate gyrus and subiculum in patients with schizophrenia,[13,18,19] and in the CA1, CA4, molecular layer and hippocampal tail in patients with MDD compared to healthy controls.[20,21] Given the partial overlap of subfield volume deficits across disorders, the variability in findings across studies, and the fact that hippocampal subfield volumes have usually been assessed in either schizophrenia or MDD rather than compared directly between them,[13,22–24] questions have arisen about the degrees of overlap and differentiation between hippocampal subfield abnormalities in these disorders. Moreover, associated studies have been limited by small and heterogeneous samples and divergent volumetry methods. In this context, a network meta-analysis may be a useful strategy for characterizing similarities and differences in hippocampal alterations, providing a quantitative approach to contrasting hippocampal volumes between schizophrenia and MDD.[25,26]

We performed a systematic review to summarize the volume alterations in hippocampal subfields in schizophrenia and MDD and a network meta-analysis to quantitatively compare those alterations between disorders. We hypothesized that volume abnormalities in hippocampal subfields would have overlapping features in the CA1 and CA4 in patients with schizophrenia and patients with MDD, and illness-specific features in other subfields.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for the reporting of systematic reviews incorporating network meta-analyses.[27] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021291470). We did not obtain institutional review board approval, because the included data had been previously published and no individual patient information was involved.

Search strategy, eligibility criteria and study selection

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) and Embase (www.embase.com) from database inception until May 8, 2021. Details of the search strategy are presented in Appendix 1, Supplementary Methods, available at www.jpn.ca/lookup/doi/10.1503/jpn.220086/tab-related-content. We also manually searched relevant publications for citations that might meet our eligibility criteria.

We included studies in the systematic review if they were MRI studies in patients with schizophrenia, MDD or both; segmented hippocampal subfields and measured volumes; compared patients with schizophrenia or MDD with healthy controls; and were published in English. The exclusion criteria were as follows: nonoriginal studies (e.g., methodological studies, reviews, meta-analyses or case reports); animal or postmortem studies, or studies using imaging modalities other than MRI; studies limited to pediatric or geriatric patients; or studies with identical samples in distinct publications. If studies used partially overlapping samples, we classified the study with the smaller sample size as an overlapping sample and excluded it from the network meta-analysis but included it in the systematic review. In addition to meeting the above inclusion and exclusion criteria, if studies used FreeSurfer with the atlas of Iglesias and colleagues[15] and reported bilateral hippocampal subfield volumes as means and standard deviations or errors, we included them in the network meta-analysis.

Two reviewers (S.Y. and H.N.) independently screened and selected the studies. They resolved inconsistencies through discussion, and examples of inconsistencies are provided in Appendix 1, Supplementary Methods. We obtained the full texts of all publications identified as relevant to extract information. We contacted the corresponding authors to obtain unpublished study details, if necessary. Details of study quality assessment are presented in Appendix 1, Supplementary Methods.

Data extraction and summary measures

We obtained data according to 2 analysis plans. First, for studies included in the systematic review, we extracted information about each participant group, including the group category, number of participants, sex ratio, mean age, field strength of the MRI scanner, method of segmentation, study design and main findings. Then, for the studies that met the inclusion criteria for network meta-analysis, we also extracted information about mean age at onset, mean duration of illness, mean number of previous illness episodes, mean symptom ratings, medication status and history of substance use. We extracted mean values and standard deviations of volume measurements for the whole hippocampus and 12 hippocampal subfields, including the CA1, CA3, CA4, granule cell layer of the dentate gyrus, subiculum, presubiculum, parasubiculum, molecular layer, hippocampal tail, fimbria, hippocampal fissure and hippocampus–amygdala transition area (HATA). According to the atlas definition by Iglesias and colleagues,[15] CA3 included CA2, and CA4 included the polymorphic layer of the dentate gyrus; the molecular layer consisted of the corresponding layers of the CA and subiculum; and the hippocampal fissure separated the subiculum and the CA from the dentate gyrus as a sulcus.

If only standard errors were reported, we performed conversions to generate standard deviations. If data were reported only graphically, we used WebPlotDigitizer (automeris.io/WebPlotDigitizer) to extract mean values and standard deviations. This tool is a semiautomated, Internet-based application for extracting data from plots, images and maps. For multicentre studies, we treated multiple data sets as separate samples. For studies that divided patient groups into subgroups, we merged the subgroup data (Appendix 1, Supplementary Methods). In the meta-analysis, some studies did not measure smaller hippocampal subfields because of concerns about segmentation reliability; as a result, not all included studies reported every subfield. For each hippocampal subfield, we summarized the number of studies and participants included in the network meta-analysis.

Statistical analysis

In a frequentist framework, we implemented network meta-analysis using R software (version 4.1.3; R Foundation for Statistical Computing) with the metafor and netmeta packages. We obtained direct volume comparisons for patients with schizophrenia versus healthy controls and patients with MDD versus healthy controls by synthesizing the respective original studies. We obtained indirect volume comparisons for patients with schizophrenia versus patients with MDD by synthesizing the studies that compared patients with schizophrenia versus healthy controls and patients with MDD versus healthy controls. To better control for heterogeneity across studies, we selected random-effects models for network meta-analysis. We set a 2-tailed p value of less than 0.05 as statistically significant for the case–control and schizophrenia–MDD contrasts. We used false discovery rate to correct for multiple comparisons. We analyzed 12 hippocampal subfields and the whole hippocampus for each hemisphere, so the number of tests for each analysis was 13.

We evaluated transitivity and inconsistency as the basis of network meta-analysis. We assessed heterogeneity using the I^2 statistic,[28] with values of 75%, 50% and 25% indicating high, medium and low degrees of heterogeneity, respectively. For each direct comparison with an I^2 value greater than 50%, we analyzed the source of the heterogeneity by assessing the potential effects of relevant variables on effect size (mean difference). We performed random univariate effects meta-regression for continuous variables. The dependent variable was effect size (mean difference) between patients and healthy controls for each study. The independent variables were the continuous variables extracted from each study, including age at study, age at onset, illness duration and severity score.

Although only 7 of 15 studies reported intracranial volume (ICV), we reperformed network meta-analysis for these 7 studies to explore the effect of ICV. We did not control for sex effects because no differences in sex ratio were found between patients with schizophrenia and healthy controls ($\chi^2 = 0.10$, $p = 0.75$) or between patients with MDD and healthy controls ($\chi^2 = 1.36$, $p = 0.24$). We also performed direct cross-sectional comparisons between patients with schizophrenia and patients with MDD after controlling for ICV. Details are presented in Appendix 1, Supplementary Methods.

Because of the limited number of included studies, it was not feasible to use funnel plots to detect publication bias.[29] Instead, we chose the Egger linear regression test, which quantitatively assesses bias with high detection efficacy for small samples and continuous variables.[30] We used comprehensive meta-analysis software (version 3; BioStat) for meta-regression and the assessment of publication bias.

Results

Study selection

The search strategy identified 840 records, of which 45 studies[16,20,21,23,31–71] were included in the systematic review. Appendix 1, Figure S1, shows the flowchart for literature screening and eligibility assessment. A total of 2624 patients with schizophrenia (1767 males and 857 females; mean age 34.4 years), 1417 patients with MDD (523 males and 894 females; mean age 37.6 years) and 4788 healthy controls (2516 males and 2272 females; mean age 33.9 years) were included. Of the 45 studies, 17 compared volumetric metrics between patients with schizophrenia and healthy controls, 27 compared volumetric metrics between patients with MDD and healthy controls and 1 compared volumetric metrics among patients with schizophrenia, patients with MDD and healthy controls. The magnetic field strengths of MRI scanners were 7 T (3 studies), 4.7 T (3 studies), 3 T (33 studies), 1.5 T (4 studies) and both 1.5 T and 3 T (1 study); the remaining study did not report magnetic field strength. Forty-one studies segmented the hippocampus along the transverse axis, and 4 studies[62,65–67] employed a more detailed segmentation method (e.g., further dividing certain subfields into heads and bodies). The main characteristics of each study are summarized in Table 1. Several studies reported findings with overlapping samples.[21,41,42,47,61,62,63,67]

For the network meta-analysis, 15 eligible studies did not have overlapping samples.[16,20,21,31–41,70] The main characteristics of these individual studies are shown in Table 2. The total sample size was 2698 (ranging from 27 to 349 per study; 47.6% female), including 779 patients with schizophrenia, 627 patients with MDD and 1292 healthy controls. The mean age of the participants varied from 23.0 to 45.3 years, and the mean age at onset ranged from 18.3 to 40.6 years. The mean duration of illness was 0.64 to 18.2 years. Table 3 and Table 4 characterize the statistical heterogeneities among these studies. Means and standard deviations for the hippocampal subfield volumes are listed and summarized in Appendix 2, available at www.jpn.ca/lookup/doi/10.1503/jpn.220086/tab-related-content. In terms of study quality, all studies in the network meta-analysis achieved Newcastle–Ottawa Scale scores of 6 to 7 points, indicating moderate to high quality (Appendix 1, Table S2). Of the 15 studies included in the network meta-analysis, 3 used FreeSurfer 5.3 for data preprocessing[16,31,38] and all used the atlas of Iglesias and colleagues[15] for segmentation of hippocampal subfields, generating consistent boundaries for each hippocampal subfield.

Table 1: Characteristics of studies included in the systematic review (part 1 of 3)

Author (year)	Participants, *n* (% female, mean age)	MRI scanner	Segmentation method	Study design	Main findings
Alnæs et al.[42] (2019)*†	Schizophrenia, 1151 (31%, 34 y) Healthy controls, 2010 (44%, 33 y)	1.5 T and 3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort, multisite; genes	Smaller volume in all subfields; larger left and right hippocampal fissure
Brown et al.[43] (2019)	MDD, 24 (38%, 40 y) Healthy controls, 20 (25%, 40 y)	7.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort	No significant difference
Cao et al.[44] (2018)	MDD, 24 (58%, 31 y) Healthy controls, 15 (66%, 33 y)	3.0 T	Automatic (FreeSurfer 5.3¶)	Longitudinal design, case–control; ECT	Baseline: no significant difference Longitudinal changes: increased left CA2/3, left and right CA4, left and right granule cell layer of the dentate gyrus, left subiculum
Cao et al.[31] (2017)	MDD, 86 (70%, 41 y) Healthy controls, 152 (63%, 35 y)	1.5 T	Automatic (FreeSurfer 5.3¶)	Cross-sectional design, case–control	No significant difference
Doolin et al.[32] (2018)	MDD, 74 (64%, 33 y) Healthy controls, 37 (51%, 31 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort	Smaller left CA1, left and right CA2/3, right CA4
du Plessis et al.[33] (2020)	First-episode schizophrenia, 79 (27%, 23 y) Healthy controls, 82 (43%, 23)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort	Statistical analysis between 2 groups was not available
Frodl et al.[45] (2014)	MDD, 43 (60%, 41 y) Healthy controls, 43 (60%, 37 y)	3.0 T	Automatic (FreeSurfer**)	Cross-sectional design, case–control; genes	Smaller CA1, CA2/3, CA4/dentate gyrus, subiculum
Frodl et al.[46] (2014)	MDD, 38 (66%, 41 y) Healthy controls, 44 (61%, 36 y)	3.0 T	Automatic (FreeSurfer**)	Cross-sectional design, case–control; genes	Smaller left CA2/3, left CA4/dentate gyrus
Han et al.[21] (2019)‡	MDD, 102 (59%, 36 y) Healthy controls, 135 (58%, 36 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Smaller left and right whole hippocampus, left and right CA1, left CA2/3, left and right CA4, left and right granule cell layer of the dentate gyrus, right subiculum, right presubiculum, left and right molecular layer
Han et al.[47] (2017)‡	MDD, 105 (82%, 43 y) Healthy controls, 85 (71%, 40 y)	3.0 T	Automatic (FreeSurfer 5.3¶)	Cross-sectional design, case–control; genes	No significant difference
Han et al.[48] (2016)	MDD, 20 (100%, 42 y) Healthy controls, 21 (100%, 42 y)	1.5 T	Automatic (FreeSurfer 5.3**)	Cross-sectional design, case–control	Smaller left whole hippocampus, left CA2/3, left CA4/dentate gyrus, left and right subiculum
Harel et al.[49] (2016)	MDD, 15 (53%, 36 y) Healthy controls, 15 (47%, 37 y)	3.0 T	Automatic (FreeSurfer 5.3**)	Cross-sectional design, case–control	Smaller right whole hippocampus, right CA1, right CA2/3, right CA4/dentate gyrus
Ho et al.[16] (2017)	Schizophrenia, 155 (32%, 32 y) Healthy controls, 79 (35%, 31 y)	3.0 T	Automatic (FreeSurfer 5.3¶)	Cross-sectional design, case–control; longitudinal design in a subcohort; multisite	Schizophrenia: smaller left and right whole hippocampus, left CA1 Early-course schizophrenia: smaller left and right whole hippocampus, left and right CA1, right granule cell layer of the dentate gyrus Longitudinal changes: decreased left and right CA1, right CA2/3, left and right granule cell layer of the dentate gyrus, right molecular layer
	Schizophrenia, 46 (22%, 43 y) Healthy controls, 46 (22%, 42 y)				Smaller left and right whole hippocampus, left and right CA1, left and right CA2/3, left and right CA4, left and right granule cell layer of the dentate gyrus, left and right subiculum, left and right molecular layer, left and right hippocampal tail
Hu et al.[66] (2020)	Never-treated long-term schizophrenia, 29 (55%, 46 y) Treated long-term schizophrenia, 40 (55%, 48 y) Healthy controls, 40 (55%, 48 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Never-treated long-term schizophrenia: smaller left and right whole hippocampus, right CA1 (body), left and right CA2/3 (head), right CA2/3 (body), left and right CA4 (head), left and right CA4 (body), left and right granule cell layer of the dentate gyrus (head), left and right granule cell layer of the dentate gyrus (body), left and right subiculum (body), left and right molecular layer (body), left and right hippocampal tail Treated long-term schizophrenia: smaller left and right whole hippocampus, left CA4 (body), left granule cell layer of the dentate gyrus (body), left and right subiculum (body), left and right molecular layer (body), left and right hippocampal tail
Hu et al.[50] (2019)	Nonresponding MDD, 13 (38%, 36 y) Early responding MDD, 25 (44%, 36 y) Healthy controls, 55 (62%, 36 y)	3.0 T	Automatic (FreeSurfer 5.3**)	Cross-sectional design, case–control, cohort	MDD: no significant difference Nonresponding MDD: larger left and right CA1, left CA2/3, left CA4/dentate gyrus, left and right subiculum
Huang et al.[67] (2013)§	Unmedicated MDD, 9 (44%, 33 y) Medicated MDD, 11 (55%, 37 y) Healthy controls, 27 (70%, 33 y)	4.7 T	Manual	Cross-sectional design, case–control	Unmedicated MDD: smaller CA1–3 (body), dentate gyrus
Hýža et al.[51] (2016)	First-episode schizophrenia, 58 (0%, 23 y) Healthy controls, 58 (0%, 24 y)	1.5 T	Automatic (FreeSurfer 5.2**)	Cross-sectional design, case–control	Larger left CA1

Table 1: Characteristics of studies included in the systematic review (part 2 of 3)

Author (year)	Participants, *n* (% female, mean age)	MRI scanner	Segmentation method	Study design	Main findings
Jiang et al.[52] (2019)	Schizophrenia with symptom remission after ECT, 10 (50%, 30 y) Schizophrenia without symptom remission after ECT, 11 (55%, 28 y) Schizophrenia treated by ECT (with and without symptom remission), 21 (52%, 29 y) Schizophrenia with symptom remission after antipsychotic medication, 12 (75%, 31 y) Schizophrenia without symptom remission after antipsychotic medication, 9 (33%, 30 y) Schizophrenia treated by antipsychotic medication (with and without symptom remission), 21 (57%, 31 y) Healthy controls, 23 (52%, 31 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Longitudinal design, cohort; ECT	Longitudinal changes: schizophrenia treated by ECT (with and without symptom remission), increased left and right whole hippocampus
Kakeda et al.[53] (2018)	First-episode MDD, 40 (50%, 47 y) Healthy controls, 47 (28%, 41 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	No significant difference
Kawano et al.[68] (2015)	First-episode schizophrenia, 19 (53%, 25 y) Subchronic schizophrenia, 6 (50%, 22 y) Chronic schizophrenia, 9 (33%, 37 y) Healthy controls, 15 (33%, 25 y)	1.5 T	Automatic (FreeSurfer 5.1**)	Cross-sectional design, case–control; longitudinal design in a subcohort	Baseline: first-episode schizophrenia, smaller left CA2/3, left CA4/dentate gyrus Subchronic schizophrenia: smaller left whole hippocampus, left CA2/3, left CA4/dentate gyrus Chronic schizophrenia: smaller left whole hippocampus, left CA2/3, left CA4/dentate gyrus
Kraus et al.[54] (2019)	Acute MDD, 20 (70%, 31 y) Remitted MDD, 28 (57%, 27 y) Healthy controls, 22 (55%, 26 y)	7 T	Automatic (FreeSurfer 6.0¶)	Longitudinal design, open-label trial	Time 1: remitted MDD, larger right hippocampal fissure Longitudinal changes: no significant difference Time 2: remitted MDD, larger right HATA
Li et al.[55] (2018)	First-episode schizophrenia, 41 (59%, 24 y) Healthy controls, 39 (51%, 24 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control; longitudinal design; antipsychotics	Baseline: larger left and right CA4, left and right granule cell layer of the dentate gyrus, left and right molecular layer Longitudinal changes: decreased left and right whole hippocampus, left CA1, left CA2/3, left and right CA4, left and right granule cell layer of the dentate gyrus, left and right molecular layer, left and right hippocampal tail, left fimbria After treatment: larger left and right CA4
Maller et al.[20] (2018)	MDD, 182 (52%, 33 y) Healthy controls, 68 (50%, 30 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Open-label trial	Baseline: larger hippocampal tail
Mathew et al.[69] (2014)	Schizophrenia, 219 (34%, 35 y) Healthy controls, 337 (55%, 37 y)	Unknown	Automatic (FreeSurfer 5.1**)	Cross-sectional design, case–control, multisite	Smaller left and right whole hippocampus, left and right CA1, left and right CA2/3, left and right CA4/dentate gyrus, left and right subiculum, left and right presubiculum
Mikolas et al.[56] (2019)	MDD, 85 (67%, 39 y) Healthy controls, 67 (67%, 36 y)	3.0 T	Automatic (FreeSurfer 5.3¶)	Cross-sectional design, case–control; genes	Smaller whole hippocampus, CA1, CA2/3, CA4, granule cell layer of the dentate gyrus, molecular layer
Na et al.[57] (2014)	MDD, 45 (76%, 42 y) Healthy controls, 72 (71%, 41 y)	3.0 T	Automatic (FreeSurfer 5.0**)	Cross-sectional design, case–control; genes	No significant difference
Na et al.[34] (2018)	MDD, 47 (100%, 45 y) Healthy controls, 30 (100%, 43 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control; genes	No significant difference
Nakahara et al.[35] (2020)	Schizophrenia, 176 (25%, 39 y) Healthy controls, 173 (29%, 38 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, multisite	Smaller CA1, CA4, granule cell layer of the dentate gyrus, molecular layer, hippocampal tail; larger hippocampal fissure
Nguyen et al.[58] (2019)	First-episode MDD, 38 (47%, 47 y) Healthy controls, 39 (28%, 41 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control; genes	No significant difference
Ohi et al.[36] (2021)	Schizophrenia, 138 (60%, 42 y) Healthy controls, 162 (33%, 37 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Smaller right HATA; larger right hippocampal fissure
Orfei et al.[59] (2017)	Schizophrenia, 45 (33%, 40 y) Healthy controls, 45 (33%, 40 y)	3.0 T	Automatic (FreeSurfer**)	Cross-sectional design, case–control	Smaller left and right whole hippocampus, left and right CA1, left and right CA2/3, left and right CA4/dentate gyrus, left subiculum, left and right presubiculum, left and right hippocampal fissure

Table 1: Characteristics of studies included in the systematic review (part 3 of 3)

Author (year)	Participants, *n* (% female, mean age)	MRI scanner	Segmentation method	Study design	Main findings
Ota et al.[23] (2017)	Schizophrenia, 20 (25%, 37 y) MDD, 36 (47%, 38 y) Healthy controls, 35 (46%, 39 y)	3.0 T	Automatic (ASHS)	Cross-sectional design, case–control	Schizophrenia: smaller whole hippocampus, CA1, dentate gyrus than healthy controls, smaller whole hippocampus, dentate gyrus than MDD without medication MDD: no significant difference
Otsuka et al.[60] (2019)	First-episode MDD, 27 (41%, 46 y); Healthy controls, 42 (26%, 41 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control; genes	No significant difference
Roddy et al.[70] (2019)	MDD, 80 (71%, 35 y) Healthy controls, 83 (59%, 32 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Smaller left CA1, left and right CA2/3, left and right CA4, left and right granule cell layer of the dentate gyrus, left and right subiculum, left hippocampal tail; larger right molecular layer
Sasabayashi et al.[37] (2021)	Schizophrenia, 77 (49%, 29 y) Healthy controls, 87 (47%, 26 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort	Smaller left and right CA1, left and right molecular layer, left hippocampal tail
Tannous et al.[71] (2020)	MDD, 71 (55%, 32 y) Healthy controls, 46 (54%, 32 y)	7.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort	No significant difference
Tesli et al.[61] (2020)†	Schizophrenia with a history of violence, 24 (4%, 34 y) Schizophrenia with no history of violence, 51 (2%, 29 y) Healthy controls, 90 (3%, 33 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control, cohort, multisite	Schizophrenia with a history of violence: smaller whole hippocampus, CA1, molecular layer, fimbria, HATA; larger hippocampal fissure Schizophrenia with no history of violence: no significant difference
Travis et al.[62] (2015)§	MDD, 15 (80%, 38 y) Healthy controls, 15 (67%, 35 y)	4.7 T	Manual	Cross-sectional design, case–control, cohort	Smaller dentate gyrus (body)
Travis et al.[63] (2016)§	MDD, 14 (64%, 36 y) Healthy controls, 14 (71%, 33 y)	4.7 T	Manual	Cross-sectional design, case–control, cohort	No significant difference
Vargas et al.[64] (2018)	Schizophrenia, 91 (26%, 38 y) Healthy controls, 70 (56%, 18 y)	3.0 T	Automatic (FreeSurfer 5.3**)	Cross-sectional design, case–control	Smaller left and right whole hippocampus, right CA1, left and right CA2/3, left and right CA4/dentate gyrus, left and right subiculum, left and right presubiculum
Xiu et al.[38] (2021)	First-episode schizophrenia, 39 (59%, 29 y) Healthy controls, 30 (57%, 28 y)	3.0 T	Automatic (FreeSurfer 5.3¶)	Cross-sectional design, case–control	No significant difference
Xu et al.[39] (2018)	MDD, 15 (100%, 35 y) Healthy controls, 12 (100%, 34 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Smaller left fimbria
Yuan et al.[40] (2020)	MDD, 41 (59%, 35 y) Healthy controls, 44 (59%, 33 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	No significant difference
Zheng et al.[41] (2019)*	Schizophrenia, 69 (16%, 38 y) Healthy controls, 72 (29%, 36 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Cross-sectional design, case–control	Smaller left and right whole hippocampus, left CA1, left subiculum, left and right presubiculum, right parasubiculum, left and right molecular layer, left hippocampal tail
Zhou et al.[65] (2020)	MDD, 44 (64%, 35 y) Healthy controls, 45 (53%, 33 y)	3.0 T	Automatic (FreeSurfer 6.0¶)	Longitudinal design; ketamine treatment	Baseline: smaller left and right whole hippocampus Longitudinal changes: increased right whole hippocampus, right CA4 (head), left CA4 (body), left granule cell layer of the dentate gyrus (body), right molecular layer (head)

ASHS = Automatic Segmentation of Hippocampal Subfields; CA = cornu ammonis; ECT = electroconvulsive therapy; HATA = hippocampus–amygdala transition area; MDD = major depressive disorder.
*Overlapped data.
†Overlapped data.
‡Overlapped data.
§Overlapped data.
**Atlas by van Leemput and colleagues.[72]
¶Atlas by Iglesias and colleagues.[15]

Systematic review

A total of 18 studies compared hippocampal subfield volumes between patients with schizophrenia and healthy controls. Specifically, 15 studies reported smaller hippocampal subfields in patients with schizophrenia than in healthy controls, and 2 studies in patients with first-episode schizophrenia found larger subfields involving the left CA1[51] and bilateral CA4, the granule cell layer of the dentate gyrus and the molecular layer.[55] One study found no volume differences between patients with first-episode schizophrenia and healthy controls.[38]

Longitudinal changes in hippocampal subfield volumes were also observed in patients with schizophrenia. Ho and colleagues[16] showed volume reductions in the bilateral CA1 and granule cell layer of the dentate gyrus, the right CA2/3 and the right molecular layer at an average follow-up of 4.5 years. Jiang and colleagues[52] reported that 4-week electroconvulsive therapy induced volume increases in the bilateral hippocampus in patients with schizophrenia relative to drug treatment. In patients with first-episode schizophrenia after short-term drug treatment, Kawano and colleagues[68] found volume increases in the left CA4/dentate gyrus, and Li and colleagues[55] reported volume decreases in

Table 2: Main characteristics of the studies included in the network meta-analysis (part 1 of 2)

	No. participants (female)			Participant age, y										
Author (year)	Patients	Healthy controls	*p* for sex	Patients	Healthy controls	*p* for age	Age at onset, y	Illness duration, y	Mean no. of episodes	Score of severity (scale type)	Medication status	Substance misuse	MRI field strength, subfield segmentation	Study design
Ho et al.[16] (2017)	155 (49)	79 (28)	0.66	32.5	31.2	0.30	25.9	6.6	NA	40.6 (PANSS)	CPZ-eq: 212.32 ± 191.25 mg/d	No substance misuse 3 mo preceding the study	3.0 T, automatic (FreeSurfer 5.3)	Cross-sectional design; case–control; longitudinal in a subcohort; multisite
	46 (10)	46 (10)	> 0.99	42.9	41.9	0.61	24.5	18.2	NA	81.6 (PANSS)	CPZ-eq: 532.45 ± 447.16 mg/d			
Zheng et al.[41] (2019)	69 (11)	72 (21)	0.06	37.7	35.9	0.046	NA	NA	NA	NA	NA	NA	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control
du Plessis et al.[33] (2020)	79 (21)	82 (35)	0.03	23.0	23.0	0.97	22.36*	0.64	First-episode schizophrenia	91.27 (PANSS)	Treated ≤ 1 mo	First-episode schizophrenia: 35 (44%) Controls: 22 (27%)	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control; cohort
Nakahara et al.[35] (2020)	176 (44)	173 (50)	0.39	38.9	37.6	0.27	21.9	17.1	NA	57.9 (PANSS)	CPZ-eq: 372 ± 390 mg/d (*n* = 144)	None	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control; multisite
Ohi et al.[36] (2021)	138 (83)	162 (54)	< 0.05†	42.0	36.7	< 0.05†	26.2	16.3	NA	33.9 (PANSS positive symptoms and PANSS negative symptoms)	CPZ-eq: 519.0 ± 524.0 mg/d	NA	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control
Sasabayashi et al.[37] (2021)	77 (38)	87 (41)	> 0.05†	28.8	26.3	< 0.05†	22.8	5.6	NA	68.7 (PANSS)	HPD-eq: 10.6 ± 8.3 mg/d (*n* = 65)	None	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control; cohort
Xiu et al.[38] (2021)	39 (23)	30 (17)	0.85	28.9	27.5	0.54	26.95*	1.95	First-episode schizophrenia	44.5 (MCCB)	All naive	None	3.0 T, automatic (FreeSurfer 5.3)	Cross-sectional design; case–control
Cao et al.[31] (2017)	86 (60)	152 (96)	> 0.05†	41.2	35.4	< 0.05†	32.3*	8.9	3‡	10.5 (HDRS-17)	On medication: 4	Drug use disorder < 10	1.5 T, automatic (FreeSurfer 5.3)	Cross-sectional design; case–control
Doolin et al.[32] (2018)	74 (47)	37 (19)	> 0.05	32.9	30.9	> 0.05	NA	NA	First-episode MDD (*n* = 39) > 1 (*n* = 35)	23.46 (HDRS-17)	On medication: 47 Medication-free: 27	NA	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control; cohort;
Maller et al.[20] (2018)	182 (95)	68 (34)	> 0.05	33.0	29.6	0.048	22.2*	10.8	9.6	21.36 (HDRS-17)	All naive or with a washout period ≥ 5 half-lives	NA	3.0 T, automatic (FreeSurfer 6.0)	Open-label trial
Na et al.[34] (2018)	47 (47)	30 (30)	> 0.05	45.3	43.0	0.41	40.6*	4.7	NA	12.9 (HDRS-17)	On medication: 35	NA	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control; genes
Xu et al.[39] (2018)	15 (15)	12 (12)	> 0.05	34.6	34.1	0.51	NA	NA	NA	33.13 (HDRS-24)	NA	None	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control

Table 2: Main characteristics of the studies included in the network meta-analysis (part 2 of 2)

Author, year	No. participants (female) Patients	Healthy controls	*p* for sex	Participant age, y Patients	Healthy controls	*p* for age	Age at onset, y	Illness duration, y	Mean no. of episodes	Score of severity (scale type)	Medication status	Substance misuse	MRI field strength, subfield segmentation	Study design
Han et al.[21] (2019)	102 (60)	135 (78)	> 0.05†	36.0	36.0	> 0.05†	32.3*	3.7	First-episode MDD (*n* = 25) > 1 (*n* = 77)	13.93 (HDRS-17)	On medication: most	None	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control
Roddy et al.[70] (2019)	80 (57)	83 (49)	0.14	34.5	31.5	0.13	32.1*	2.4	First-episode MDD (*n* = 43) > 1 (*n* = 37)	22.2 (HDRS-17)	NA	None	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control
Yuan et al.[40] (2020)	41 (24)	44 (26)	0.96	34.8	33.3	0.54	18.3*	16.5§	< 3 (*n* = 18), ≥ 3 (*n* = 13)¶	18.3 (HDRS-17)	Naive: 16 Untreated ≥ 3 w: 25	MDD with drug use disorder: 17 MDD without drug use disorder: 24	3.0 T, automatic (FreeSurfer 6.0)	Cross-sectional design; case–control

CPZ-eq = chlorpromazine equivalent; HDRS-17 or -24 = 17- or 24-item Hamilton Depression Rating Scale; HPD-eq = haloperidol equivalent; MCCB = MATRICS Consensus Cognitive Battery; MDD = major depressive disorder; NA = not available; PANSS = Positive and Negative Syndrome Scale.
*Determined based on the difference between patient mean age and illness duration.
†Inferred based on the results of the corresponding analysis of variance or χ^2 test.
‡Median.
§One participant lacked information on illness duration.
¶Ten participants lacked information on number of prior episodes.

Table 3: Direct volume comparisons between patients with schizophrenia and healthy controls

Region of interest	Mean difference (95% CI), mm³	*p* value*	I^2, %	No. of studies	No. of patients with schizophrenia	No. of healthy controls
Left whole hippocampus†	–127.840 (–209.381 to –46.298)	0.005	49	6	700	649
Left CA1†	–21.721 (–36.328 to –7.113)	0.006	0	7	779	731
Left CA3	–4.555 (–9.580 to 0.471)	0.08	42	7	779	731
Left CA4†	–6.875 (–11.728 to –2.021)	0.008	45	7	779	731
Left granule cell layer of the dentate gyrus†	–8.430 (–14.089 to –2.771)	0.006	44	7	779	731
Left subiculum†	–10.245 (–18.124 to –2.366)	0.01	36	7	779	731
Left presubiculum†	–7.667 (–14.219 to –1.116)	0.03	2	6	578	606
Left parasubiculum†	–3.041 (–4.531 to –1.551)	< 0.001	0	5	539	576
Left molecular layer†	–17.412 (–27.110 to –7.714)	0.002	0	7	779	731
Left hippocampal tail†	–24.456 (–40.346 to –8.566)	0.006	74	7	779	731
Left fimbria	–2.008 (–5.401 to 1.385)	0.25	20	5	539	576
Left hippocampal fissure†	4.941 (1.953 to 7.930)	0.004	0	5	539	576
Left HATA†	–2.044 (–3.156 to –0.932)	0.002	23	5	539	576
Right whole hippocampus†	–108.803 (–182.105 to –35.500)	0.01	35	6	700	649
Right CA1†	–16.337 (–29.533 to –3.140)	0.02	32	7	779	731
Right CA3	–2.776 (–7.850 to 2.299)	0.28	30	7	779	731
Right CA4	–4.929 (–10.152 to 0.293)	0.07	47	7	779	731
Right granule cell layer of the dentate gyrus†	–6.657 (–11.976 to –1.338)	0.02	38	7	779	731
Right subiculum†	–8.764 (–17.057 to –0.472)	0.049	8	7	779	731
Right presubiculum	–7.051 (–14.077 to –0.024)	0.06	0	6	578	606
Right parasubiculum†	–2.899 (–4.797 to –1.001)	0.01	27	5	539	576
Right molecular layer†	–13.845 (–25.233 to –2.457)	0.02	23	7	779	731
Right hippocampal tail†	–17.221 (–31.208 to –3.234)	0.02	18	7	779	731
Right fimbria†	–4.201 (–6.586 to –1.816)	0.003	0	5	539	576
Right hippocampal fissure†	9.849 (6.728 to 12.970)	< 0.001	0	5	539	576
Right HATA†	–2.727 (–3.787 to –1.667)	< 0.001	0	5	539	576

CA = cornu ammonis; CI = confidence interval; HATA = hippocampus–amygdala transition area.
*Adjusted.
†Statistically significant difference.

Table 4: Direct volume comparisons between patients with MDD and healthy controls

Region of interest	Mean difference (95% CI), mm^3	p value*	I^2, %	No. of studies	No. of patients with MDD	No. of healthy controls
Left whole hippocampus	–74.998 (–175.651 to 25.656)	0.26	88	5	422	325
Left CA1	–13.373 (–28.894 to 2.147)	0.24	83	8	598	546
Left CA3†	–7.491 (–12.873 to –2.109)	0.04	71	8	598	544
Left CA4†	–8.137 (–13.724 to –2.549)	0.04	69	7	557	504
Left granule cell layer of the dentate gyrus	–6.711 (–13.427 to 0.005)	0.22	74	6	535	508
Left subiculum	–7.580 (–16.215 to 1.055)	0.24	66	8	596	546
Left presubiculum	0.247 (–6.656 to 7.150)	0.94	72	5	494	466
Left parasubiculum	0.465 (–1.220 to 2.151)	0.77	40	4	347	222
Left molecular layer	–2.925 (–15.559 to 9.710)	0.77	81	5	493	464
Left hippocampal tail	–3.943 (–25.319 to 17.433)	0.78	88	4	445	436
Left fimbria	–4.641 (–10.825 to 1.543)	0.26	74	2	91	92
Left hippocampal fissure	4.000 (–1.544 to 9.544)	0.26	NA	1	75	79
Left HATA	0.628 (–1.139 to 2.396)	0.70	0	2	258	149
Right whole hippocampus	–39.031 (–127.489 to 49.426)	0.50	84	5	421	325
Right CA1	–9.269 (–22.842 to 4.303)	0.29	71	8	598	547
Right CA3	–4.766 (–10.052 to 0.520)	0.17	66	8	598	548
Right CA4	–7.333 (–13.175 to –1.491)	0.09	68	7	557	502
Right granule cell layer of the dentate gyrus	–6.295 (–12.299 to –0.292)	0.17	62	6	535	508
Right subiculum	–8.339 (–17.172 to 0.495)	0.17	77	8	597	547
Right presubiculum	2.210 (–4.963 to 9.384)	0.65	80	5	495	466
Right parasubiculum	1.117 (–1.101 to 3.335)	0.47	63	4	348	223
Right molecular layer	1.735 (–12.626 to 16.095)	0.81	84	5	495	466
Right hippocampal tail	2.729 (–15.585 to 21.042)	0.81	89	4	448	436
Right fimbria	–4.211 (–9.167 to 0.745)	0.18	0	2	92	92
Right hippocampal fissure	5.000 (–0.544 to 10.544)	0.17	NA	1	78	81
Right HATA†	2.413 (0.958 to 3.868)	0.01	27	2	260	149

CA = cornu ammonis; CI = confidence interval; HATA = hippocampus–amygdala transition area; MDD = major depressive disorder; NA, not available.
*Adjusted.
†Statistically significant difference.

the bilateral whole hippocampus, CA4, granule cell layer of the dentate gyrus, molecular layer, hippocampal tail, left CA1, CA2/3 and fimbria.

In 28 studies, hippocampal subfield volumes were compared between patients with MDD and healthy controls. Of those, 14 studies found no volume differences between groups, and 12 studies reported smaller volumes in patients with MDD, including all subfields except the parasubiculum and HATA. Four studies reported larger hippocampal subfields in patients with MDD compared to healthy controls: Hu and colleagues[50] reported larger volumes in the bilateral CA1 and subiculum and left CA2/3 and CA4/dentate gyrus in patients who did not respond to antidepressants; Kraus and colleagues[54] found larger volumes in the right HATA in remitted patients with MDD; and Maller and colleagues[20] and Roddy and colleagues[70] identified a larger hippocampal tail and a larger right molecular layer, respectively.

In terms of longitudinal changes in patients with MDD, Cao and colleagues[44] found that electroconvulsive therapy induced volume increases in the bilateral CA4 and granule cell layer of the dentate gyrus, and in the left CA3 and subiculum. Zhou and colleagues[65] reported increased volumes after ketamine treatment in the right hippocampus, CA4 (head) and molecular layer (head), and in the left CA4 (body) and granule cell layer of the dentate gyrus (body). Kraus and colleagues[54] did not detect antidepressant-related changes in subfield volumes in patients with MDD.

Network meta-analysis

Because 12 hippocampal subfields and the whole hippocampus were considered in each hemisphere, we performed network meta-analyses 26 times in total. We performed direct comparisons between patients with schizophrenia and healthy controls and between patients with MDD and healthy controls; we also performed indirect comparisons between patients with schizophrenia and patients with MDD (because the comparison was not based on a direct group comparison in the same study). Subfield volumes were measured in the CA1, CA3 and subiculum by 15 studies; in the CA4 by 14 studies; in the granule cell layer of the dentate gyrus by 13 studies; in the molecular layer by 12 studies; in the whole hippocampus, presubiculum and hippocampal tail by 11 studies; in the parasubiculum by 9 studies; in the fimbria and HATA by 7 studies; and in the hippocampal fissure by 6 studies. For each hippocampal subfield, Table 3 and Table 4 show the number of studies and participants included in the network meta-analysis.

We found volume differences in the bilateral parasubiculum and right HATA between patients with schizophrenia and patients with MDD in the network meta-analysis; forest plots for these subfields are shown in Figure 1. We found no volume differences in other hippocampal subfields between patients with schizophrenia and patients with MDD; related forest plots are shown in the Supplementary Materials (Appendix 1, Figure S2).

Through direct volume comparisons with healthy controls, we determined that patients with schizophrenia had smaller volumes in the whole hippocampus bilaterally and in 17 of 24 hippocampal subfields, including the bilateral CA1, granule cell layer of the dentate gyrus, subiculum, parasubiculum, molecular layer, hippocampal tail and HATA; the left CA4 and presubiculum; and the right fimbria. No hippocampal subfields were larger in patients with schizophrenia than in healthy controls (Table 3). Patients with MDD had smaller volumes in the left CA3 and CA4 than healthy controls. Patients with MDD had larger volumes in the right HATA than healthy controls (Table 4). Through indirect comparisons, we found that patients with schizophrenia had smaller subfields than patients with MDD in the bilateral parasubiculum and the right HATA. No hippocampal subfields were larger in patients with schizophrenia than in patients with MDD (Table 5).

The results of network meta-analysis of 7 studies that reported ICV were not completely consistent with the results from the 15 studies reported above. Through direct comparisons, we found that patients with schizophrenia had smaller volumes in the whole hippocampus bilaterally and in 15 of 24 hippocampal subfields (bilateral CA1, CA4, granule cell layer of the dentate gyrus, subiculum and molecular layer; left hippocampal tail; and right CA3, parasubiculum, fimbria and HATA). No hippocampal subfields were larger in patients with schizophrenia than in healthy controls (Appendix 1, Table S3). Patients with MDD had larger volumes in the right HATA than healthy controls. No hippocampal subfields were smaller in patients with MDD than in healthy controls (Appendix 1, Table S4). Through indirect comparisons, we found that patients with schizophrenia had smaller volumes in the right HATA than patients with MDD. No hippocampal subfields were larger in patients with schizophrenia than in patients with MDD (Appendix 1, Table S5).

Direct comparisons between patients with schizophrenia and patients with MDD

Through direct cross-sectional volume comparisons between patients with schizophrenia and patients with MDD, we found that patients with schizophrenia had larger volumes in the whole hippocampus bilaterally and in 19 of 24 hippocampal subfields (bilateral CA1, CA3, CA4, granule cell layer of the dentate gyrus, subiculum, presubiculum, parasubiculum, molecular layer and hippocampal tail; and right HATA). Patients with schizophrenia had smaller volumes in the left HATA than patients with MDD (Appendix 1, Table S6). We did not perform direct comparisons for the bilateral fimbria and hippocampal fissure because few studies measured all of the subfields.

Meta-regression

The results of the preplanned meta-regression are presented in Appendix 1, Table S7. Corresponding meta-regression graphs are shown in Appendix 1, Figure S3.

For the direct comparison between patients with schizophrenia and healthy controls, heterogeneity in results for the left hippocampal tail was related to age, illness duration and scores on the Positive and Negative Syndrome Scale.

For the direct comparison between patients with MDD and healthy controls, heterogeneity in results for the left CA3 and CA4 was related to age and scores on the Hamilton Depression Rating Scale. Heterogeneity in results for the left granule cell layer of the dentate gyrus was related to age. Heterogeneity in results for the right CA3 and CA4 could be explained by scores on the Hamilton Depression Rating Scale. For these comparisons, all results were initially significant but did not survive false discovery rate correction.

For the direct comparison between patients with MDD and healthy controls, we did not perform meta-regression for the whole hippocampus, parasubiculum, hippocampal tail or left fimbria because few studies measured all subfields. For the remaining hippocampal subfields with I^2 greater than 50%, we did not identify any source of heterogeneity.

Heterogeneity, transitivity, inconsistency and publication bias

We evaluated heterogeneity using the I^2 statistic; findings are presented in Table 3 and Table 4. From the results of direct meta-analysis, we found evidence for statistical heterogeneity, most notably in pair-wise comparisons between patients with MDD and healthy controls. Because not all included studies consistently reported potential effect modifiers, we could not statistically assess transitivity. Therefore, we evaluated transitivity by comparing the main participant characteristics for the included studies. Because we lacked a direct comparison between patients with schizophrenia and patients with MDD, we did not directly estimate inconsistency. The results of the Egger linear regression test indicated no publication bias in network meta-analysis except for the right HATA in the comparisons between patients with schizophrenia and healthy controls (Appendix 1, Table S8).

Discussion

In this systematic review and network meta-analysis, we investigated the common and specific features in volume abnormalities of hippocampal subfields based on MRI studies in patients with schizophrenia and patients with MDD. The systematic review found that patients with schizophrenia

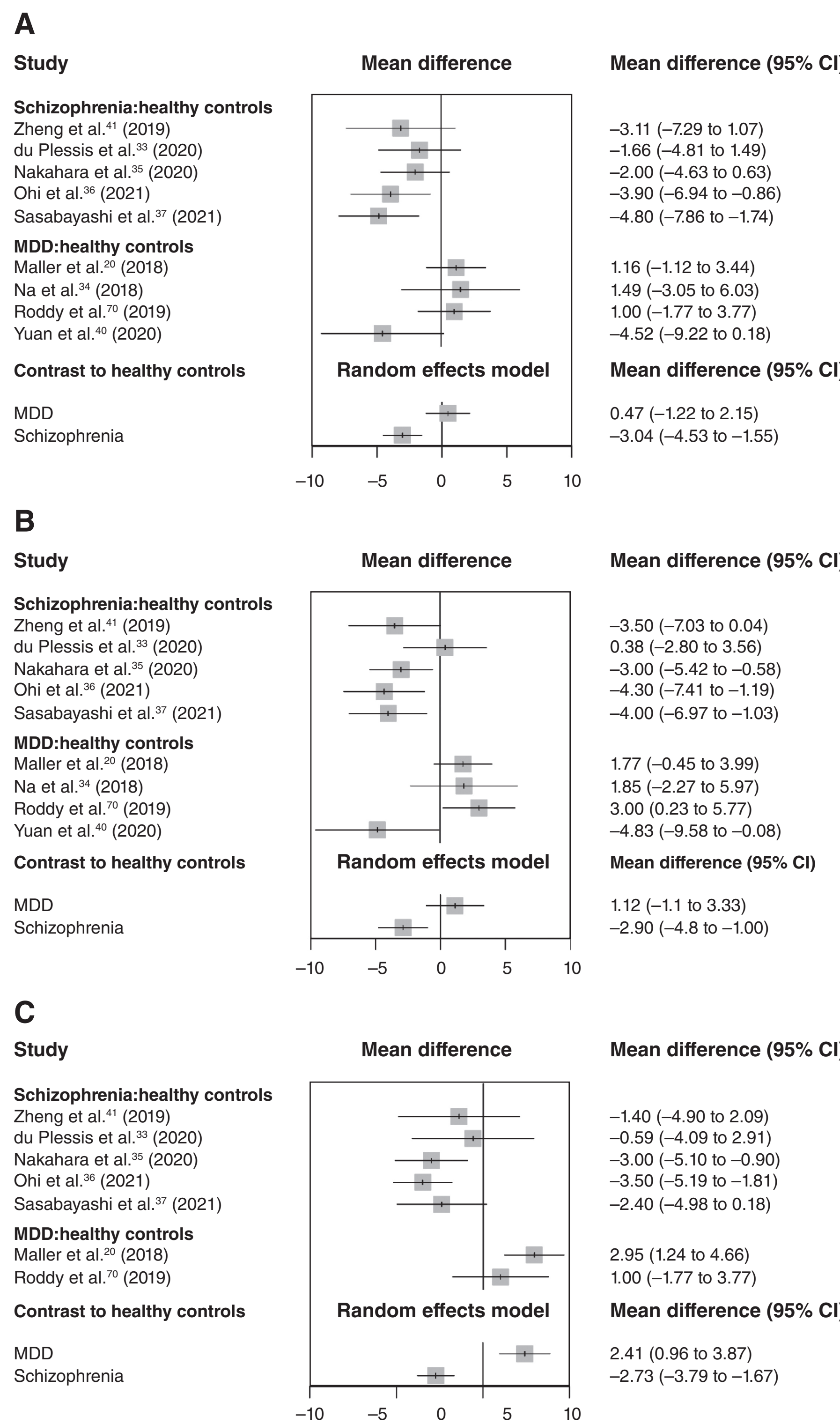

Figure 1: (A) Forest plot for the left parasubiculum. (B) Forest plot for the right parasubiculum. (C) Forest plot for the right HATA. CI = confidence interval; HATA = hippocampus–amygdala transition area; MDD = major depressive disorder.

Table 5: Indirect volume comparisons between patients with schizophrenia and patients with MDD

Region of interest	Mean difference (95% CI), mm³	*p* value*
Left whole hippocampus	–52.842 (–182.380 to 76.696)	0.67
Left CA1	–8.347 (–29.661 to 12.966)	0.67
Left CA3	2.936 (–4.428 to 10.300)	0.67
Left CA4	1.262 (–6.139 to 8.663)	0.77
Left granule cell layer of the dentate gyrus	–1.719 (–10.501 to 7.063)	0.77
Left subiculum	–2.665 (–14.354 to 9.025)	0.77
Left presubiculum	–7.914 (–17.431 to 1.602)	0.34
Left parasubiculum†	–3.506 (–5.755 to –1.256)	0.03
Left molecular layer	–14.488 (–30.416 to 1.440)	0.32
Left hippocampal tail	–20.513 (–47.148 to 6.122)	0.34
Left fimbria	2.633 (–4.420 to 9.687)	0.67
Left hippocampal fissure	0.941 (–5.357 to 7.239)	0.77
Left HATA	–2.672 (–4.761 to –0.584)	0.08
Right whole hippocampus	–69.772 (–184.654 to 45.111)	0.43
Right CA1	–7.067 (–25.997 to 11.863)	0.75
Right CA3	1.990 (–5.337 to 9.317)	0.77
Right CA4	2.404 (–5.432 to 10.240)	0.77
Right granule cell layer of the dentate gyrus	–0.362 (–8.383 to 7.659)	1.00
Right subiculum	–0.426 (–12.542 to 11.691)	1.00
Right presubiculum	–9.261 (–19.302 to 0.780)	0.25
Right parasubiculum†	–4.016 (–6.935 to –1.097)	0.046
Right molecular layer	–15.580 (–33.907 to 2.748)	0.25
Right hippocampal tail	–19.950 (–42.993 to 3.094)	0.25
Right fimbria	0.011 (–5.489 to 5.510)	1.00
Right hippocampal fissure	4.849 (–1.513 to 11.211)	0.29
Right HATA†	–5.140 (–6.940 to –3.340)	< 0.001

CA = cornu ammonis; CI = confidence interval; HATA = hippocampus–amygdala transition area; MDD = major depressive disorder.
*Adjusted.
†Statistically significant difference.

had more extensive hippocampal subfields with volume reduction. We also compared the whole hippocampus and 12 hippocampal subfields in each hemisphere using network meta-analysis. Through direct comparisons with healthy controls, we observed volume abnormalities (increases, decreases or both) in 17 subfields in patients with schizophrenia and in 3 subfields in patients with MDD; only the left CA4 was smaller in both groups compared to healthy controls. Indirect comparisons between patient groups showed that the bilateral parasubiculum and right HATA were smaller in patients with schizophrenia compared to patients with MDD. These findings indicate common and distinct hippocampal volume abnormalities at the subfield level in patients with schizophrenia and patients with MDD. The left CA4 was the only shared hippocampal subfield that showed a volume reduction in both.

Direct comparisons between patients with schizophrenia and healthy controls demonstrated widespread volume deficits across hippocampal subfields in patients with schizophrenia.[16,69,73,74] Our findings partially echoed the findings of a study that compared patients with schizophrenia, patients with MDD and healthy controls simultaneously. This study found volume reductions not only in the CA1 and dentate gyrus in patients with schizophrenia compared to healthy controls, but also in the dentate gyrus in patients with schizophrenia compared to patients with MDD.[23] Notably, this study used Automatic Segmentation of Hippocampal Subfields (ASHS) as the segmentation tool, rather than FreeSurfer. According to the segmentation protocol,[15,75] the dentate gyrus traced by ASHS is roughly equivalent to the combined area of the CA4 and the granule cell layer of the dentate gyrus parcellated by the atlas of Iglesias and colleagues.[15] Some original studies in patients with schizophrenia that used a previous segmentation method of FreeSurfer[72] also found extensive volume reductions in hippocampal subfields compared to healthy controls, involving the CA1, CA2/3, CA4/dentate gyrus, subiculum and presubiculum.[59,64,69] Their results were generally consistent with our findings in these subfields. Although we did not detect a significant difference in CA2/3 volume, the left CA2/3 did show a tendency toward volume decrease. A meta-analysis of postmortem studies in patients with schizophrenia also reported fewer neurons in the CA1, CA2/3 and subiculum[76] compared to healthy controls, which was concordant with our findings in the CA1 and subiculum.

Relative to healthy controls, we found fewer hippocampal subfields with volume alterations in patients with MDD than in patients with schizophrenia. A 4.7 T MRI study using manual segmentation found that medication-naive or unmedicated patients with MDD had smaller volumes in the dentate gyrus and CA1 to 3 than healthy controls,[67] and this finding was compatible with our direct comparison evidence of a smaller CA2/3. Our findings related to CA2/3 and CA4 also replicated those of studies[45,46,48,49] that used a previous segmentation method in FreeSurfer.[72] An open-label trial found that patients with remitted MDD had larger volumes in the right HATA, in line with our findings.[54] Nevertheless, our findings did not replicate those of the study that used ASHS.[23] A large sample study showed a larger hippocampal tail in patients with MDD than in healthy controls,[20] and a 7 T MRI study failed to detect any volume abnormalities in hippocampal subfields.[71] These inconsistencies in the results may be because of the heterogeneity inherent in mood disorders (related to illness duration and treatment effects) probably along with less robust and more limited findings of hippocampal alterations in patients with MDD.

Greater hippocampal atrophy in the parasubiculum and HATA in patients with schizophrenia relative to patients with MDD may contribute to the distinct clinical presentations associated with the 2 disorders. The parasubiculum is a major input structure of the medial entorhinal cortex[77] and is involved in scene-based cognitive and spatial processing.[77] A study found that the performance of scene processing was significantly impaired in patients with schizophrenia compared to patients with depression.[78] The parasubiculum is also associated with the integration of hippocampal and cortical information processing,[79] which has been found to be impaired in patients with schizophrenia.[80] The HATA, closely connected with amygdala nuclei that pertain to the hippocampal–amygdala network, is related to fear regulation and situational learning.[81,82] A previous study that measured skin conductance response to interpersonal stimuli found that patients with schizophrenia exhibited poorer fear conditioning than patients with depression.[83] Thus, in aggregate, differences between schizophrenia and MDD in terms of parasubiculum and HATA volumetric alterations might contribute to the distinct cognitive impairments and emotional dysregulation seen in the 2 disorders. However, considering the publication bias we found in relation to findings for the right HATA in patients with schizophrenia, these findings should be interpreted with caution and warrant further study.

The deficient CA4 (including the polymorphic layer of the dentate gyrus in our study) in patients with schizophrenia and patients with MDD suggests a common structural feature of the disorders. The CA4/dentate gyrus is the initial hippocampal substructure along the trisynaptic pathway, and it acts as the input gate for the dentate gyrus–CA3–CA1–subiculum circuit.[84] As proposed in a pathophysiological model of schizophrenia,[85] disruptions in the CA4/dentate gyrus may weaken glutamate transmission to the CA3, which in turn promotes local neuronal hypersensitivity to stimuli via hippocampal plasticity. It has been proposed that this mechanism strengthens information processing and contributes to the generation of inappropriate associations and psychotic memory constructions.[86] Negative psychotic symptoms, including anhedonia and apathy, have been associated with volume reductions in the C4/dentate gyrus in clinical studies.[68,73] An animal study of MDD proposed that reduced expression of brain-derived neurotrophic factor in the dentate gyrus reduces neurogenesis and affects behaviour associated with depression.[87] The CA4/dentate gyrus has also been found to be vulnerable to childhood trauma and stress,[88] which are risk factors for MDD. Furthermore, some molecular alterations in the CA4 have been reported in patients with schizophrenia and patients with MDD. These involved fibroblast growth factor receptor mRNA and glutamic acid decarboxylase mRNA,[89,90] which are related to normal hippocampal synaptology, signal transmission, plasticity and circuitry. Therefore, the overlap in CA4/dentate gyrus volume deficits may be considered a shared neurobiological feature that underlies the 2 disorders. It is of note that the volumetric reductions in the CA4 or CA4/dentate gyrus mentioned above were reported across the entire hippocampus.

Limitations

Our study had several limitations that need to be considered. Previous medication exposure and substance use might have influenced our findings. For example, postmortem evidence has suggested an association between antidepressant treatment and a larger dentate gyrus in patients with MDD.[91] Short-term antipsychotic treatment may reduce the volumes of previously enlarged subfields in antipsychotic-naive patients with first-episode schizophrenia.[55] Inversely, long-term use of certain antipsychotics may protect hippocampal substructures in patients with schizophrenia.[66] However, limited information in the primary literature makes it difficult to control for these confounders.

We performed cross-sectional comparisons only in subfield volumes. Longitudinal research from the early course of illness is needed to understand developmental trajectories and potential differences in hippocampal subfield volumes between schizophrenia and MDD.

Study heterogeneity was more noteworthy in the direct comparison of patients with MDD and healthy controls. Because heterogeneity in the results for the right parasubiculum was higher in the comparison of patients with MDD and healthy controls, the related results should be interpreted with caution. To control for heterogeneity, we used random-effects models in all analyses, and the source analysis highlighted age, illness duration and symptom severity as potential contributors to heterogeneity. Another contributor could be insufficient disclosure of some subfield features in the primary literature.

Limited by inconsistent volumetry and uneven reports of hippocampal subfields in the original studies, our statistical power to detect group differences was lower in some subfields.

We did not control for the confounding effects of ICV in the network meta-analysis. Only 7 of the 15 studies reported ICV, and the results obtained from the 7 studies were slightly different from those obtained from the 15 studies. Such insufficient stability may have been because of the relatively small sample size of 7 studies, the confounding effects of ICV or both. The results of direct comparisons between patients with schizophrenia and patients with MDD after controlling for ICV should be interpreted with caution because of the demographic differences between patients.

Hippocampal subfields might not be uniformly affected along the longitudinal axis (i.e., head, body and tail in sequence) in psychotic disorders.[92] However, few studies have investigated such detailed anatomy, so it was not feasible to distinguish more subtle alterations within each subfield.

Finally, the automatic segmentation algorithm of Iglesias and colleagues[15] is based on previous and visible features, possibly ignoring individual variations in hippocampal subfield anatomy.[93] The developers of this algorithm acknowledged that volumes of internal subfields, such as the CA4, the granule cell layer of the dentate gyrus and the molecular layer, must be interpreted with caution (surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfields).

Conclusion

Patients with schizophrenia and patients with MDD had overlapping and distinct volume abnormalities in hippocampal subfields. The 2 disorders showed a common lower volume in the left CA4. Inter-disorder differences included greater volume reductions in the bilateral parasubiculum and right HATA in patients with schizophrenia compared to patients with MDD. This combination of similarities and differences may help us to better understand the pathophysiology of both disorders.

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