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Hippocampal volume and hippocampal neuron density, number and size in schizophrenia: a systematic review and meta-analysis of postmortem studies

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Abstract

Reduced hippocampal volume is a consistent finding in neuroimaging studies of individuals with schizophrenia. While these studies have the advantage of large sample sizes, they are unable to quantify the cellular basis of structural or functional changes. In contrast, postmortem studies are well suited to explore subfield and cellular alterations, but low sample sizes and subject heterogeneity impede establishment of statistically significant differences. Here we use a meta-analytic approach to synthesize the extant literature of hippocampal subfield volume and cellular composition in schizophrenia patients and healthy control subjects. Following pre-registration (PROSPERO CRD42019138280), PubMed, Web of Science, and PsycINFO were searched using the term: (schizophrenia OR schizoaffective) AND (post-mortem OR postmortem) AND hippocampus. Subjects were adult men and women with schizophrenia or schizoaffective disorder or non-psychiatric control subjects, and key outcomes, stratified by hippocampal hemisphere and subfield, were volume, neuron number, neuron density, and neuron size. A random effects meta-analysis was performed. Thirty-two studies were included (413 patients, 415 controls). In patients, volume and neuron number were significantly reduced in multiple hippocampal subfields in left, but not right hippocampus, whereas neuron density was not significantly different in any hippocampal subfield. Neuron size, averaged bilaterally, was also significantly reduced in all calculated subfields. Heterogeneity was minimal to moderate, with rare evidence

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Conflict of interest

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of publication bias. Meta-regression of age and illness duration did not explain heterogeneity of total hippocampal volume effect sizes. These results extend neuroimaging findings of smaller hippocampal volume in schizophrenia patients and further our understanding of regional and cellular neuropathology in schizophrenia.

Introduction

The hippocampus is one of the brain regions most consistently abnormal in structural and functional studies of patients with schizophrenia [1]. The most robust hippocampal pathology observed in living subjects is smaller volume, supported by numerous neuroimaging studies and several meta-analyses, with effect sizes (ESs) ranging from 0.37–0.66 [2–8]. Alterations in neuron number, density, or size can all contribute to regional brain volume changes. However, routine neuroimaging methods cannot determine which of these processes lead to volume changes in schizophrenia patients.

Changes in cytologic measures may be generalized to all neuronal types or may be specific to certain neuron classes. The majority of hippocampal neurons are excitatory glutamatergic neurons, including large, pyramidal-shaped neurons and densely packed granule cells of the dentate gyrus. The remaining neurons are smaller, nonpyramidal, GABAergic, inhibitory interneurons of many different subpopulations with specialized properties [9,10]. These neuronal subpopulations tightly regulate an excitation-inhibition balance that is integral for hippocampal function. Recent models have proposed that an excitation-inhibition imbalance in the hippocampus may contribute to the development of schizophrenia [11,12]. Thus, changes in the number, density, or size of these neurons have important implications for understanding the pathophysiology of schizophrenia and the development of effective treatment strategies.

Recent studies suggest that hippocampal volume reductions in schizophrenia patients affect almost all hippocampal subfields [7,13], though techniques to resolve individual hippocampal subfields can vary considerably between research groups [14]. Given that individual subfields of the hippocampus contribute to distinct components of cognition [15], a key question is whether cytologic changes in neuron number, density, or size are generalized across the hippocampus, or specific to certain subfields. The hippocampal formation consists of the hippocampus proper (cornu ammonis (CA) 1–4 and the dentate gyrus (DG)), the subicular complex, and the entorhinal cortex [16]. The complex anatomy of the hippocampus reflects specialization of cellular layers, circuitry, and function [7]. Therefore, cytologic changes that drive volume decreases in specific subfields can have important functional implications. Recent circuit models propose a pathophysiological framework of hippocampal dysfunction driven specifically by subfield changes that begin in CA1 and progress to other regions as the illness advances [17,18]. While neuroimaging methods have become increasingly precise at differentiating between hippocampal subfields [19], the gold standard is to use hippocampal tissue in postmortem studies to differentiate between hippocampal subfields and quantify structural and cytological measures in patients with schizophrenia.

Many postmortem studies have not corroborated the neuroimaging finding of smaller hippocampal volume in schizophrenia [1]. Several possibilities may account for this discrepancy, including limited power to detect modest ESs in small postmortem sample sizes, demographic differences in individuals contributing to neuroimaging versus postmortem studies, or artefactual differences due to processing of *in vivo* versus fixed postmortem human brain tissue. In addition, the neuronal populations and subfields reported in postmortem studies vary widely. Meta-analytic synthesis is a powerful tool to unify and build on a rich and extensive literature of postmortem studies of hundreds of schizophrenia patients and non-psychiatric control subjects. In particular, meta-analysis enables greater power to detect differences of modest ES that might lead to non-significant results at the individual study level and enables exploration of moderators of heterogeneity such as demographic, clinical, or methodological variables. To our knowledge, this is the first meta-analysis of postmortem hippocampal volume, neuron density, neuron number and neuron size in schizophrenia.

We aim to answer three questions with this study. First, do postmortem studies confirm the robust volume findings of the neuroimaging literature? Second, what cytologic changes are associated with changes in volume? Lastly, are cytologic and/or volumetric changes specific to a hemisphere or subfield, or are they generalized? In this study, we quantitatively synthesize postmortem findings in patients as compared to non-psychiatric control subjects and discuss the implications of these findings for the current understanding of schizophrenia.

Materials and Methods

Registration and Search Strategy

This study was prospectively registered in the PROSPERO International Prospective Register of Systematic Reviews (#CRD42019138280). On June 13, 2019, PubMed, Web of Science, and PsycINFO were searched for articles published between 1/1/1952 and 6/1/2019 using the search term: (schizophrenia OR schizoaffective) AND (post-mortem OR postmortem) AND hippocampus. Additional details are available in the Supplementary Methods.

Study Selection, Inclusion and Exclusion Criteria

Study selection was performed by two authors (MJR and ASL) and discrepancies resolved. Briefly, studies were included if they included men or women with a diagnosis of schizophrenia or schizoaffective disorder without neurological disorders or serious non-schizophrenia psychiatric conditions. Non-psychiatric controls were men or women without known history of major psychiatric or neurological disorders or history of drug or alcohol abuse. Detailed criteria for subject and study inclusion or exclusion are available in the Supplementary Methods. Thirty-two studies were ultimately included in our analyses (413 patients, 415 controls).

Data Extraction

Data extraction was performed by one author (MJR) and all data were independently checked by a second author (ASL). Discrepancies were resolved by discussion. Mean values

and standard deviations for the total hippocampus and/or the subfields CA1, CA2/CA3, CA4, DG, and subiculum were extracted for each hemisphere (when hemispheric identity was available) as well as from anterior or posterior hippocampus (when available). Because most studies reported data from a single region denoted as “CA2/CA3”, we combined these data when they were reported separately and calculated the mean and pooled standard deviation to yield a “calculated” CA2/CA3 to facilitate appropriate comparisons. In studies where data was presented graphically rather than numerically, we used open-source plot digitizer software [20] to extract mean and variance measures. As available, we extracted the mean and standard deviation of age at death, percentage of male participants, postmortem interval (PMI), sample pH, and percent death by suicide for patients and controls in each study. For patients, we also extracted percent of subjects abusing alcohol and/or drugs and mean and standard deviation of both chlorpromazine equivalents and duration of illness. For studies that reported measures for males and females separately, we used the mean and pooled standard deviation of reported measures. In studies otherwise meeting criteria for inclusion, we reached out directly to authors for raw data when the reported data were incomplete or in a format that could not be incorporated into the meta-analysis. Finally, one study [21] only reported statistical descriptions of subfields that significantly differed between patients and controls and reported only means elsewhere. We used the statistics reported for significant regions to estimate percent variation in the other subfields, which when combined with the mean data from these regions allowed us to extract data and contribute to the meta-analysis.

Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (CMA), Version 3 (BioStat, Englewood, NJ, USA). Data were analyzed using a random effects model. The average number of subjects per study was 26. Because of the small size of some studies, we used Hedges' g as a measure of effect size (ES). Hedges' g is Cohen's d multiplied by a correction factor that gives an unbiased estimation of d for smaller samples [22]. The minimum number of independent studies for which a meta-analytic calculation was performed was three. Heterogeneity between studies was measured using the I^2 statistic, which describes the percentage of the variability in estimates that is due to heterogeneity [23]. Publication bias was assessed for each group of studies by visual inspection of funnel plots, and tested with Egger's regression test for funnel plot asymmetry [24]. A p value < 0.05 (two-tailed) was considered statistically significant. Subgroup analyses were performed to evaluate the potential effects of discrete moderators, including diagnosis and application of stereology. Random effects meta-regression was performed in CMA to assess the effects of continuous moderators, including subject age and duration of illness on total hippocampal volume difference between patients and controls.

Results

Systematic literature review

The literature search yielded 789 unique results, of which 128 were assessed for eligibility from full text review. Twelve studies [25–36] met our criteria for inclusion in the quantitative synthesis, but were ultimately excluded from the meta-analysis due to an inability to

incorporate the data (e.g. insufficient statistical reporting or measurement of dependent variables differing from our study goal) (exclusion reasons are described in Supplemental Table 1). Thirty-two studies ultimately contributed to the meta-analysis (Figure 1). Sufficient number of studies were identified to calculate an overall ES for volume, neuron number, and neuron density, stratified by left or right hippocampus, for hippocampal subfields, whereas for the total hippocampus we were able to calculate an ES for volume only. Due to fewer studies of neuronal size we were unable to stratify hippocampal subfields by laterality for this outcome, however we were still able to calculate an overall ES by averaging samples from either hemisphere. Finally, we were unable to identify a sufficient number of studies that stratified by excitatory or inhibitory neuronal subpopulation to include these data in the meta-analysis except for excitatory neuron density in the CA3 subfield. Organized extracted raw data from all studies included in the meta-analysis are available in Supplemental Data File 1, Sheets 1–7 and 12, and data from studies not meeting inclusion/exclusion criteria and therefore not incorporated in the meta-analysis are available in Supplemental Data File 1, Sheets 8-12.

Total Hippocampus

We identified twelve studies [37–48] that reported on volume, neuron number, or neuron density in the total hippocampus (Figure 2). There were insufficient studies to report on the neuron density or neuron number in either hemisphere for the total hippocampus. Nine studies reported on volume in the left hemisphere (127 patients, 126 controls), and seven reported on volume in the right hemisphere (108 patients, 109 controls). Volume was significantly reduced in the left hemisphere but not in the right. I^2 statistic revealed significant heterogeneity in the right hemisphere (Supplemental Table 2). There was no evidence for publication bias in either hemisphere. An additional meta-analysis of volume including all twelve studies (183 distinct patients, 173 distinct controls) regardless of hemisphere (studies reporting both left and right hemispheres separately were averaged to create a single volume estimate), demonstrated a significant reduction in volume in patients (Supplemental Figure 1). The I^2 statistic indicated significant heterogeneity, and there was no evidence for publication bias.

Subiculum

We identified eight studies [38–40,48–52] that reported on volume, neuron number, or neuron density in the subiculum subfield (Figure 3). Seven reported on the left hemisphere (100 patients, 99 controls), six reported on the right hemisphere (89 patients, 90 controls), and 1 did not differentiate by hemisphere and therefore was not included in the analysis. In the left hemisphere, both volume and neuron number are significantly reduced. Neuron density was unchanged. In the right hemisphere, volume, neuron number, and neuron density did not significantly differ between groups. There was no evidence for significant heterogeneity or publication bias in either hemisphere (Supplemental Table 2). The single study that did not differentiate results by hemisphere reported a non-significant increase in subiculum neuron density [51].

CA1

We identified fifteen studies [37,39,40,46,48–58] that reported on volume, neuron number, or neuron density in the CA1 subfield (Figure 4). Nine reported on the left hemisphere (111 patients, 115 controls), eight reported on the right hemisphere (110 patients, 103 controls), and four did not differentiate by hemisphere and therefore were not included in the analysis. In the left hemisphere, both volume and neuron number were significantly reduced. Neuron density was unchanged. There was no evidence for significant study heterogeneity or publication bias (Supplemental Table 2). In the right hemisphere, volume, neuron number, and neuron density were not different between groups. The I^2 statistic revealed significant heterogeneity in volume, but there was no evidence of publication bias. The four studies not differentiating by hemisphere reported non-significant increases in subfield volume [58] and neuron number [53], as well as non-significant increases [51] or decreases [54] in neuron densities of patients.

CA2/3

We identified nine [38,40,46,48,49,51,55–57] studies that reported on volume, neuron number, or neuron density in the CA2/3 combined subfield (Supplemental Figure 2). Eight reported on the left hemisphere (96 patients, 98 controls), seven reported on the right hemisphere (95 patients, 86 controls), and three did not differentiate by hemisphere and therefore were not included in the analysis. In the left hemisphere, volume and neuron number were significantly reduced. Neuron density was unchanged. The I^2 statistic revealed low heterogeneity in volume and neuron density, but significant heterogeneity in neuron number. There was no evidence for publication bias (Supplemental Table 2). In the right hemisphere, volume, neuron number, and neuron density did not demonstrate significant differences. There was no evidence for significant heterogeneity or publication bias. The three studies not differentiating by hemisphere reported non-significant decreases in subfield volume [58] and neuron number [53], and a non-significant increase in neuron density [51].

CA4

We identified fifteen studies [38,39,54–58,40,46,48–53] that reported on volume, neuron number, or neuron density in the CA4 subfield (Supplemental Figure 3). Ten studies reported on the left hemisphere (124 patients, 126 controls), eight reported on the right hemisphere (110 patients, 103 controls), and four studies did not differentiate by hemisphere and therefore were not included in the analysis. In the left hemisphere, volume is significantly reduced. Neuron number and density were unaffected. The I^2 statistic revealed significant heterogeneity for volume, and Egger's regression test for neuron number was significant, suggesting evidence of publication bias (Supplemental Table 2). In the right hemisphere, no differences were observed in volume, neuron number, and neuron density. There was evidence for significant heterogeneity in neuron number, and no evidence for publication bias. Of the studies that did not differentiate by hemisphere, two reported non-significant decreases in subfield volume [58] and neuron density [51]. The remaining two studies reported non-significant increases in patient neuron number [53] and density [54].

Dentate Gyrus

We identified seven studies [21,38,39,46,48,49,56] that reported on volume, neuron number, or neuron density in the DG (Supplemental Figure 4). Seven studies reported on the left hemisphere (83 patients, 82 controls) and five reported on the right hemisphere (69 patients, 70 controls). In the left hemisphere, volume is significantly reduced. The I^2 statistic revealed significant heterogeneity in neuron number, and an Egger's regression test for volume was significant, suggesting evidence of publication bias (Supplemental Table 2). In the right hemisphere, no differences were observed in volume, neuron number, and neuron density. There was no evidence for study heterogeneity or publication bias.

Hippocampal Neuron Size

Ten studies measured hippocampal neuron size (Supplemental Figure 5). We were unable to include one study [28] that met all criteria but only reported neuron size sampled from the total hippocampus rather than a specific subfield. In order to have a sufficient number of studies for subfield analyses, all nine remaining studies [21,46,47,51,59–63], regardless of hemisphere, were grouped together in a single meta-analysis (125 patients, 133 controls). Neuron size was significantly decreased in all tested subfields (subiculum, CA1, CA2/3, and CA4). The I^2 statistic indicated significant heterogeneity in CA1 (Supplemental Table 2). There was evidence for publication bias in all tested subfields. We did not have sufficient studies to conduct a meta-analysis of neuron size in the DG or total hippocampus.

Excitatory and Inhibitory Neuron Number and Density

We explored evidence for subfield changes specifically in excitatory or inhibitory neuronal populations. Four studies contributed data on excitatory neuron number [38,47,58,64] (Supplemental Data File 1, Sheets 8-10), demonstrating either significantly reduced or statistically unchanged number of excitatory neurons in multiple subfields. We identified two studies that reported on inhibitory neuron number [46,58]. Benes et al. did not differentiate between inhibitory neuron subtypes and reported reductions in areas CA2 and CA3 in patients (Supplemental Data File 1, Sheet 9). Konradi et al. showed reductions in both somatostatin- and parvalbumin-positive inhibitory neurons in the CA1 and CA4 subfields, but not CA2/3.

Five studies [25,38,57,58,65] measured excitatory neuron density (summarized in Supplemental Data File 1, Sheet 10). Using the data reported in these studies, we were able to perform meta-analysis using only the left CA3 subfield, which showed no significant change in patients ($ES = -0.28$; $p = 0.57$) [38,57,65]. One of these studies reported statistically significant reduction of excitatory neuron density in patient CA3 and CA4 subfields [57]. There have been many reports of the density of inhibitory neurons or specific interneuron sub-populations. Two studies investigating non-pyramidal cell density reported significant decreases in schizophrenia patients in the CA2 subfield [58] and bilaterally in both the subiculum and DG [65]. Studies of parvalbumin-positive interneurons were mixed, with some studies reporting significantly decreased density in hippocampal subfields [46,66], and others showing increased density [67]. While one study showed no change in the subiculum, it did show a decrease in both somatostatin- and parvalbumin-positive inhibitory neurons in neighboring parahippocampal regions [34]. Individual studies

also reported somatostatin-, calbindin-, and calretinin-positive interneuron density without identifying significant changes (summarized in Supplemental Data File 1, Sheet 11).

Effects of moderators

Subject age, duration of illness, diagnosis (schizophrenia versus schizoaffective disorder), methodology (stereological versus non-stereological methods), antipsychotic drug dosage and use duration, and drug and alcohol abuse may all serve as confounds or moderators of heterogeneity in our study, and we sought to describe their prevalence and quantify their influence when possible.

Age and duration of illness: All 32 studies reported participant ages and 31 studies (97%) matched the ages of patients to controls. Fourteen studies (44%) reported duration of illness for patients. We used meta-regression to quantify how these two continuous variables moderated ES heterogeneity of total hippocampal volume between patients and controls (see studies from Supplemental Figure 1). We found no significant effect of age (Supplemental Figure 6) or duration of illness (Supplemental Figure 7), suggesting that the extent of total hippocampal volume reduction in patients with schizophrenia compared to age-matched controls is stable from approximately 40 to 70 years of age and from approximately 10 to 30 years of illness.

Diagnosis: Only 10 (2.4%) of the 413 patients included in this study were diagnosed with schizoaffective disorder. Three studies included a single patient with schizoaffective disorder, but their individual patient data were not provided and thus we were unable to remove them from our meta-analyses [21,51,52]. One study included seven schizoaffective patients and presented data from schizoaffective patients separately from those with schizophrenia, enabling us to remove schizoaffective subjects and conduct a set of subgroup analyses almost entirely consisting of patients with a schizophrenia diagnosis for outcomes reported by this study [47]. This subgroup analysis was consistent with the original analyses (Supplemental Table 3).

Antipsychotic drug effects: Nine studies (28%) reported on antipsychotic drug dosage enabling calculation of chlorpromazine equivalents, and ten studies (31%) reported on presence of drug or alcohol abuse (extracted data are available in Supplemental Data File 1). Because of its continuous nature, we sought to conduct a meta-regression to assess moderating effects of chlorpromazine equivalents. However there were no outcomes of interest in our study for which there existed greater than six studies reporting chlorpromazine equivalents, precluding our ability to conduct a properly powered meta-regression [68]. Similarly, there were no outcomes of interest in our study reported by a sufficient number of studies with drug and alcohol information to perform meaningful subgroup analyses to test moderating effects.

Stereology: We explored the impact of stereological techniques, used in thirteen studies (41%) [39–41,44–46,48,49,55,58,61,63,67], on neuron number and neuron density estimates, the key outcomes most likely influenced by the use of these methods. A subgroup analysis of subfield neuron number and neuron density, including only stereological studies,

yielded comparable ESs and statistical significance to the overall meta-analysis, though CA2/3 no longer reached the threshold for statistical significance (Supplemental Table 4).

Discussion

Our meta-analysis of postmortem studies of the hippocampus in schizophrenia validates and extends the main finding of neuroimaging studies: hippocampal volume is smaller in schizophrenia. In addition, our study adds novel and important details of hippocampal pathology. First, postmortem changes are prominent in the left hemisphere. Second, volume of the left hippocampus is reduced in all measured subfields. Third, neuron numbers are decreased in three subfields (subiculum, CA1, and CA2/3), but neuron density is not significantly affected in any subfield of either hemisphere. Fourth, neuron size is decreased in several subfields when averaged across both hemispheres (overall findings are summarized in Figure 5). To our knowledge, this is the first meta-analysis of postmortem studies of hippocampal volume, neuron number, and neuronal density in patients with schizophrenia, reporting lateralized measures from individual hippocampal subfields.

The results agree with the finding of decreased hippocampal volume in the left hemisphere of patients, shown in numerous, large-sample neuroimaging studies and meta-analyses [2–8]. The ES of reduction in the postmortem total hippocampus volume ($g = -0.50$) is consistent with ESs in neuroimaging studies (0.37 to 0.66) [5,8], as are the ESs from subiculum (-0.47), CA1 (-0.41), CA2/3 (-0.39), and DG (-0.59) volume reductions. Only the ES of CA4 volume reduction (-0.74) exceeded the findings of neuroimaging meta-analyses. The lateralization of our findings to the left side differs from a large meta-analysis of neuroimaging studies of hippocampal volume in first-episode and chronic schizophrenia patients, which showed bilateral volume reductions in patients, with a smaller left hippocampus than right hippocampus [3]. The reason for this discrepancy between neuroimaging and postmortem studies is unclear. The human hippocampus demonstrates a right > left volume asymmetry [69] and left > right internal connectivity asymmetry [70]. Alterations in these normal asymmetry patterns have been postulated as relevant for the etiology of schizophrenia [71]. Although this lateralization hypothesis has been refuted [72], other postmortem studies in schizophrenia patients corroborate our findings of more severe pathology in the left hemisphere [73–75].

Postmortem studies provide insight into factors underlying reduced hippocampal volumes. Changes in the hippocampus appear to be largely generalized across subfields. While neuron number was significantly reduced in the left hemisphere, total neuron density did not differ in any subfield, suggesting that reduction in volume may be due to reduction in neuron number. Importantly, we cannot claim causality in the relationship between neuron number deficits and volume reduction. Several potential degenerative or disrupted developmental processes may contribute to decreases in volume and neuron number. The total number of hippocampal neurons in schizophrenia was not reduced to the degree seen in neurodegenerative disorders such as Alzheimer's disease or temporal lobe epilepsy [1], suggesting hippocampal pathology in schizophrenia might differ from neurodegenerative disorders or disorders of neuronal death. The neurodevelopmental hypothesis of schizophrenia provides an alternative framework for pathophysiological

changes emphasizing that disturbances during development of the nervous system drive abnormalities in brain structure and function. Environmental impacts during development, together with genetic vulnerabilities, could derail neuronal and glial migration, cell proliferation, axonal growth, and synaptogenesis [76]. Disrupted developmental processes could be cause or contributor to the reported lower hippocampal neuron counts and volume. Furthermore, the left hippocampus completes development more slowly than the right, increasing its vulnerability to developmental and prenatal stressors [77]. This increased susceptibility is consistent with our asymmetrical results and the predominance of left hippocampus findings in schizophrenia literature. A consistent neuropathological finding supporting schizophrenia as a neurodevelopmental process is the lack of gliosis typically seen in neurodegenerative or adult-onset brain disorders [78].

There were not enough data in the extant literature to permit substantive meta-analyses of neuronal subpopulations (i.e., principal neurons versus interneurons), though individual studies report reductions in excitatory neurons as well as inhibitory interneurons [34,46,66,67]. Meta-analysis of three studies of excitatory neuron density in left CA3 found non-significant reduction in patients, but there were no other hippocampal subfields with three or more studies of subpopulation indices. Although interneurons make up a minority of neurons in the hippocampus [10], their prominent and large reduction in some studies led to the hypothesis of an excitation-inhibition imbalance and hippocampal hyperactivity [12,79]. In support of this hypothesis, patients at-risk for schizophrenia demonstrate a hypermetabolic CA1 that spreads to the subiculum after psychosis onset [18]. CA1 hypermetabolism is predictive of hippocampal atrophy during psychosis progression, and the degree of hippocampal hyperactivity is connected to the severity of hippocampal volume loss [18]. Our findings of extensive changes in CA1 and subiculum support these findings in living patients.

Although the CA1 subfield is implicated in volume loss, other postmortem studies of the hippocampus in schizophrenia indicate CA1 is least implicated in synaptic protein and glutamatergic receptor expression alterations. Rather, the CA4 subfield is most altered [73,74]. A recent RNAseq analysis in the postmortem hippocampus showed a subfield-specific molecular profile pattern in the DG, CA3, and CA1 subfields of schizophrenia patients when compared to controls [80]. Taken together with the volume and neuronal morphometry studies analyzed in our current study, postmortem studies indicate regional heterogeneity in schizophrenia pathology.

Our search criteria initially included patients with schizoaffective disorder, in order to maximize the number of relevant studies and to explore differences between the two patient groups. However, our systematic review identified only four studies reporting a total of 10 schizoaffective patients. Thus, we were unable to compare the two diagnostic groups. Examining a subgroup of patients almost entirely with a diagnosis of schizophrenia did not differ from the results of our original study (Supplemental Table 3). The dearth of postmortem studies involving patients with schizoaffective disorder suggests a critical need for future studies exploring neuropathological correlates of mood symptoms in schizophrenia patients. Benes et al. reported a small sample (N = 7 per group) comparing hippocampal volume and cell indices in schizophrenia patients without mood symptoms

compared to those with mood symptoms [47]. Patients with mood symptoms showed significantly greater cell numbers in area CA1 but fewer cells in area CA3, without significant differences in cell size, hippocampal size, or cell orientation. More extensive analyses of hippocampal neuropathology in bipolar disorder have been conducted, including a systematic review and meta-analysis [81], which primarily support reduction in non-pyramidal neurons with particular reduction of parvalbumin-positive neurons. In contrast to our findings in schizophrenia, there is no consistent evidence strongly supporting alterations in hippocampal volume, suggesting important differences in the underlying neuropathology between these disorders.

Our study has several limitations. First, the studies included in our meta-analysis vary with respect to tissue preparation and quantification. For instance, estimates of hippocampal volume in post-mortem studies are vulnerable to differential shrinkage during tissue processing [82,83]. Our meta-analysis cannot overcome this limitation. However, stereological estimates of total cell number are unbiased and can be compared across studies, yet stereological techniques were not applied until 1990 [40]. When we included only studies using stereological techniques in an analysis of neuron number and density, we found ESs comparable to those calculated in the overall analyses (Supplemental Table 4). However, the reduction of neuron number in CA2/3 no longer reached statistical significance. Additionally, while most studies provided information on hemispheres, few reported whether samples originated from the anterior or posterior hippocampus. Connectivity, gene expression, and function are thought to differ considerably across the longitudinal axis of the hippocampus in healthy subjects as well as in schizophrenia [84,85], and thus the information may have helped explain some of the observed heterogeneity.

Finally, there are a number of important potential moderators of the relationship between schizophrenia spectrum disorder diagnosis and changes in hippocampal volume or neuronal morphometric properties, which can be assessed in a quantitative manner in meta-analysis given an appropriate sample size. Schizophrenia illness duration [86] and normal aging [87] are both consistently associated with greater reductions in hippocampal volume, and the interaction between schizophrenia and aging may accelerate hippocampal volume loss. However, meta-regression did not demonstrate any effect of age or illness duration on the ES of total hippocampal volume difference, suggesting the observed volume reduction in chronic schizophrenia patients relative to age-matched controls is stable across long periods of time. Unfortunately, for several other potential moderators, including antipsychotic drug dosage and duration as well as presence of drug or alcohol abuse, we lacked sufficient studies to quantitatively assess their effects. The role of antipsychotic medication on hippocampal volume loss remains an area of intense investigation, with methodological challenges to identifying antipsychotic drugs as a cause of volume loss as opposed to illness progression, which has been investigated in medicated and unmedicated patients as well as animal models [88,89]. A variety of other potential confounds exist that must be considered, including smoking status, nutritional status, and other cardiovascular and health considerations that may substantially differ between patients and control subjects. Taken together, our observation that only a minority of studies reported many of these important potential moderators illustrates some of the logistical challenges of postmortem studies, whereby extensive clinical data from decedents is not always known or available.

In summary, postmortem studies strongly support changes in the left hippocampus in schizophrenia. Subfield volumes, total neuron counts, and neuron size are reduced, but neuron density is preserved. These changes are generalized across all hippocampal subfields on the left side. These results support findings from neuroimaging studies and encourage increasingly targeted hypotheses in mechanistically-focused future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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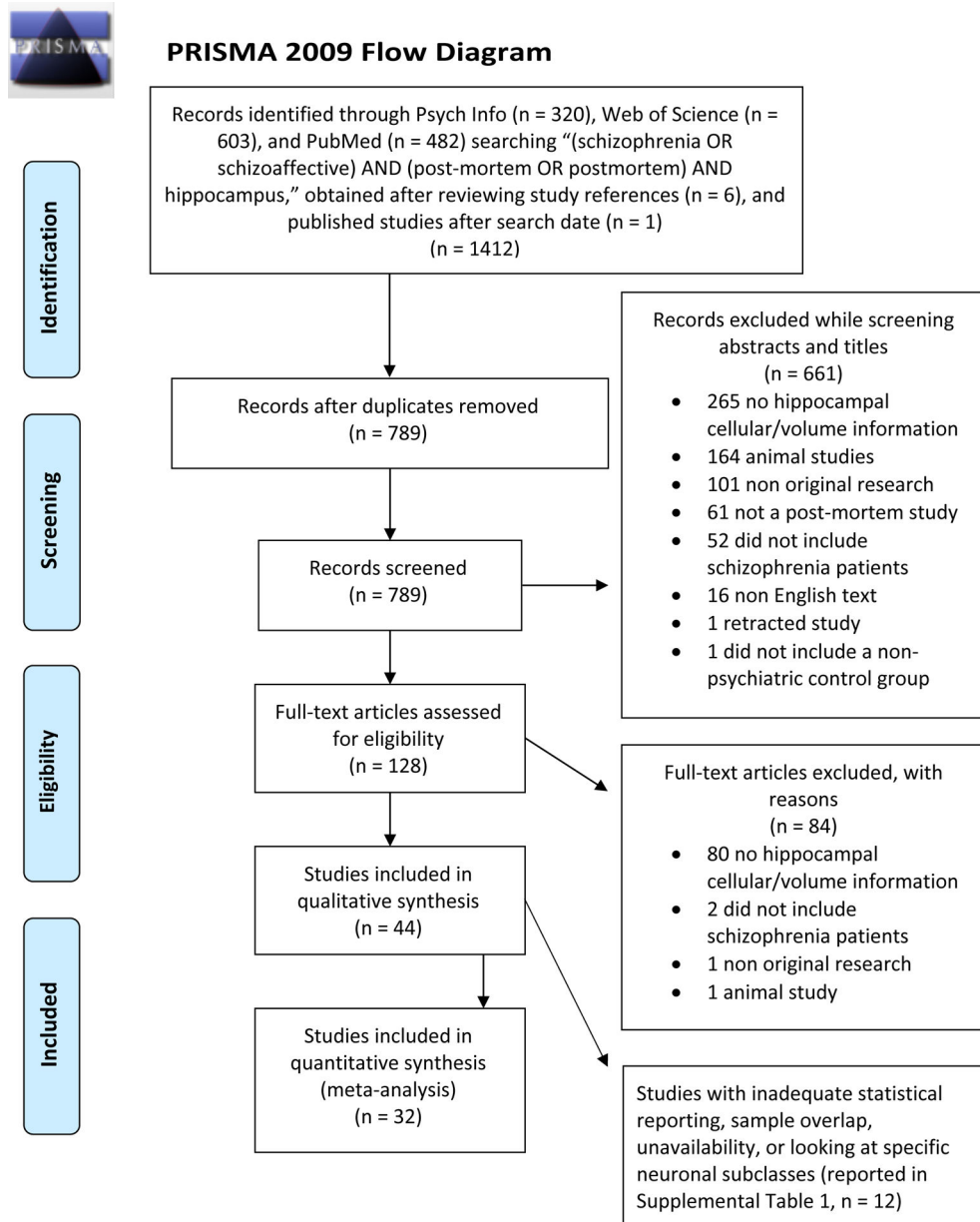


Figure 1: Prisma diagram for study selection.

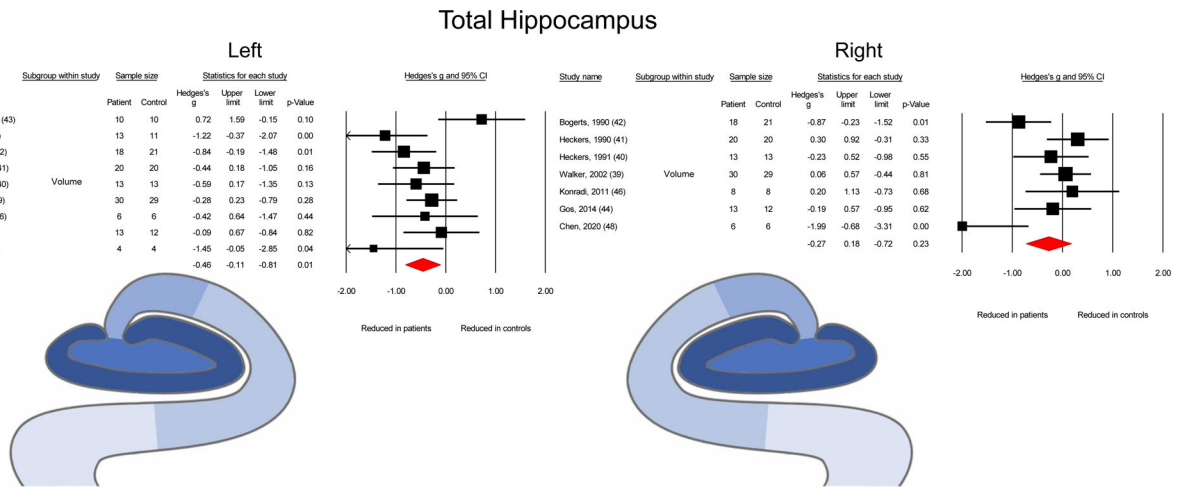


Figure 2: Forest plot depicting the effect sizes for studies reporting on the total hippocampus in the left and right hemisphere. Significant reductions in volume were observed on the left side. The blue gradient in the hippocampus demonstrates the different subfields that make up the total hippocampus (from light to dark: the subiculum, CA1, CA2/3, CA4, and dentate gyrus).

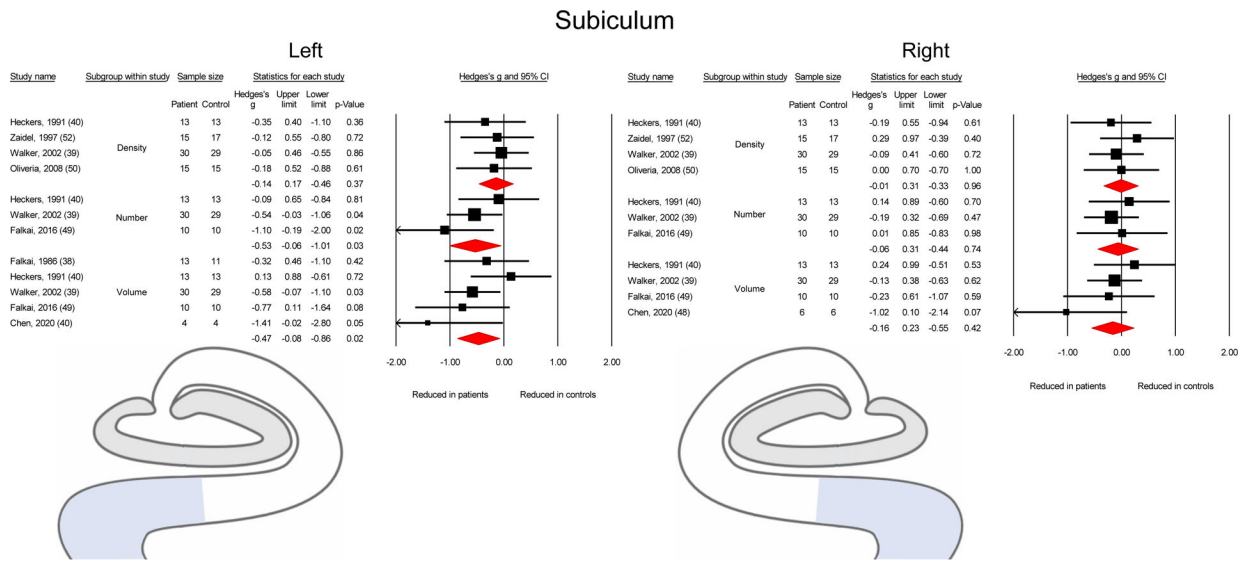


Figure 3: Forest plot depicting the effect sizes for studies reporting on subiculum in the left and right hemisphere. Significant reductions in number and volume were observed on the left side. The light blue, shaded region in the hippocampus depicts the subiculum.

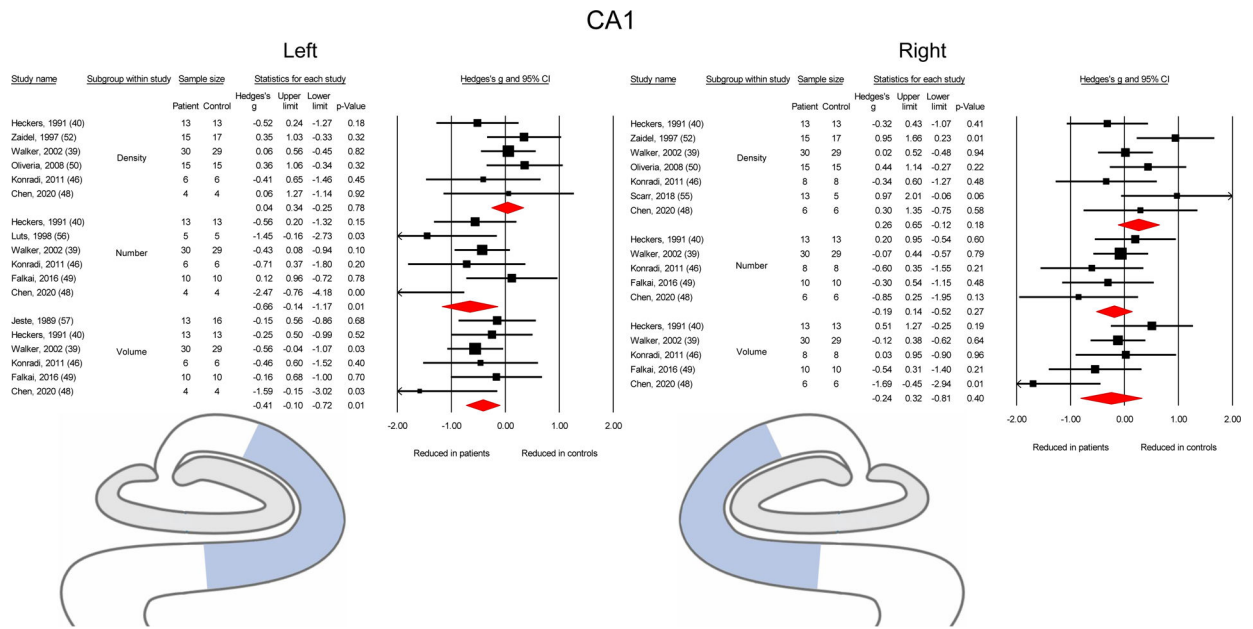
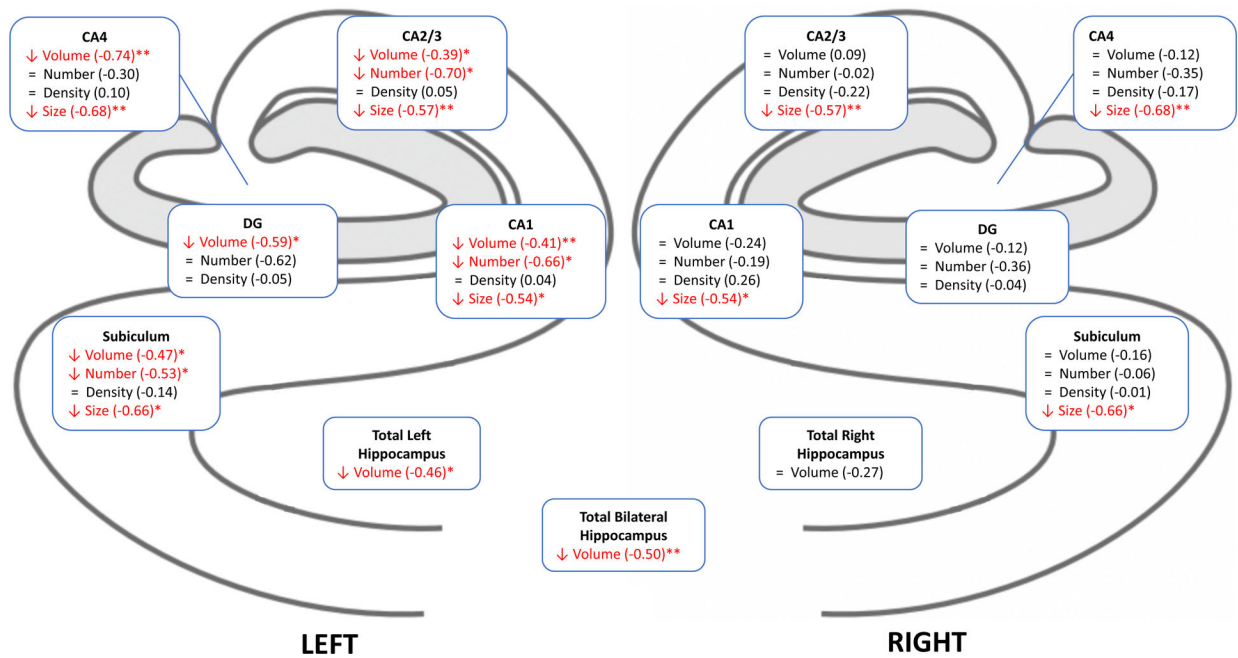


Figure 4:

Forest plot depicting the effect sizes for studies reporting on CA1 in the left and right hemisphere. There were significant reductions in number and volume on the left. The light blue, shaded region in the hippocampus depicts the CA1 subfield.

**Figure 5:**

Summary of overall meta-analysis findings between patients and control subjects: hippocampal volume, neuron number, neuron density, and neuron size changes by subfield and hemisphere. “↓” indicates a significant reduction, with level of significance indicated by asterisks (* $p < 0.05$; ** $p < 0.01$). “=” indicates no significant difference. Numbers in parentheses are effect sizes (Hedge’s g) for each measure. Measures that did not have sufficient study number for meta-analysis are not included in this figure.