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Synaptic density in the hippocampus of depressed patients: A quantitative electron microscopic study

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ABSTRACT

Background: Synaptic dysfunction or loss of synapses is implicated in the pathophysiology of major depressive disorder (MDD). Recent in vivo functional neuroimaging studies document reduced number of synapses in the brains of MDD patients. Here, we performed a post-mortem quantitative electron microscopic study to confirm the putative synaptic loss in the hippocampus of patients with depression.
Methods: Hippocampal tissue from subjects with MDD (n = 11, aged 19–79 years) and psychiatrically healthy controls (n = 17, aged 18–77 years) were investigated. A systematic quantitative analysis was performed to determine the synaptic densities based on unbiased counting principles. Neuropil of the three main subareas of the hippocampal formation (dentate gyrus, CA3, and CA1) were examined.
Results: Hippocampal synaptic densities were comparable between control and depressed subjects. The average density of hippocampal synapses was 3.6 ± 0.2/μm^3 in controls and 3.5 ± 0.2/μm^3 in MDD patients. A more focused analysis however revealed that synaptic densities were significantly lower in the CA3 area of a subset of MDD patients with a single depressive episode. Age had no effect on synaptic density.
Limitations: The sample size of the cohorts was relatively small. Only one segment of the rostral hippocampal body was analyzed.
Conclusions: Our study provides further evidence that synaptic changes may contribute to the pathophysiology of MDD. We did not find the expected widespread synapse loss, instead a region-specific reduction was observed only in a subset of patients. The methodological limitations of our study may explain the contradiction between the results of in vivo neuroimaging data and the present post-mortem findings.

1. Introduction

Major depressive disorder (MDD) is a debilitating mental disorder and a leading cause of global disease burden (GBD 2019 Diseases and Injuries Collaborators, 2020). Significant progress has been made in understanding the pathophysiology, but the exact neurobiology of this disease is still not fully understood (Otte et al., 2016; Ferrari and Villa, 2017; Cui et al., 2024). Several hypotheses have been suggested to explain the pathophysiology, and one prominent theory proposes that depression is caused by dysfunctional synaptic plasticity, eventually resulting in synaptic loss and consequently in disrupted emotion circuitry (Duman and Aghajanian, 2012; Duman et al., 2016; Sanacora et al., 2022; Fries et al., 2023; Thompson, 2023). Multiple lines of evidence support this model. In vivo neuroimaging data consistently document volume loss of limbic structures, such as the prefrontal cortex and hippocampus, in patients with MDD (Campbell et al., 2004;

Abbreviations: CA, Cornu Ammonis; DG, dentate gyrus; EM, electron microscope; GFAP, glial fibrillary acidic protein; Hu, Hungarian; MDD, major depressive disorder; PET, positron emission tomography; PMI, post-mortem interval; SV2A, synaptic vesicle glycoprotein 2A; US, United States; TEM, transmission electron microscope.

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Videbech and Ravnkilde, 2004; Koolschijn et al., 2009; McKinnon et al., 2009; Cole et al., 2011; Kempton et al., 2011; Schmaal et al., 2017). While the exact cellular changes contributing to this volume shrinkage are not fully understood, the loss of dendritic material has been documented in patients with MDD (Hercher et al., 2010; Soetanto et al., 2010). Such debranching of the dendritic arbor is likely to contribute to regional volume shrinkage (Kassem et al., 2013) and implies the loss of dendritic spines and synapses (Kaul et al., 2020). Transcriptomic analysis of postmortem brain tissue of patients with MDD revealed altered expression of synapse-related genes and dysregulated synaptic signaling (Kang et al., 2012; Duric et al., 2013; Goes et al., 2025). Specific changes in the expression levels of synaptic proteins and their mRNAs have been found in the brains of patients with MDD (Al Shweiki et al., 2020; Leung et al., 2022). The most compelling evidence originates from recent in vivo positron emission tomography (PET) studies that examine synaptic densities using the radioligand [^{11}C]UCB-J (Finnema et al., 2016). This radioligand labels the synaptic vesicle glycoprotein 2 A (SV2A) and allows the in vivo imaging of nerve terminals, and by that it provides an indirect estimate of synaptic densities (Finnema et al., 2016; Howes et al., 2024). Reduced synaptic density in depressed patients was demonstrated with this method which could be linked to symptom severity and to neuronal network alterations (Holmes et al., 2019, 2023; Asch et al., 2022, 2024; Van Cauwenberge et al., 2025). A postmortem study using immunolabeling against SV2A reported a reduction in synaptic density in the frontal, parietal and occipital lobe and in the hippocampus (Didikoglu et al., 2024). Finally, electron microscopic

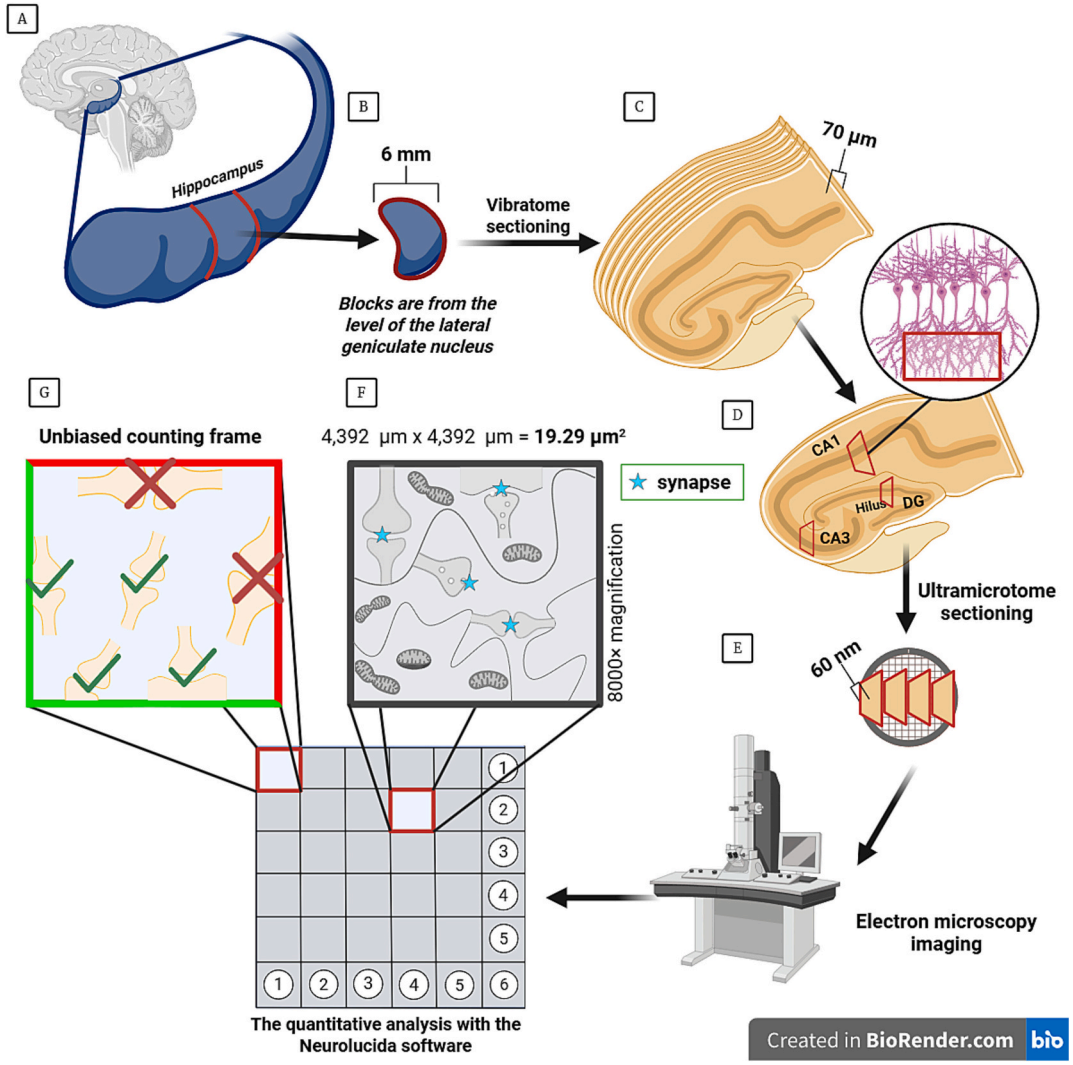

Fig. 1. Flow chart of the procedures from sample preparation to quantification of synaptic densities. We carried out a systematic random sampling protocol when cutting the hippocampus and making the EM micrographs; then, we applied the size-frequency method to quantify the numerical density of synapses per hippocampal tissue unit volume (µm^3). A: Postmortem brain tissue was collected at autopsy. B: Hippocampal tissues were divided along the rostrocaudal axis into 6 mm thick slabs. C: The hippocampal slabs were cut into serial, 70 µm thick, coronal sections. D: Two sections were selected for EM analysis with at least 200 µm interval between them. The selected sections were viewed under a stereomicroscope, and areas of interest were chosen and cut out for re-embedding and electron microscopic sectioning. The areas of interest sampled the neuropil from the three main hippocampal subareas: one from the DG, one from the CA3, and one from the CA1. The red rectangles in the inset of D displays the area where tissue blocks were cut out for EM analysis.E: Tissue blocks of the areas of interest were further sectioned into ultrathin (60 nm) sections using a microtome. From each subject, we examined 24 ultrathin sections with a transmission electron microscope, and photomicrographs were taken at 8000× magnification. F: In every ultrathin section, starting from a random starting point, we made 4–5 non-overlapping EM photomicrographs using a sampling grid. We analyzed ~100 EM images in the hippocampus of each subject. G: Quantitative analysis was performed under the visual control of a single experimenter who used the Neurolucida software. Synapses were counted using an unbiased counting frame. Synaptic profiles touching the exclusion (red) lines were not counted. The average number of synapses counted in each counting frame was 3; therefore, we analyzed ~300 synapses in every subject. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

analysis demonstrated a reduced number of spine synapses in the dorsolateral prefrontal cortex of patients with MDD (Kang et al., 2012). Synaptic changes have been studied in the hippocampus of patients with depression using PET imaging (Holmes et al., 2019); however, to the best of our knowledge, this finding has not yet been complemented with quantitative electron microscopic data. Electron microscopy is still considered as a gold standard method for examining synaptic numbers and morphology (Merchán-Pérez et al., 2009).

Here, we performed a quantitative electron microscopic analysis of synapses in postmortem hippocampal tissue samples from patients with MDD and psychiatrically healthy controls matched for age and sex. The procedure of sample preparation and synapse quantification is depicted in Fig. 1. Hippocampal tissue samples originated from two independent brain collections. A post-mortem brain tissue collection at the University of Mississippi Medical Center (USA) provided the samples originating from patients with MDD and most of the control samples. Further control brain tissue samples were acquired from the collection of the HUN-REN Institute of Experimental Medicine (Hungary, EU). We analyzed the three main subareas of the hippocampal formation (dentate gyrus, CA3, and CA1) separately. Our hypothesis was that we would find reduced number of hippocampal synapses in patients with depression.

2. Material and methods

2.1. Subjects

In the case of the American samples, the tissues were collected at autopsy at the Cuyahoga County Medical Examiner's Office, Cleveland, OH, and the cause of death was determined by the Medical Examiner.

All subjects underwent retrospective assessment for Axis I diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV) (American Psychiatric Association (APA), 1994) by a trained interviewer using the Structured Clinical Interview for DSM Axis I Disorders, modified for third-person reporting (First et al., 1995). Interview notes and clinical histories were reviewed independently by two licensed mental health clinicians who assigned consensus diagnoses in a conference.

Each participant diagnosed with MDD ($n = 11$) was paired with a control participant ($n = 10$) matched for sex, age (±5 years), postmortem interval (PMI) (± ~ 7.5 h), and tissue pH. There were no significant differences between the MDD and Control groups in terms of age, PMI, tissue pH, or fixation time in formalin (Table 1). Urine and blood collected at autopsy were examined by the medical examiner for the presence of psychotropic medication or psychoactive substances. The laboratory personnel were unaware of the individual diagnoses throughout the study. The clinical characteristics of the MDD Cohort are summarized in Table 2. For individual subject details, refer to Supplementary Tables 1–3.

All MDD subjects met the criteria for depression within the last two weeks of life, except for one subject in remission. No Control subject met the criteria for any current or past mood disorder or other psychiatric disorders. The American subjects were identical to those studied in our earlier publications (Cobb et al., 2013, 2016).

In the case of the Hungarian samples, the tissues were collected at autopsy at the St. Borbála Hospital in Tatabánya, and the cause of death was determined by the Medical Examiner. Control, non-psychiatric cases were selected based on the hospital records. Written informed consent was obtained from the legal next-of-kin for tissue collection.

The additional Hungarian control subjects ($n = 7$) were also paired with the MDD subjects and matched for sex and age (±5 years). Tissue pH and post-mortem toxicology data were not available for these samples. There was a significant difference between the Hungarian Control and US Control groups in PMI due to the different fixation protocols (Table 1).

Table 1
Demographic characteristics of the three cohorts.

	Control (Hu)	Control (US)	MDD	Statistics
	$n = 7$	$n = 10$	$n = 11$	
Age (years)	61.71 ± 6.26	47.80 ± 5.36	51.18 ± 4.87	$F = 1.64$, $P = 0.21$ #
Age range (years)	27–77	18–66	19–79	–
Sex (Male / Female)	5 / 2	9 / 1	8 / 3	$\chi^2 = 1.21$, $P = 0.54$ §
Female proportion	28%	10%	27%	–
Post-mortem interval (hours)	3.42 ± 0.33	**23.80 ± 2.13** ****	**23.65 ± 3.15** ****	**$F = 17.96$, $P < 0.0001$** #
	Combined control (US + Hu)		MDD	
	$n = 17$		$n = 11$	
Age (years)	53.53 ± 4.30		51.18 ± 4.87	$t = 0.55$, $P = 0.59$ ¥
Age range (years)	18–77		19–79	–
Sex (Male/ Female)	14 / 3		8 / 3	$\chi^2 = 0.37$, P = 0.54 §
Female proportion	18%		27%	–
Post-mortem interval (hours)	15.41 ± 2.79		23.65 ± 3.15	$U = 53.50$, $P = 0.06$ ¶

Data are shown as mean ± S.E.M. Significant difference is highlighted in bold. Statistics: # One-way ANOVA followed by Tukey *post-hoc* test. **** P < 0,0001 versus Control (Hu). § Chi-Square test; ¥: Two-tailed unpaired Student's *t*-test. ¶: Mann-Whitney *U* test.
Abbreviations: Hu: Hungarian; MDD: major depressive disorder; US: United States.

Table 2
Clinical characteristics of the depressed patients.

Clinical parameters	Major depressive disorder
Age of onset of depression (years)	45.23 ± 5.77
Duration of depression (years)	5.49 ± 2.42
Percent of life in depression (%)	7.99 ± 3.14
Single episode versus Recurrent/Chronic MDD	6/5
Suicide (Yes / No)	7/4 (64%)
Antidepressant detected in postmortem toxicology (Yes / No)	2/9 (18%)

Data are shown as mean ± S.E.M. Abbreviations: MDD: major depressive disorder.

2.2. Ethics

In the case of American samples, the protocol for recruitment, tissue collection, and interviews was approved by the Institutional Review Boards of the University Hospitals of Cleveland and University of Mississippi Medical Center. Ethical approval numbers: Protocol 1999–1002 University of Mississippi Medical Center / approval date: 10/26/1999 and Protocol 11–88-233 University Hospitals Case Medical Center / approval date: 02/13/2018. Written informed consent was obtained from the legal next-of-kin for tissue collection and informant-based retrospective diagnostic interviews. Tissues were collected at autopsy at the Cuyahoga County Medical Examiner's Office, and the cause of death was determined by the medical examiner. Patients with a history or evidence of neurological injury or disorder were excluded.

In the case of the Hungarian samples, tissue collection was approved by the ethics committee at the Regional and Institutional Committee of Science and Research Ethics of the Scientific Council of Health (ETT TUKEB 15032/2019/EKU) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants prior to death for tissue collection.

2.3. Brain tissue fixation

The post-mortem brain tissue fixation procedure differed significantly between the American and Hungarian brain collection sites.

2.3.1. The American brain samples

The left temporal lobe was collected at autopsy and submerged in phosphate-buffered formalin (10%) for 21–369 weeks (141.1 ± 13.1 weeks, mean ± SEM). The temporal lobes were divided along the rostrocaudal axis into 6 mm-thick slabs (Fig. 1B).

2.3.2. The Hungarian brain samples

Brains were extracted from the skull 2–5 h after death, and the internal carotid and vertebral arteries were cannulated. Brain tissue was perfused first with physiological saline (1.5 L in 30 min) containing 5 mL of heparin, followed by Zamboni fixative solution containing 4% paraformaldehyde, 0.05% glutaraldehyde, and 0.2% picric acid in phosphate buffer (PB, pH 7.4) (4–5 L in 1.5–2 h). After perfusion, 0.5–1 cm thick tissue blocks were prepared from the cortical regions of the brain and post-fixed overnight in the same Zamboni fixative solution, without glutaraldehyde.

2.4. Sample preparation for the EM analysis

We prepared brain tissues for ultrastructural analysis as described in detail previously (Csabai et al., 2017, 2018). The hippocampal slabs were cut into serial, 70 μm thick, coronal sections (Fig. 1C) using a vibratome (Leica VT1200 S). Two sections were selected for EM analysis, with at least a 200 μm interval between them (Fig. 1D). The sections were osmicated (1% OsO_4 in PB for 30 min) and then dehydrated in graded ethanol (70% ethanol containing 1% uranyl acetate). After complete dehydration in an ascending ethanol series, the sections were immersed in propylene oxide and then in a mixture of propylene oxide and Durcupan resin. Finally, the sections were flat-embedded in Durcupan resin (Fluka-Sigma–Aldrich, Hungary). After polymerization at 56 °C for 48 h, the sections were viewed under a stereomicroscope, and areas of interest were selected for re-embedding and electron microscopic sectioning (Fig. 1D). Ultrathin (60 nm) sections were cut using a Leica Ultracut UCT microtome (Fig. 1E) and collected on Formvar-coated single-slot copper grids, stained with uranyl acetate and lead citrate.

2.5. Quantification of synaptic densities

All samples were coded before quantification, and the investigator analyzing the data was blinded to the identity of the subjects throughout the entire data analysis. We applied the size-frequency method to quantify the numerical density of synapses per hippocampal tissue unit volume (μm^3), as reported in our previous study (Csabai et al., 2018). We applied this method because DeFelipe et al. (1999) demonstrated that this method is a solid method to quantify synapses, and it is more efficient and easier to apply than the disector method. First, we performed a systematic random sampling protocol when cutting the hippocampus and creating EM micrographs (Fig. 1). We selected two 70 μm thick coronal sections at the level of the lateral geniculate nucleus between the MNI levels of −26 and − 30 based on the human brain atlas of Mai et al. (2015). There was a distance of at least 200 μm between the two selected sections. From these two thick sections, we cut out three blocks for further EM analysis: one from the DG, one from the CA3, and one from the CA1 (Fig. 1D). Tissue blocks for EM analysis were cut from the distal molecular layer of the dentate gyrus and from the distal region of the stratum radiatum/stratum lacunosum moleculare of the Cornu Ammonis. These six blocks were flat-embedded in Durcupan resin and sectioned into serial ultrathin (60 nm) sections. From each of these six series of ultrathin sections, we selected a minimum of 4–4 evenly distributed sample sections from every subject. The selected ultrathin sections were approximately 5–6 μm distances between them. We examined 24 ultrathin sections from each subject using a JEOL JEM 1400 FLASH transmission electron microscope (TEM; Fig. 1E). Photomicrographs were captured digitally at 8000× magnification using iTEM software (Olympus Soft Imaging Solutions, Munster, Germany). In every ultrathin section, starting from a random starting point, we made 4–5 non-overlapping EM photomicrographs using a sampling grid with the following parameters: 10 μm (X) × 10 μm (Y) (Fig. 1F). Therefore, we analyzed approximately 100 EM images from the hippocampal sample of each subject. Synapses were counted in these photomicrographs using an unbiased counting frame overlay (Fig. 1G). These unbiased counting frames (Gundersen, 1977) covered a 19.29 μm^2 (4.392 × 4.392 μm) area (Fig. 1F-G). One investigator (AST) performed the quantification in a blinded manner using Neurolucida software (Version 11.08.2, MicroBrightField, Williston, VT, USA). During the EM analysis, we focused on the distal dendritic arbor of the principal neurons. Synapses were identified based on the morphology of the postsynaptic density and shape of the synaptic vesicles (Fig. 2B). The average number of synapses counted in each counting frame was three; therefore, we analyzed ~300 synapses in each subject. The results of our quantitative data are reported here as synaptic density (number of synapses / μm^3). When quantifying the synapses, we also measured the synaptic junction length, that is, the length of paired membrane densities at each junction.

2.6. Estimation of total hippocampal volume

Volumetric data were available only for the American samples. The temporal lobes were divided into 6 mm-thick slabs along the rostrocaudal axis (see Section 2.3). Subsequently, the slabs were embedded in celloidin and sectioned using a microtome (40 μm). Cresyl violet stain for Nissl substance was used on every tenth section. Starting at the anterior pole, throughout the entire rostrocaudal length of the hippocampal formation approximately every sixth Nissl-stained section was selected for each subject. The contour outline of the hippocampal formation in each tissue section was traced with a Nikon Eclipse 80i microscope at 20× magnification using a Nikon Plan UW 2× objective (N. A. = 0.06, W.D. = 7.5 mm) (Nikon Instruments, Melville, NY, USA) using Stereo Investigator version 7.0 (MBF Bioscience, Williston, VT, USA). The area within the contour was determined cartographically using Stereo Investigator. Hippocampal volumes were estimated by multiplying the contour areas by the distance between each section and then summed to yield the estimated total volume, as previously described (Cobb et al., 2013; Uylings et al., 1986).

2.7. Statistical analysis

IBM SPSS Statistics Software version 27.01. was used for data analysis. The dependent variables were tested by cohort for normality of distribution using the Shapiro-Wilk test. Most of the group value comparisons were performed using the two-tailed unpaired Student's *t*-test. When we compared the three groups, the data were analyzed using a one-way ANOVA followed by Tukey's multiple comparisons post hoc test. Categorical variables, such as gender distribution, were analyzed using the chi-square test. The threshold for statistical significance was set at $\alpha = 0.05$, and non-significant trends were noted at $0.05 \leq P \leq 0.10$. The results are presented as mean ± SEM.

3. Results

3.1. Demographic data and clinical characteristics

The demographic data are presented in Table 1. Further details on the subjects involved in this study, including the causes of death, are listed in Supplementary Material (Supplementary Tables 1–2). Since the samples were carefully selected for this study, most parameters were comparable between the groups. However, in the case of the Hungarian

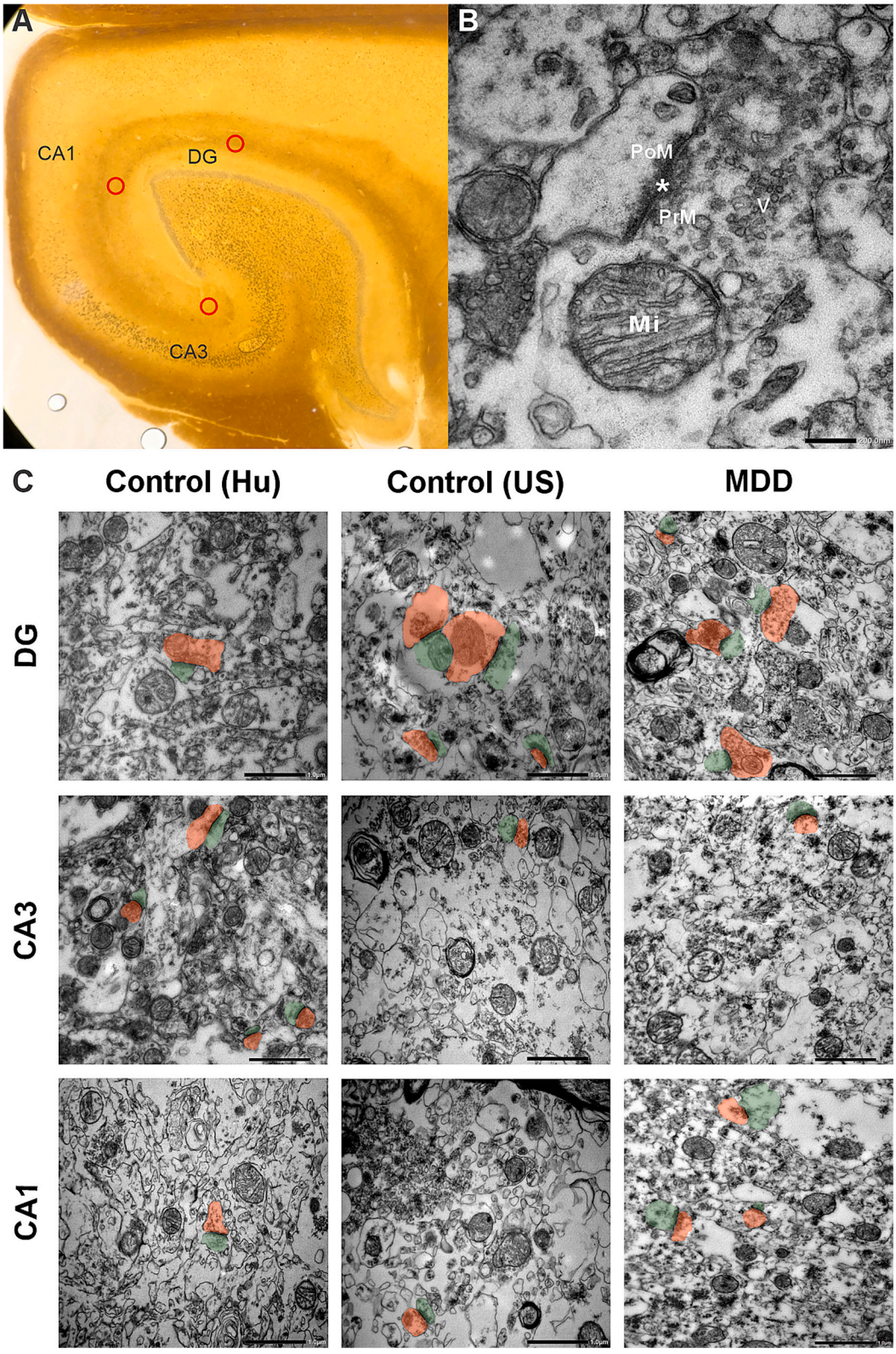

Fig. 2. Sampling sites for EM analysis and representative electron microscopic photomicrographs from the areas of interest. A: A hippocampal coronal section indicating the areas where EM analysis was performed. The red circles indicate the areas where synapses were counted. These areas were in the distal molecular layer of the dentate gyrus and from the distal region of the stratum radiatum/stratum lacunosum moleculare of the Cornu Ammonis. During the EM analysis, we focused on the distal dendritic arbor of the principal neurons. B: Representative EM image of a synapse from a Hungarian control subject. Synapses were identified based on the morphology of the postsynaptic density and shape of the synaptic vesicles. C: Representative EM images of the three study groups displaying the analyzed hippocampal subregions. Pseudocoloring with red indicates the presynaptic axon terminals, while green identifies post-synaptic structures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Abbreviations: CA: Cornu Ammonis; DG, dentate gyrus; Hu, Hungarian; MDD, major depressive disorder; Mi, mitochondria; PoM, postsynaptic membrane; PrM, presynaptic membrane; US, United States; V, synaptic vesicles; *, synaptic cleft. Scale bars: 200 nm in (B) and 1 μm in (C).

samples, the post-mortem interval was significantly shorter than that of the American samples (Table 1). The clinical characteristics of the participants with MDD are listed in Table 2, and more detailed information, including the chronicity of the illness, is presented in the Supplementary Material (Supplementary Table 3).

3.2. Hippocampal volume

Data on hippocampal volume were available only for the US samples. Results are presented in Table 3. Volumetric data were obtained from an earlier study by Cobb et al. (2013) because the participants of the present study were a subset of the cohorts studied by Cobb et al. (2013). There was no significant difference in the total hippocampal volume between the MDD and control groups. Since previous studies have shown that MDD may affect hippocampal subfields differently (Huang et al., 2013; Liu et al., 2021; Xu et al., 2024), we also calculated the volumes of the hippocampal subdivisions (head, middle, and tail); however, this approach did not yield any differences. Since there is evidence that depressed subjects with multiple depressive episodes are more likely to have hippocampal volume reductions (MacQueen et al., 2003; Frodl et al., 2008; Lemke et al., 2022), we compared hippocampal volume between MDD patients with a single depressive episode and patients with chronic/recurrent illness; however, we found no difference between these subsets of patients (Supplementary Table 4).

3.3. Synaptic density

Representative electron microscopic images of the three study cohorts are presented in Fig. 2. Post-mortem tissue preservation was variable between subjects; however, in general, synapses were well preserved. Unfortunately, the ultrastructural preservation of the tissue was not sufficient to reliably distinguish between asymmetric and symmetric synapses; therefore, when we performed the counting, we did not distinguish between these two types. Since the post-mortem time interval was significantly shorter in the Hungarian control group, we expected that the tissue preservation might also be significantly better, resulting in higher synapse numbers compared to the American samples. Thus, we first compared synaptic densities in the American and Hungarian control samples, but we found no difference between them (Table 4); therefore, during the subsequent analyses, we merged the data from these two control groups. In Table 5, we present the results of the comparisons of synaptic densities between the MDD group and the American control subjects and between the merged control group, where the results of the American and Hungarian control subjects were combined. We found no significant difference in the average hippocampal synaptic density between the MDD and control groups (Table 5). However, a comparison of synaptic densities in the different subareas yielded a few trend-level differences. We found a clear tendency for lower synaptic densities in the dentate gyrus and CA3 subarea in samples originating from patients with MDD (Table 5). Synaptic lengths were also similar both in depressed patients and in control subjects (Table 6).

To evaluate whether chronicity of illness had any effect on synaptic densities, we divided the MDD group into two subgroups: MDD patients with a single depressive episode and MDD patients with chronic/recurrent illness. Patients with MDD with a single depressive episode had significantly reduced synaptic density in the CA3 area (Fig. 3). This significant difference was present when we compared synaptic densities between patients with single-episode MDD and the US control group ($t = 2.23$, $P = 0.04$, Fig. 3B) and when we compared the single-episode MDD group to the combined (US + Hu) control group ($t = 2.28$, $P = 0.03$, Fig. 3F).

3.4. Correlating synaptic density with age

Synaptic densities were not influenced by age, as older individuals had synaptic densities comparable to those of young subjects (Fig. 4).

Table 3
Hippocampal volume of the American cohort.

Volume	Control (US)	MDD	Statistics
Rostral third (head)	1421.16 ± 189.04	1386.53 ± 87.03	$t = 0.15$, $P = 0.88$
Middle third (body)	698.54 ± 129.86	914.27 ± 52.79	$t = 1.49$, $P = 0.16$
Caudal third (tail)	471.55 ± 94.91	599.37 ± 44.99	$t = 0.98$, $P = 0.34$
Entire hippocampal formation	2629.80 ± 206.76	2895.75 ± 105.25	$t = 1.03$, $P = 0.32$

Data are shown as mean ± S.E.M. Volumes are in mm^3. Statistics: Two-tailed unpaired Student's *t*-test. Abbreviations: MDD: major depressive disorder; US: United States.

Table 4
Comparison of synaptic densities in the hippocampus of the American and Hungarian controls.

Hippocampal areas	Control (US)	Control (Hu)	Statistics
Dentate gyrus	3.12 ± 0.41	3.56 ± 0.33	$t = 0.83$, $P = 0.42$
CA3	2.89 ± 0.33	3.02 ± 0.27	$t = 0.30$, $P = 0.77$
CA1	3.26 ± 0.37	2.71 ± 0.44	$t = 0.94$, $P = 0.37$
Entire hippocampus	3.55 ± 0.34	3.61 ± 0.32	$t = 0.12$, $P = 0.91$

Data are shown as mean ± S.E.M. Synaptic density: $n/\mu m^3$. Statistics: Two-tailed unpaired Student's *t*-test. Abbreviations: CA: Cornu Ammonis; Hu: Hungarian; US: United States.

Table 5
Synaptic densities in the hippocampus of depressed patients versus psychiatrically healthy controls.

Hippocampal areas	Control (US)	MDD	Statistics
Dentate gyrus	3.56 ± 0.33	2.72 ± 0.29	**$t = 1.91$, $P = 0.07$**
CA3	3.02 ± 0.27	2.34 ± 0.30	**$t = 1.66$, $P = 0.12$.**
CA1	2.71 ± 0.44	3.53 ± 0.38	$t = 1.42$, $P = 0.18$
Entire hippocampus	3.61 ± 0.32	3.46 ± 0.17	$t = 0.42$, $P = 0.68$
	Control (US + Hu)	MDD	Statistics
Dentate gyrus	3.39 ± 0.26	2.72 ± 0.29	**$t = 1.67$, $P = 0.11$**
CA3	2.97 ± 0.21	2.34 ± 0.30	**$t = 1.71$, $P = 0.10$**
CA1	2.97 ± 0.29	3.53 ± 0.38	$t = 1.21$, $P = 0.24$
Entire hippocampus	3.59 ± 0.23	3.46 ± 0.17	$t = 0.40$, $P = 0.69$

Data are shown as mean ± S.E.M. Synaptic density: $n/\mu m^3$. Statistical results of trend levels or approaching the trend levels are highlighted in bold. Statistics: Two-tailed unpaired Student's *t*-test. Abbreviations: CA: Cornu Ammonis; Hu: Hungarian; MDD: major depressive disorder; US: United States.

Table 6
Synaptic lengths in the hippocampus of depressed patients versus psychiatrically healthy controls.

Hippocampal areas	Control (US)	MDD	Statistics
Dentate gyrus	0.24 ± 0.01	0.24 ± 0.01	$t = 0.25$, $P = 0.80$
CA3	0.24 ± 0.01	0.23 ± 0.00	$t = 0.94$, $P = 0.36$
CA1	0.25 ± 0.01	0.25 ± 0.01	$t = 0.23$, $P = 0.82$
Entire hippocampus	0.24 ± 0.00	0.24 ± 0.00	$t = 0.20$, $P = 0.84$
	Control (US + Hu)	MDD	Statistics
Dentate gyrus	0.23 ± 0.01	0.24 ± 0.01	$t = 0.85$, $P = 0.40$
CA3	0.23 ± 0.00	0.23 ± 0.00	$t = 0.44$, $P = 0.66$
CA1	0.25 ± 0.01	0.25 ± 0.01	$t = 0.34$, $P = 0.73$
Entire hippocampus	0.24 ± 0.00	0.24 ± 0.00	$t = 0.46$, $P = 0.65$

Data are shown as mean ± S.E.M. Synaptic length: μm. Statistics: Two-tailed unpaired Student's *t*-test. Abbreviations: CA: Cornu Ammonis; Hu: Hungarian; MDD: major depressive disorder; US: United States.

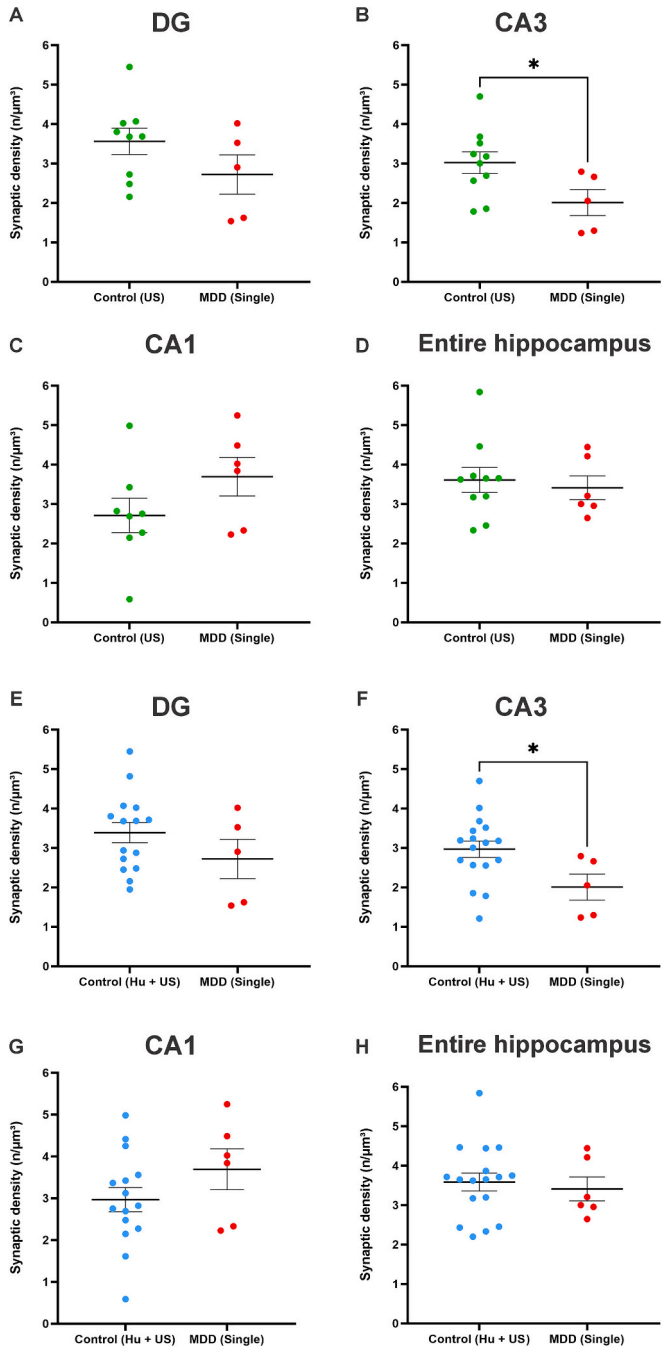

Fig. 3. Synaptic densities in the hippocampus of patients with a single depressive episode. We observed significantly reduced synaptic density in the CA3 area. This significant difference was present when we compared synaptic densities between patients with single-episode MDD and the US control group (A,B,C, and D) and when we compared the single-episode MDD group to the combined (US + Hu) control group (E,F,G, and H).

4. Discussions

The present study is the first quantitative ultrastructural study to investigate hippocampal synaptic density in post-mortem tissue samples from patients with depression and compare the data with those of psychiatrically healthy control subjects. Based on in vivo neuroimaging data, we expected to find lower synaptic densities in patients with MDD. In contrast, our study found that the average hippocampal synaptic density was similar in both depressed and control subjects. However, a more focused analysis revealed a clear tendency for lower synaptic densities in the dentate gyrus and hippocampal CA3 area in patients with depression. Furthermore, we found a significant reduction in synaptic density in the hippocampal CA3 area of patients with MDD with a single episode of depression. Notably, age had no effect on synaptic density, as synapse numbers were preserved in the aged subjects. Hippocampal volumes were also comparable in control and depressed individuals.

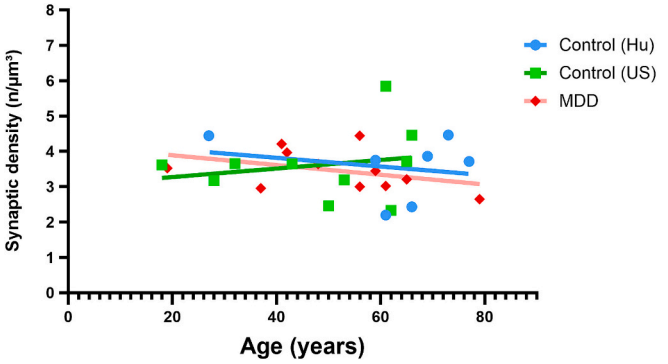

Fig. 4. Correlation between age and average synaptic density in the hippocampus. Synapse numbers were preserved in the aged subjects, and there was no significant correlation between synaptic density and age in any of the three cohorts.

4.1. Hippocampal neuropathology in depressed patients: comparison to previous studies

Previous studies investigating post-mortem hippocampal tissue from depressed patients typically found either no difference or only minor neuropathological alterations. A study focusing specifically on apoptotic cell death found no evidence of major cell death in the hippocampus of depressed patients (Lucassen et al., 2001). A parallel immunohistochemistry study by the same group reported no evidence of neuronal cell loss or any other major morphological alterations, nor was there any evidence of synaptic changes in the hippocampus of depressed patients (Müller et al., 2001). They only found a subtle reduction in the expression of the astroglial marker (glial fibrillary acidic protein, GFAP) (Müller et al., 2001). Another study found that post-mortem hippocampal tissue samples originating from patients with depression shrink to a greater extent than those from controls, resulting in a significantly increased density of neurons and glial cells (Stockmeier et al., 2004). These data imply that the reduction in neuropil may account for hippocampal volume shrinkage in patients with MDD, as detected by neuroimaging studies (Stockmeier et al., 2004). A previous study examining a cohort partially similar to that of the present study found no evidence of neuronal or glial cell loss in the hippocampus of patients with MDD (Cobb et al., 2013). Furthermore, the hippocampal volume of patients with MDD did not differ from that of control subjects; however, in patients with recurrent/chronic MDD, the total volume decreased with the duration of depressive illness (Cobb et al., 2013). In a follow-up study, the same authors focused on astrocytes and found that the density of astrocytes was significantly decreased in the hilus of depressed subjects not receiving antidepressant medication, but not in depressed subjects taking an antidepressant drug (Cobb et al., 2016). Another study investigating neural stem cell proliferation in the dentate gyrus found no evidence of impaired adult neurogenesis in depressed patients (Reif et al., 2006). However, later studies reported decreased numbers of dentate progenitor cells in the hippocampus of patients with depression (Lucassen et al., 2010; Boldrini et al., 2012; Márquez-Valadez et al., 2025). In contrast to the findings of these reports, a more recent study documented pronounced hippocampal volume loss (−27%), together with a substantial reduction in neuron numbers (15–33% reduction) and glial cells (25–38% reduction) in all hippocampal subregions of patients

with depression (Chen et al., 2020). Notably, the same study found no difference when comparing the density of neurons and glial cells between control subjects and patients with depression (Chen et al., 2020). Overall, the results of the present study on minor morphological differences are in harmony with most previous studies reporting only subtle neuropathological changes in the hippocampi of patients with depression.

4.2. Synaptic changes in depressed patients

Recent theories on the neurobiology of depressive disorders emphasize the role of dysfunctional synapses, suggesting that synaptic dysfunction and/or synaptic loss may underlie the emotional and cognitive disturbances that are characteristic of the disease (Price and Duman, 2020; Sanacora et al., 2022; Tartt et al., 2022; Fries et al., 2023; Thompson, 2023). Multiple lines of evidence support this concept, but the most convincing data originate from recent in vivo PET studies that image synaptic densities using a radioligand (Finnema et al., 2016). Using this method, a reduced synaptic density was demonstrated in patients with depression, which could be linked to symptom severity and neuronal network alterations (Holmes et al., 2019, 2023; Asch et al., 2022, 2024; Van Cauwenberge et al., 2025). However, these results are not without controversy. A recent study using the same PET imaging method documented evidence of preserved synaptic density in late-life depression, while volumetric analysis revealed a trend of lower gray matter volumes in the hippocampus and prefrontal cortex in subjects with late-life depression (Vande Casteele et al., 2024).

In the present study, we investigated the hippocampus, partially because numerous earlier neuropathological studies focused on this brain area and abundant neuroimaging data demonstrated hippocampal volume shrinkage in patients with MDD and because we had access only to the hippocampal tissue of these patients. Other limbic structures, such as the prefrontal cortex and amygdala, also play vital roles in the pathophysiology of the disease. Tissue of the prefrontal cortex from these patients has been used for another study and results on synaptic changes in this area have already been published. An earlier extensive examination of the prefrontal cortex by Kang et al. (2012) included an electron microscopic analysis of synapse numbers and demonstrated a reduced number of spine synapses in the dorsolateral prefrontal cortex of the same brain samples as those used in the present study. That study quantified synaptic density in layer II/III of the dorsolateral prefrontal cortex using electron microscopic stereological analysis and found a marked decrease in spine synapse numbers in patients with MDD compared to those in controls (Kang et al., 2012). Unfortunately, the amygdalae from these subjects were completely used for another study examining the total number of neurons and glia (Rubinow et al., 2016); therefore, we could not examine the amygdala.

Overall, our study provides further evidence that synaptic changes are detectable in the brains of patients with depression. Although we did not find a general reduction in hippocampal synapse numbers, we observed a subarea-specific reduction in synaptic density only in a subset of patients. Contrary to our expectations, this synaptic change was present in patients with a single depressive episode and not in patients with chronic/recurrent illness. Typically, patients with chronic/recurrent illnesses display more pronounced changes in hippocampal volume reduction (Sheline et al., 1996; MacQueen et al., 2003; Frodl et al., 2008; Taylor et al., 2014; Elbejjani et al., 2015; Schmaal et al., 2016; Lemke et al., 2022). However, hippocampal volume shrinkage may also be present in patients with first-episode depression (Frodl et al., 2002; Ahdidan et al., 2011; Cole et al., 2011; Kempton et al., 2011), and recent evidence suggests that the morphological alterations in hippocampal subfields along the long axis differ between first-episode and recurrent depression (Sun et al., 2025). A potential explanation for the unexpected finding that patients with chronic/recurrent depression had no detectable change in synaptic densities is that most of the MDD patients received antidepressant treatment; thus, we cannot rule out the effects of such treatments on the observed variables. Patients with chronic illnesses most likely receive antidepressant therapy over a longer period, and there is experimental evidence that antidepressive treatment may influence synaptic plasticity and increase the number of synapses (Hajszan et al., 2005; Chen et al., 2010; Duman et al., 2016; Holmes et al., 2023; Johansen et al., 2023; Laroy et al., 2024; Corvo et al., 2025; Liao et al., 2025). Finally, to elucidate the potential factors contributing to synaptic changes in the hippocampal CA3, we refer to the results of a rodent study in which rats were injected with corticosterone, the primary glucocorticoid in rodents, for 60 days (Tata et al., 2006). Such long-term corticosterone treatment did not reduce the number of neurons but caused a pronounced loss of synapses, which was independent of volume loss (Tata et al., 2006).

4.3. Potential functional consequences of hippocampal synapse loss

The symptoms and severity of MDD are closely tied to the imbalance of monoamines and dysregulation of excitatory/inhibitory equilibrium and neuropeptides. The primary event responsible for dendritic synapse loss, resulting in a ‘synaptic disconnection’ syndrome within and between key limbic structures that regulate emotions, is the abnormal enhancement of glutamate release in excitatory synapses induced by stress (Tartt et al., 2022; Thompson, 2023). Decreased expression of brain-derived neurotrophic factor (BDNF) may also contribute to synaptic loss (Cavaleri et al., 2023).

Synapse loss within the hippocampus is likely to have widespread consequences, as it may impair information processing within the hippocampus and/or disrupt functional connectivity with key limbic structures, such as the prefrontal cortex and amygdala. As demonstrated recently, the human hippocampal CA3 area is a fundamental circuit for memory storage, as it has unique microcircuit properties (Watson et al., 2025). Disruption of the human CA3 microcircuit due to synapse loss may result in learning and memory impairments, and there is strong evidence that cognitive impairment is present already at the first episode of depression (Varghese et al., 2022). In addition, in vivo functional neuroimaging data provide compelling evidence of altered limbic network functioning in patients with depression. Resting-state functional magnetic resonance imaging data report on functional hyperconnectivity between the medial prefrontal cortex and hippocampus (Kaiser et al., 2015) and impaired connectivity between the hippocampus and amygdala (Cullen et al., 2014).

In the present study, when counting the synapses, we did not differentiate between asymmetric (Type I) synapses that are mostly excitatory (glutamatergic) and symmetric (Type II) synapses that are typically inhibitory (GABAergic) because in many cases the ultrastructural preservation of the tissue was not sufficient to reliably distinguish between these two. Since the vast majority of synapses in the hippocampus are excitatory (Megías et al., 2001), most of the synapses that we counted were likely excitatory. This implies that the loss of synapses mainly affects glutamatergic neurotransmission; however, we cannot rule out the possibility that inhibitory synapses are affected in the same manner. GABAergic dysfunction is likely to contribute to the pathophysiology of depression, as postmortem studies indicate an excitation-inhibition imbalance in cortical-subcortical limbic regions with decreased GABAergic signaling and increased glutamatergic signaling (Hu et al., 2023). The disrupted inhibitory network in key limbic structures should result in altered oscillatory patterns in spontaneous and task-specific electroencephalogram (EEG) recordings, and indeed, there is ample evidence of altered EEG oscillatory patterns in patients with MDD (Fingelkurts and Fingelkurts, 2015; Fitzgerald and Watson, 2018). More detailed studies should differentiate between asymmetric and symmetric synapses when quantifying them. Combining electron microscopy with immunocytochemistry could also help differentiate between excitatory and inhibitory synapses.

Synaptic changes may also disrupt serotonergic and noradrenergic neurotransmission, which are the most common sites of action of

antidepressant drugs. Almost all pre- and postsynaptic serotonin receptors have been identified in the hippocampus, and the serotonin transporter (SERT, which plays a key role in serotonergic neurotransmission) and tryptophan hydroxylase (TPH, the rate-limiting enzyme for serotonin production) have also been found in the hippocampus (Berumen et al., 2012). Notably, in the human brain, the highest densities of 5-HT1A receptors are found in the hippocampus (Pazos et al., 1987). Noradrenergic neurons of the locus coeruleus send projections to the forebrain, including the hippocampus, and disrupted noradrenergic neurotransmission may contribute to the cognitive and behavioral deficits in patients with depression (Holland et al., 2021). Altogether, the fact that a wide range of behaviors altered in depression suggests that multiple synaptic circuits are adversely affected.

4.4. Hippocampal volume

Meta-analytic studies evaluating data from in vivo magnetic resonance imaging studies have consistently reported reduced hippocampal volume in patients with depression (Campbell et al., 2004; Videbech and Ravnkilde, 2004; McKinnon et al., 2009; Kempton et al., 2011; Schmaal et al., 2016). However, individual studies often report no difference in hippocampal volume between controls and patients with depression (for example, Vakili et al., 2000; Rusch et al., 2001; Posener et al., 2003; Hastings et al., 2004; Vythilingam et al., 2004; Tannous et al., 2020). These negative findings are most likely due to the small sample sizes of the individual studies. The single post-mortem histopathological study that examined hippocampal volume in extracted tissue samples from depressed patients found that in patients with recurrent/chronic MDD, the total volume decreased with the duration of depressive illness (Cobb et al., 2013).

4.5. Limitations of the current study

Similar to most post-mortem studies, the current study is limited by the relatively small number of subjects. Furthermore, while we made every effort to create balanced study groups regarding age and sex, it was not possible to reach a perfect age match and an equal distribution of male/female ratios.

Electron microscopy studies of human brain tissue are limited by technical challenges, particularly in obtaining and preparing high-quality post-mortem tissue. The quality of ultrastructural preservation in post-mortem brain tissue is highly variable and depends on numerous factors, with PMI being the most critical. While robust structures can persist for some time, finer details deteriorate rapidly because of autolytic processes. In our study, samples from the Hungarian brain collection had a significantly shorter PMI than the American samples. Therefore, we expected that synapse numbers would be higher in the Hungarian control samples than in the US controls. However, this was not the case. This finding implies that synapses are more robust structures that can persist for longer periods.

The most important limitation of the present study is that only one segment of the rostral hippocampal body was examined. Ideally, a truly systematic sampling protocol should include evenly distributed samples from the entire rostrocaudal axis of the hippocampus. Unfortunately, such sampling is rarely available from post-mortem brain tissue collections.

Another limitation is that we had incomplete information on the medical history of the subjects; therefore, we cannot perform correlation analysis between symptom severity/duration of episode/medication and hippocampal synaptic density due to incomplete information on the exact number, duration, and treatment of episodes in most subjects and the lack of such information in suicide subjects. As discussed in 4.2. Most patients received antidepressant medication; thus, we cannot rule out the effects of such treatments on the observed variables. Unfortunately, the medication records of patients included in this study were not always available; therefore, we could not provide data on this. Most patients with depression receive antidepressant medications, but switching from one type of treatment to another or combination/augmentation treatments may also occur. Notably, different classes of antidepressant medications could have different outcomes on synapse numbers.

4.6. Conclusion

Our study provides further evidence that synaptic changes are detectable in the brains of patients with depression. We could not confirm the expected pronounced and general hippocampal synaptic loss in the hippocampus of patients with depression; instead, we observed a region-specific reduction in synaptic density only in a subset of patients with MDD with a single episode of depression. The methodological limitations of our study may explain the present contradictory findings compared to the in vivo PET neuroimaging data.

CRediT authorship contribution statement

Abigél Sebők-Tornai: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Dávid Csabai:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Péter Szocsics:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation. **Péter Gombás:** Writing – review & editing, Resources, Methodology, Data curation. **Justin A. Cobb:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Gouri J. Mahajan:** Writing – review & editing, Resources, Methodology, Data curation. **Craig A. Stockmeier:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization. **Boldizsár Czéh:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Ethical statement

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committees.

In the case of American samples, the protocol for recruitment, tissue collection, and interviews was approved by the Institutional Review Boards of the University Hospitals of Cleveland and University of Mississippi Medical Center. Ethical approval numbers: Protocol 1999-1002 University of Mississippi Medical Center / approval date: 10/26/1999 and Protocol 11-88-233 University Hospitals Case Medical Center / approval date: 02/13/2018.

Written informed consent was obtained from the legal next-of-kin for tissue collection and informant-based retrospective diagnostic interviews.

In the case of the Hungarian samples, tissue collection was approved by the ethics committee at the Regional and Institutional Committee of Science and Research Ethics of the Scientific Council of Health (ETT TUKEB 15032/2019/EKU) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants prior to death for tissue collection. Written informed consent was obtained from the legal next-of-kin for tissue collection.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2026.111661.

Data availability

Data will be made available on request.

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