

Morphological alterations of the pyramidal and stellate cells of the visual cortex in schizophrenia

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Abstract. Schizophrenia is a severe brain disorder characterized by certain types of delusion, hallucination and thought disorder. Studies have revealed impaired synaptic plasticity and reduced gamma-aminobutyric acid levels of the visual cortex in patients with schizophrenia. While previous work established a critical role for interneurons and cortical connectivity in the generation of hallucinations, the present study set out to examine the morphology of pyramidal cells and interneurons from layers 3 and 4 in the primary visual cortex from schizophrenic brains and to identify any dendritic and spinal alterations in comparison to normal control brains. The morphological and morphometric changes of the pyramidal cells and the interneurons of the visual cortices of 10 brains obtained from patients with schizophrenia, in comparison to 10 age-matched controls, were studied using the Golgi method and 3D neuronal reconstruction techniques. Analysis using the Golgi impregnation technique revealed a significant loss of distal dendritic segments, tortuous branches and varicosities and an overall restriction of the dendritic field in the brains of schizophrenic patients in both pyramidal cells and in

aspiny interneurons. The present results may explain certain clinical phenomena associated with the visual cortex usually encountered in schizophrenia.

Introduction

Schizophrenia is a severe brain disorder characterized by certain types of delusion, hallucination and thought disorder (1,2). In addition to these aforementioned symptoms that may be associated with enhanced brain activity, schizophrenic patients develop additional symptoms of inhibition, including avolition, alogia and affective flattening (2). Macroscopically, schizophrenic brains exhibited enlargement of the ventricles and an overall reduction in the temporal volume, while microscopical examination of the brain revealed synaptic and spinal alterations, as well as gliosis, in various brain areas, including hippocampal formation and the prefrontal and the entorhinal cortices (3-9). Additional studies have revealed increasing neuronal packaging density, as well as decreased neuropil and smaller cell somata of the pyramidal neurons in layer 3 in different brain areas, including the primary and association auditory cortices, in schizophrenia (9-12). Dendritic spines perform a crucial role in regulating neuronal excitability while receiving the vast majority of excitatory synapses in the cortex (13,14). Deficits in spines are related to impairments in the working memory, attention, sensory-motor processing and sociability (15-17). Spine density has been reported to be significantly reduced in neurons of the auditory cortex (12) and the basilar dendrites of deep layer 3 pyramidal neurons (10), but did not differ for pyramidal neurons in the superficial layer 3 or layers 5 and 6 of area 46 (10,18). The spinal changes are thought to arise during development and are probably related to disturbances of the mechanisms underlying the formation and maintenance of spines.

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Visual hallucinations are the second most common type of hallucinations in schizophrenia (2). Previous studies demonstrated a critical role for interneurons and cortical connectivity in the generation of hallucinations (19,20). At the same time, studies on the visual cortex of schizophrenic brains have revealed impaired synaptic plasticity and reduced gamma-aminobutyric acid (GABA) levels (21-23).

In the present study, the morphology of the pyramidal cells and interneurons in the visual cortex from brains of schizophrenic patients were examined. It was attempted to describe any possible dendritic and spinal alterations compared to normal control brains.

Patients and methods

Subjects. Brain samples were obtained from 10 neurologically normal individuals with no history of neurological or psychiatric illness, and 10 patients with schizophrenia, between January 2010 to December 2014 from the Department of Forensic Medicine and Toxicology, at the Aristotle University of Thessaloniki, Greece. All of the subjects were aged between 40 and 58 years (Schizophrenia: Mean age, 48.6 ± 5.7 years; 6 males and 4 females; Controls: Mean age, 46.3 ± 4.97 years; 7 males and 3 females) and died from heart attack. The average autolysis time for all subjects was 12 ± 4 h. After their excision from the skull, all brains were immersed in 10% neutral buffered formalin for at least 25 days. All possible information on each subject regarding their previous physical and illness history was obtained from autopsy reports and medical records. The mean duration of the disease was 21 ± 7 years and they had all been prescribed antipsychotic medication. Written informed consent regarding the use of the tissue for research purposes was obtained from the relatives of each of the deceased. The present study was performed according to the legislation of the Greek Democracy (v.2,472/1997, 2,819/2000, 2,915/2001, 3,235/2004 and 3,471/2006) and the Committee for Research Deontology Principles of the Aristotle University of Thessaloniki (24). The ethical approval number was 23/4/4521/2018. The brains were macroscopically and microscopically examined by an independent neuropathologist and did not exhibit any trauma, oedema or other pathology. Independent psychiatrists based at the Psychiatric Hospital of Thessaloniki, made the diagnosis of schizophrenia based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders Text Revision 5. All of the patients exhibited visual hallucinations in their disease history.

Tissue selection and processing. A tissue block measuring $10 \times 5 \times 20$ mm was excised from the primary visual cortex or V1 area (calcarine sulcus) (25) (Fig. 1A). The primary visual cortex may be easily recognized by a band of myelinated axons that run parallel to the surface (line of Gennari; Fig. 1B). The tissue blocks were coded to prevent experimental bias and were processed with the Golgi method and subjected to Nissl staining (26).

Cell selection criteria. Two neuronal types were selected for the present study; the first one corresponds to the third cortical layer's pyramidal neurons and the second to the inhibitory aspiny stellate interneurons of the visual cortex. All neurons chosen for the study were uniformly stained, there was no

precipitated debris around them and a good contrast between them and background were present (27).

Golgi method. For silver impregnation, the specimens were immediately immersed in a dilution of potassium dichromate (7 g of potassium dichromate and 20 ml of formaldehyde solution 37% in 300 ml of tap water) at room temperature. They remained in that solution for one week and were then immersed in an aqueous solution of 1% silver nitrate, where they remained for one more week at a temperature of 15°C .

After fixation, the specimens were immersed in paraffin and cut into thick sections $\sim 120 \mu\text{m}$ thick, as neuronal fields can be seen at their whole thickness at $\sim 120 \mu\text{m}$ (25), using a Reichert slicing microtome. A total of 5 randomly selected sections were obtained, with a $480 \mu\text{m}$ distance between each sample. All of the specimens were examined with an AxioStar Plus bright field microscope (Zeiss AG).

Nissl staining. Adjacent sections were cut at a thickness of $20 \mu\text{m}$ and used for Nissl staining to evaluate the neuronal population and define the depth of cortical layers and measure the thickness of the cortex (25).

Neuronal tracing and dendritic quantification. For each one of the 20 brains, 50 pyramidal cells and 50 interneurons were selected. The neurons were then analyzed based on the method described in a previous study by our group (26).

Dendritic measures and Sholl analysis. For the morphometric estimation, soma size, total dendritic length, cell contraction, dendritic field asymmetry, the total number of dendritic segments and bifurcations, and the length and number of dendritic segments per order were measured. Furthermore, the tracings were quantitatively analyzed with Fiji software (version 2017; Fiji) and the Simple Neurite Tracer plugin based on Sholl's method of concentric spheres (28,29). Concentric spheres were drawn at intervals of $10 \mu\text{m}$ centred on the cell bodies and dendritic intersections within each sphere were counted (25).

Spine counts. The dendritic spine density was measured in 360 images, which were taken at a magnification of $\times 1,000$. Two different investigators (FP and SC) independently counted visible spines on three random segments of the dendritic tree of $20-30 \mu\text{m}$ in length, the first one being on a first-order dendrite, the second on a second-order dendrite and the third on a tertiary branch (30).

Statistical analysis. Statistical analysis was performed using Student's t-test based on 320 cells in R Studio (v. 4.04). To make sure that the autolysis time did not affect dendritic measurements, two-tailed Pearson product correlation analyses were performed between all dependent measures and autolysis time (31). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Dendritic changes of pyramidal neurons. Analysis with the Golgi impregnation technique revealed a significant loss

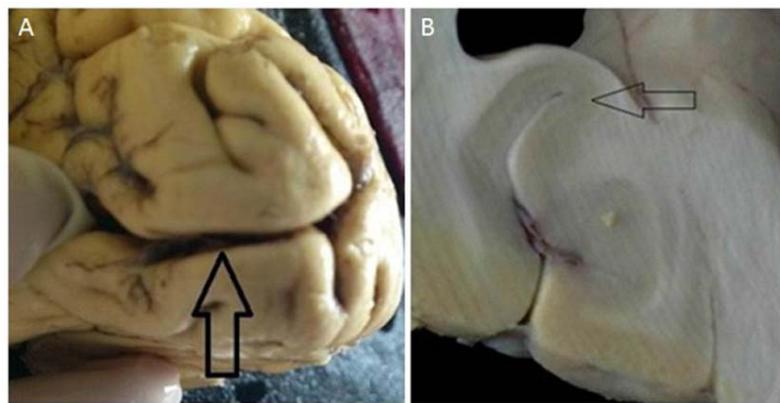


Figure 1. (A) The primary visual cortex is located in and around the calcarine fissure in the occipital lobe (arrow). Occipital lobe sagittal view demonstrating the calcarine fissure. (B) It may be easily recognized by a white band of myelinated axons that run parallel to the surface (line of Gennari; arrow).

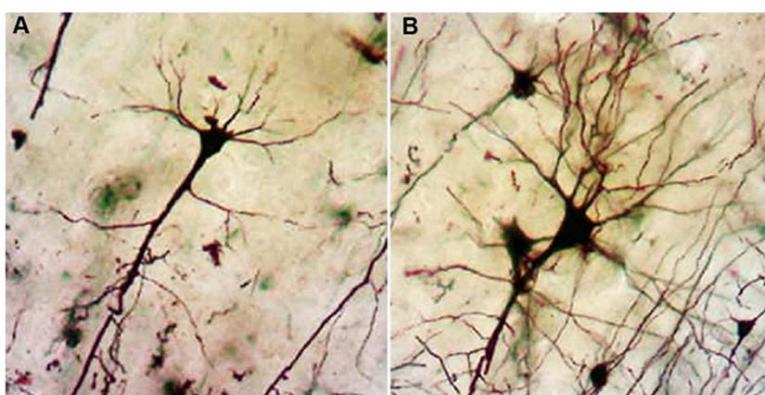


Figure 2. Representative images of pyramidal neurons impregnated with the Golgi method, from (A) a schizophrenic brain and (B) a normal control (Golgi method; magnification, $\times 100$).

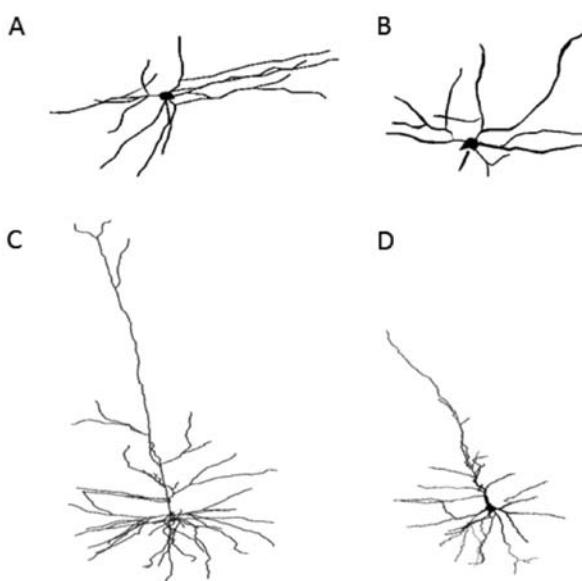


Figure 3. Schematic representation based on neuronal tracings of (A) aspy in normal controls, (B) aspy in schizophrenic brains, (C) pyramidal neurons in normal controls and (D) pyramidal neurons in schizophrenic brains showing markedly decreased dendritic arborizations in each cell type in Schizophrenia.

of distal dendritic segments, tortuous branches and varicosities and an overall restriction of the dendritic field in

the schizophrenic brains compared to the normal brains (Fig. 2A and B).

In the brains of schizophrenic subjects, the dendritic field's total length was significantly decreased as compared with that of normal subjects (Figs. 3A-D and 4A). A severe loss of distal dendritic branches (quaternary) (Fig. 4B), and a decrease in the number of terminal branches (Fig. 4C) and dendritic bifurcations were also noted (Fig. 4D).

Compared to the normal controls, the branching ratio was reduced in the schizophrenic group, and the average branch length (Fig. 5A) and the maximum branching order were likewise affected (Fig. 5B). As presented in Fig. 6, Sholl analysis indicated a restriction of the dendritic field due to the loss of distal branches, although the proximal ones in the pyramidal cells remained intact (Fig. 6A). A small amount of degenerated pyramidal neurons was also noted in the schizophrenic brains, and none were identified in the control group (Fig. 7).

Interneurons. Aspy stellate interneurons of the visual cortex from the schizophrenic brains exhibited a significant decrease of the total dendritic length (Figs. 8A and B and 9A), severe loss of dendritic branches (Fig. 9B) and a substantial reduction of the number of terminal dendritic branches (Fig. 9C). The branching ratio was grossly reduced, and the average branch length and the maximum branch order were significantly

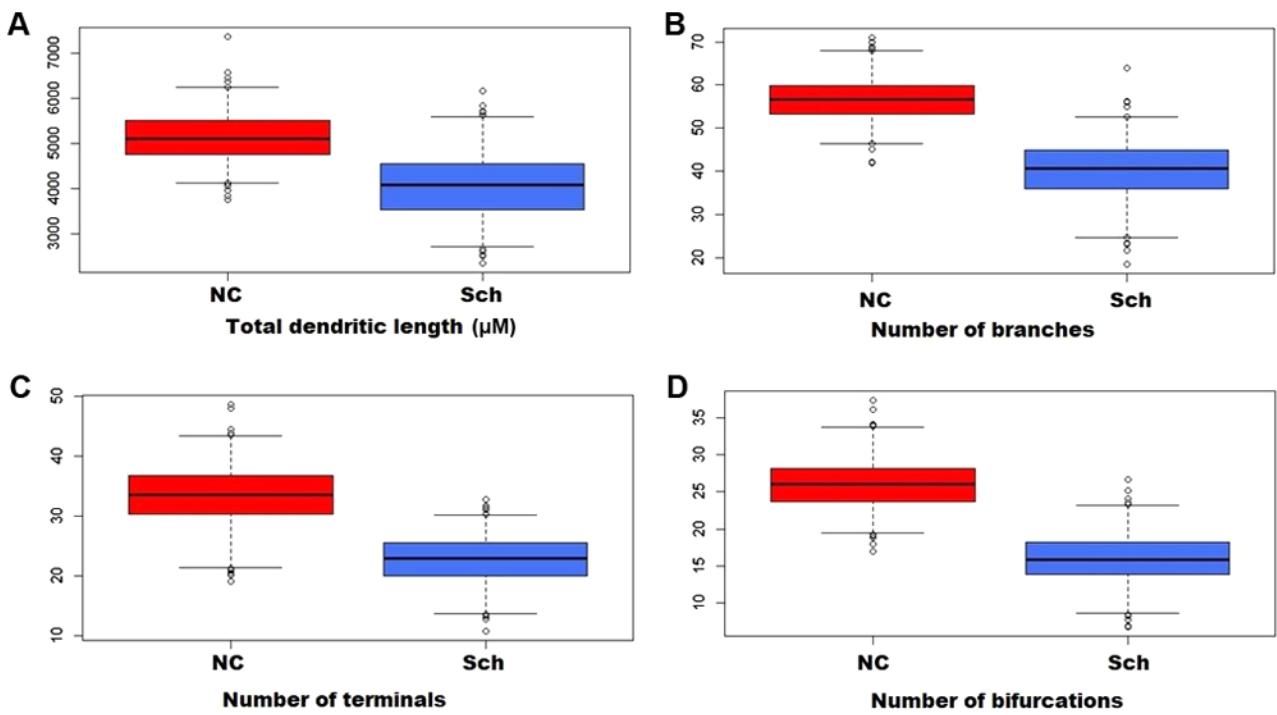


Figure 4. Comparison of (A) total dendritic length ($P=0.0002$), (B) number of dendritic branches ($P=0.0032$), (C) number of terminals ($P=0.00001$) and (D) bifurcations ($P=0.0001$) of the pyramidal cells from NC and schizophrenic brains. Boxplots represent skewness and error bars indicate the standard deviation. NC, normal controls; Sch, schizophrenia group.

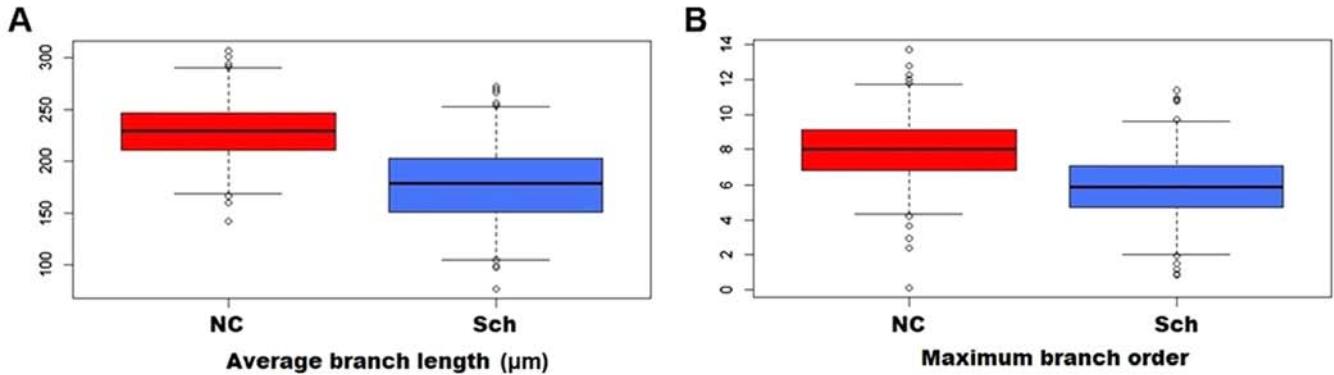


Figure 5. Comparison of (A) average branch length ($P=0.00049$) and (B) branch order ($P=0.0001$) of the pyramidal cells from NC and schizophrenic brains. Boxplots represent skewness and error bars indicate the standard deviation. NC, normal controls; Sch, schizophrenia group.

affected (Fig. 10A and B). Sholl analysis of interneurons indicated extensive loss of distal dendritic branches and decline of the dendritic field density at a distance $>100 \mu\text{m}$ from the cell soma (Fig. 6B). The number of bifurcations was markedly lower in schizophrenic brains compared with controls (Fig. 9D).

Spinal changes. Pyramidal neurons exhibited a significant decrease in spinal density, affecting mainly the distal dendritic segments, while dystrophic and giant spines were also observed (Figs. 11 and 12).

Cortical thickness. The thickness of the primary visual cortex measured in Nissl preparations was significantly different between the groups of the study (Schizophrenia, $1,956 \pm 105 \mu\text{m}$; Controls, $2,124 \pm 96 \mu\text{m}$; $P=0.023$; Fig. 13).

Discussion

There remains a lack of consensus or set of quantified patient characteristics in regards to Schizophrenia and it has remained an enigma to neuropathologists (32). Accumulating evidence from macroscopic and microscopic pathology has been provided in the last 20 years. The main macroscopic findings include a decrease in brain weight (33-35), brain length (36) and volume of the cerebral hemispheres (37). An additional enlargement of the lateral ventricles (36,37), changes to limbic structures (38), reduced size of temporal lobe structures (39-41), decreased thalamic volume (34,42) and enlarged basal ganglia (43) have also been described. Certain findings regarding synaptic and spinal pathology, cell orientation, neuronal density, neuronal size, protein expression and neurotransmitter deficits have also been consistently reported by numerous studies (6).

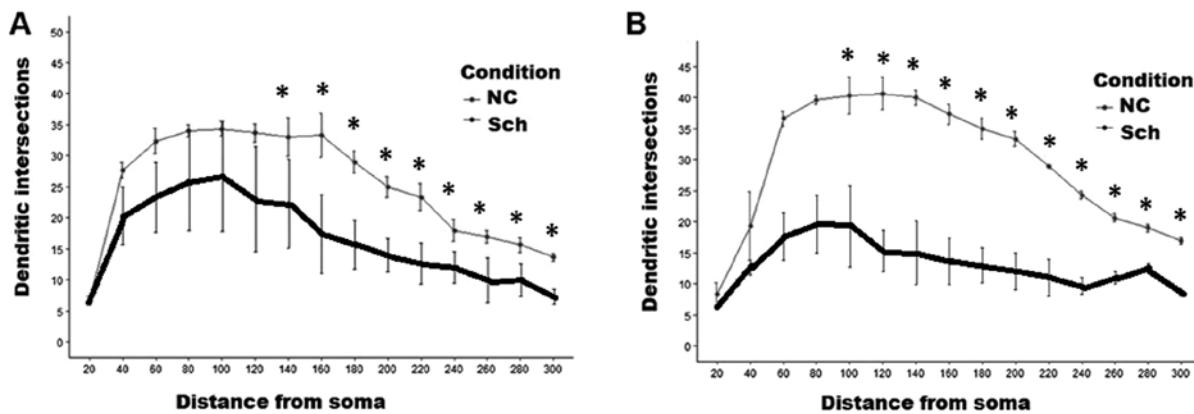


Figure 6. Sholl analysis of (A) the pyramidal cells and (B) interneurons of the visual cortex from NC and schizophrenic brains (bold line). Statistical significance was identified for distances $>120 \mu\text{m}$ for pyramidal neurons and $>100 \mu\text{m}$ for stellate neurons * $P < 0.05$ vs. the NC group. NC, normal controls; Sch, schizophrenia group.

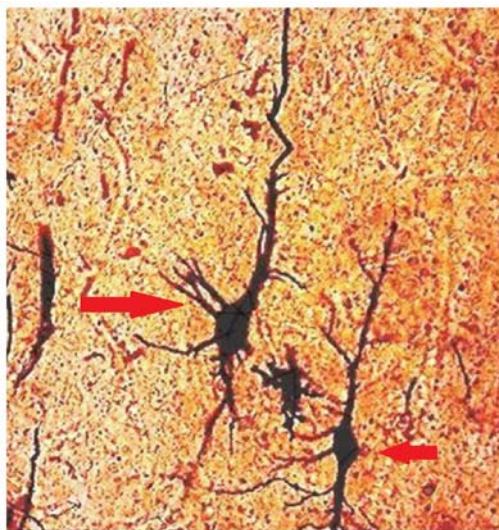


Figure 7. In schizophrenic brains, certain degenerated pyramidal neurons were noted (red arrows). No degenerated neurons were identified in the controls (Golgi method; magnification, $\times 100$).

The majority of existing studies are focused on hippocampal formation, the temporal lobe, prefrontal cortex and basal ganglia. To the best of our knowledge, no previous study has reported on the morphological changes of the pyramidal and stellate neurons of the occipital lobe. In 1998, Garey *et al* (44) reported decreased spinal density on the pyramidal cells of lamina III from Brodmann areas 11 and 38 observed on Golgi staining, and in the same year, Woo *et al* (45) indicated a selective decrease of terminal branches in Brodmann areas 9 and 46 chandelier neurons.

In 1996, Roberts *et al* (46) revealed changes of the dendritic spines at the striatum, and in the same year, Uranova *et al* (47) described certain changes in the postsynaptic density of axo-spinous synapses.

In addition, Dorph-Petersen *et al* (22) reported significantly decreased neuronal volume with no significant reduction of the neuronal density in the primary visual cortex of schizophrenic brains. These results were confirmed by neuroimaging studies using voxel-based morphometry, which reported a significant reduction in the occipital lobe's overall

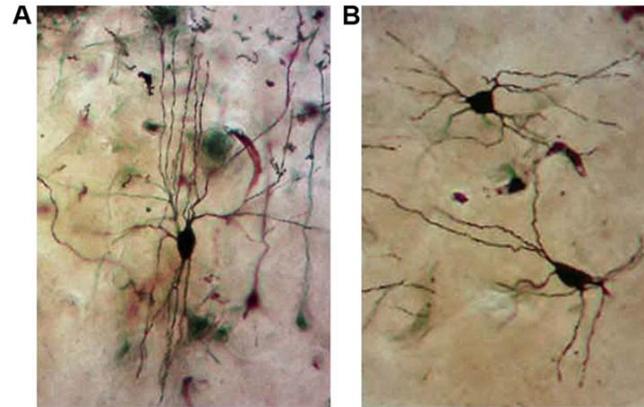


Figure 8. Representative examples of aspiny interneurons impregnated with the Golgi method from (A) normal controls and (B) schizophrenic brains (Golgi method; magnification, $\times 100$).

volume with a decrease in grey matter in schizophrenic patients (48-52).

In the present study, no significant changes in the neuronal density of the primary visual cortex were obtained, but the overall thickness of the primary visual cortex was substantially decreased in schizophrenic brains, corroborating the findings of the earlier study by Dorph-Petersen *et al* (22). Golgi silver staining and 3D reconstruction of neurons revealed several morphological changes on both cortical aspiny interneurons and pyramidal cells. The total neuronal volume was decreased in both populations. The aspiny interneurons exhibited a severe restriction of their dendritic field areas, along with a loss of distal and terminal dendritic branches. Pyramidal neurons from lamina III similarly exhibited a significant loss of terminal branches and substantially lower dendritic spines, mainly on the distal branches.

Regarding the clinical significance of the present results, visual hallucinations are amongst the most common symptoms associated with increased brain activity in patients with schizophrenia (48). They have been correlated to GABA deficits and functional impairment of cortical interneurons, as well as a disturbance of cortico-thalamic or intracortical connections (19). Furthermore, studies have revealed certain functional deficits of the visual cortex in schizophrenic

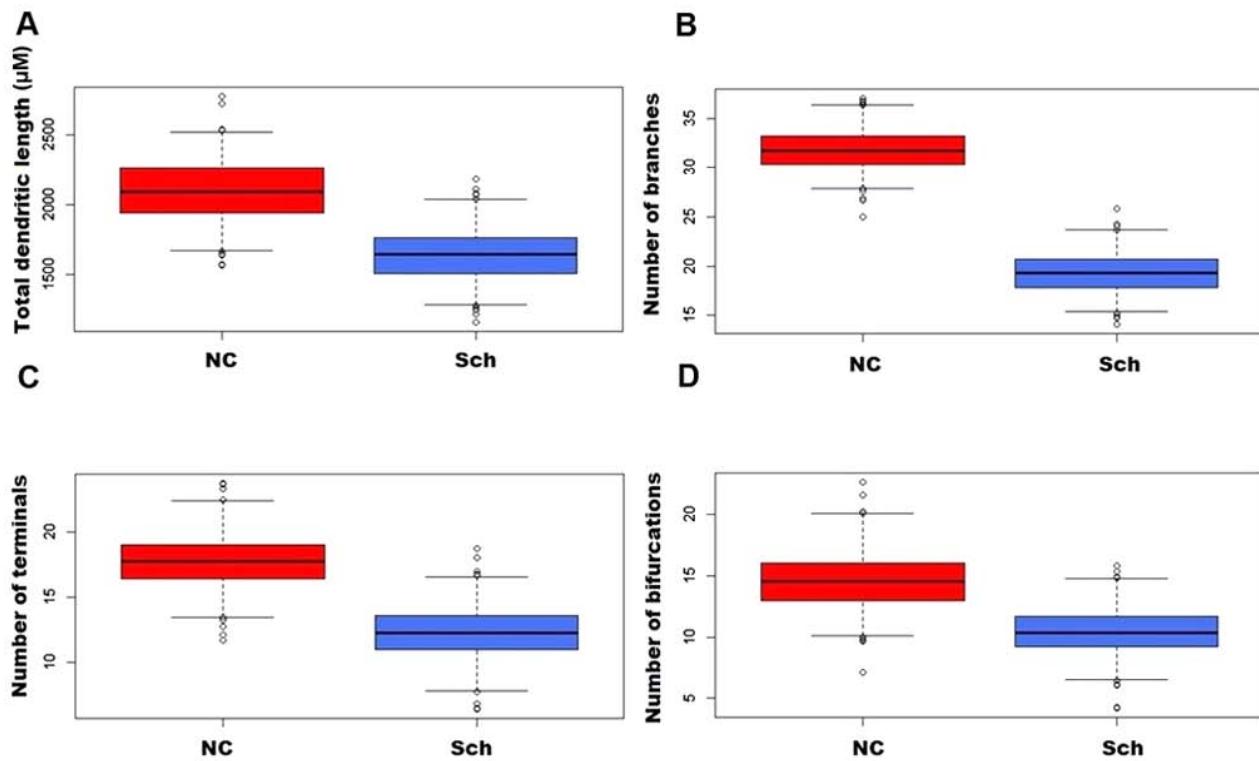


Figure 9. Comparison of (A) total dendritic length ($P=0.0049$), (B) number of branches ($P=0.003$), (C) numbers of terminals ($P=0.00021$) and (D) bifurcations ($P=0.0001$) of interneurons from NC and schizophrenic brains. Boxplots represent skewness and error bars indicate the standard deviation. NC, normal controls; Sch, schizophrenia group.

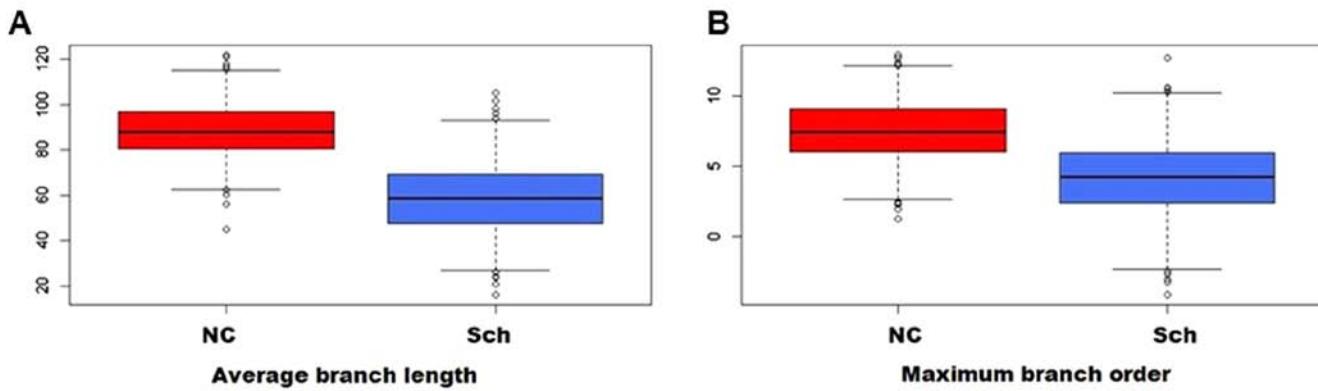


Figure 10. Comparison of (A) average branch length in μm ($P=0.001$) and (B) branch order ($P=0.001$) of interneurons from NC and schizophrenic brains. Boxplots represent skewness and error bars indicate the standard deviation. NC, normal controls; Sch, schizophrenia group.

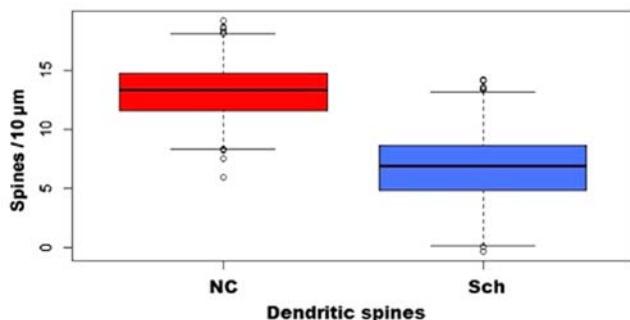


Figure 11. Spinal density of the pyramidal neurons of the visual cortex from NC and schizophrenic brains ($P=0.0034$). Boxplots represent skewness and error bars indicate the standard deviation. NC, normal controls; Sch, schizophrenia group.

patients, including early-stage visual processing, contrast sensitivity abnormalities, surround suppression and motor processing disturbance (53,54). Lamina III pyramidal neurons contribute to reception, elaboration and transmission of the visual information to other cortical areas, while the aspiny interneurons provide inhibitory control and modulate the synchronized oscillations (55). Both neuronal populations are critical for the integrity of the cortico-thalamic and intra-cortical circuits. The loss of dendrites and dendritic spines of both pyramidal cells and interneurons leads to a substantial decrease of the synaptic contacts and a significant impairment of the pyramidal-interneuronal connectivity, as well as of the connections of the cells of the visual cortex with the neurons of other cortical and subcortical areas, which may be

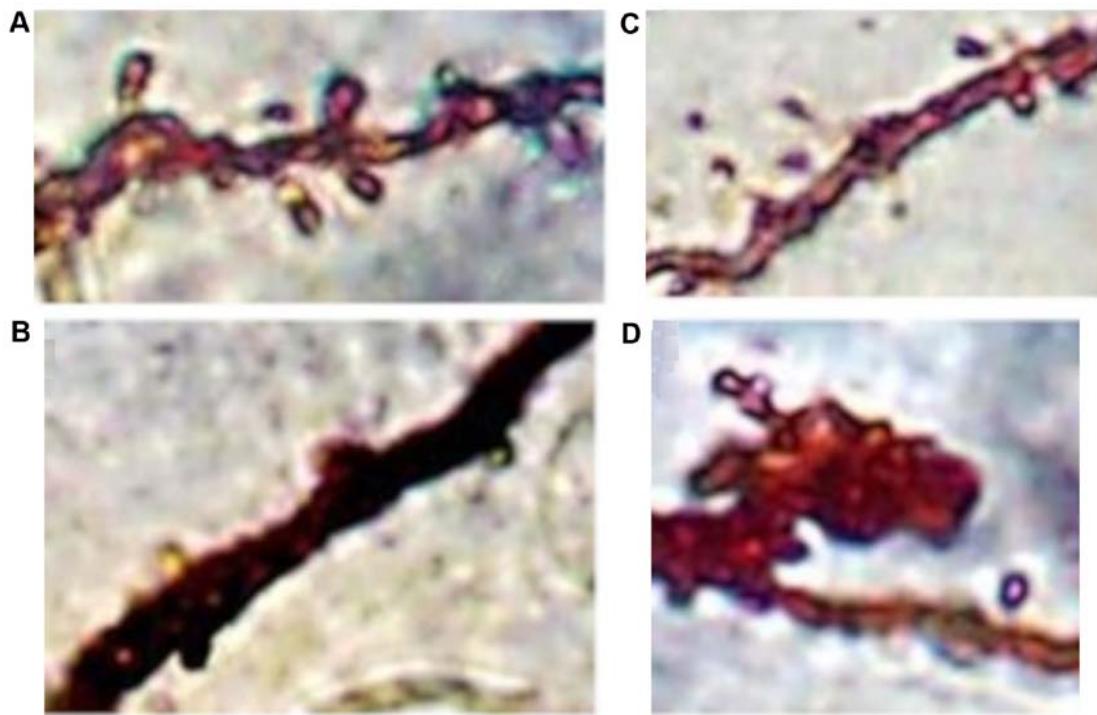


Figure 12. Representative examples of dendritic segments from (A) normal controls and (B-D) schizophrenic brains indicating (B) significant loss of dendritic spines, (C) patchy areas devoid of spines and (D) dystrophic spines (Golgi method; magnification, $\times 1,000$).

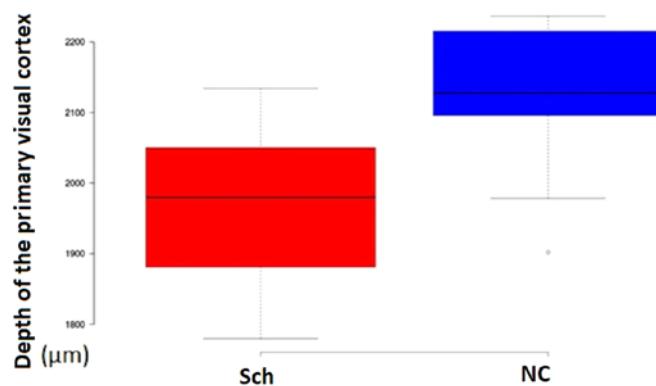


Figure 13. The depth of the primary visual cortex in patients with Sch and NCs. Boxplots represent 1st and 3rd quartiles, whiskers represent lower and higher values. Sch, Schizophrenia; NC, control.

implicated in the modulation of the visual information (30,55). Although other cortical areas beyond the primary visual cortex are related to the production of visual hallucinations, the interruption of connectivity of the primary visual cortex with secondary visual, temporal and parietal areas may have a crucial role in the pathophysiology of visual hallucinations and other functional deficits of the visual cortex in schizophrenia.

To the best of our knowledge, the present study was the first to describe the morphological alterations in pyramidal and spinal stellate neurons on the primary visual cortex in patients with schizophrenia. The results may provide novel insights into the brain changes exhibited by patients with schizophrenia. It may be concluded that the present observations may be related to certain clinical phenomena associated with the visual cortex usually encountered in schizophrenia.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

IM prepared the manuscript and supervised the data collection and analysis. FP, SC, EK and DK collected and analyzed the data, and prepared the specimens. AC, ACI, RD and CT prepared the manuscript and analyzed the data. SN, VC and SB made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data. IM and SB confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed according to the legislation of the Greek Democracy (v.2,472/1997, 2,819/2000, 2,915/2001, 3,235/2004 and 3,471/2006) and the Committee for Research Deontology Principles of the Aristotle University of Thessaloniki (24) (approval no. 23/4/4521/2018). Written informed consent was obtained from relatives.

Patient consent for publication

For each of the patients and controls, and written informed consent was obtained from their relatives and power of attorneys regarding the publication of data and associated images.

Competing interests

The authors declare that they have no competing interests.

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