Size, Shape, and Orientation of Neurons in the Left and Right Hippocampus: Investigation of Normal Asymmetries and Alterations in Schizophrenia

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Objective: *Schizophrenia may involve the two cerebral hemispheres differentially. This study was conducted to determine whether left and right hippocampal neuronal size, shape, and orientation are normally asymmetrical or asymmetrically affected in schizophrenia.* *Method:* *The authors examined postmortem tissue from the left and right hippocampus of 17 normal individuals and 14 individuals with schizophrenia. They measured the size, shape, and variability in orientation of pyramidal neurons in hippocampal subfields CA1–CA4 and the subiculum in computer images of 10-μm coronal sections stained with cresyl violet.* *Results:* *Both neuronal size and shape showed significant effects of diagnosis and a three-way interaction between diagnosis, hemisphere, and subfield. Neurons of the schizophrenic subjects were smaller than those of the normal subjects in the left CA1, left CA2, and right CA3 subfields; their shape differed from that of the normal subjects in the left CA1, left subiculum, and right CA3 subfields. There were no group differences in variability of neuronal orientation, but neurons in the CA3 genu in the schizophrenic subjects were less variable on the right than on the left. In the normal subjects, except for larger neurons in the left than in the right CA2 subfield and some left-right differences in variability of neuronal orientation, no statistically significant asymmetries were observed.* *Conclusions:* *The data confirm that hippocampal neuronal size is decreased in schizophrenia and reveal that the shape of neurons is altered, supporting the view that hippocampal cytoarchitectural abnormalities may be part of the cerebral substrate of schizophrenia. They also provide further evidence that the abnormalities are localized and lateralized.*

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Ever since the classic studies of Ramón y Cajal on the brain (1), of Sherrington on the spinal cord (2), and of Eccles on the synapse (3), the single neuron has been viewed as a fundamental building block of the central nervous system. Measuring structural neuronal parameters such as size, shape, and orientation, among others, may provide important clues for understanding the brain's neural cytoarchitecture and connectivity in both health and disease. Interest in cytoarchitectural indexes in schizophrenia has been kindled by data showing reduced neuronal size (4, 5), neuronal disarray (6, 7), and altered neuronal density (8–10) occurring in the disease, especially in the hippocampal formation. Such abnormalities provide the first clues to the anatomical substrate of the altered functional connectivity thought to underlie the pathophysiology of schizophrenia (11–13). For example, decreased perikaryal size may indicate neurons that have a smaller axodendritic tree or that are making fewer (or, possibly, aberrant) afferent and efferent synaptic connections (14, 15). Similarly, one would predict that differences in the orientation, shape, and packing density of neurons would also have an impact on the functional characteristics of the neural circuitry. However, as a result of an incomplete body of data and negative reports (16, 17), a clear picture of the histology of schizophrenia is still evolving (18).

The inconsistency in the published findings on schizophrenia may stem partly from a traditional focus on unilateral brain morphometry in brain diseases, assuming equal hemispheric involvement. This approach overlooks known human functional brain asymmetries in general (19, 20) and memory asymmetries in particular (21–23), which could be supported by asymmetrical

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neural wiring and could, in turn, provide a possible basis for asymmetrical susceptibility to brain disease in humans (24). In a disease such as schizophrenia, where the histological changes are subtle, the hemispheric issue may prove to be critical. Thus, we have embarked on systematic morphometric postmortem studies of the left and right hippocampus in both normal individuals and individuals with schizophrenia (10, 24) in order to address the possibility that some neuronal parameters might be normally asymmetrical and/or asymmetrically affected by the disease.

TABLE 1. Demographic Data on Subjects With Schizophrenia and Normal Subjects in a Postmortem Study of Neuronal Characteristics in the Hippocampus

	Subjects With Schizophrenia (N=14)			Normal Subjects (N=17)		
Item	Mean	SD	Range	Mean	SD	Range
Age at death (years)	57	16	28–83	63	15	22–84
Age at onset of symptoms (years)	30	8	16–47			
Fixation time (weeks)	12	6.2	—	10	4.8	—
Brain pH	6.3	0.34	—	6.5	0.24	—
Postmortem interval before autopsy (hours)	52.07	20.93	—	37.70	19.12	—

In an earlier study we found increased neuronal density in some right hippocampal subfields in schizophrenic subjects compared to normal subjects, although neuronal density did not differ between homologous subfields on the left and right sides in either the normal subjects or the subjects with schizophrenia (10, 24). In addition, the pattern of neuronal density correlations between subfields differed between the two diagnostic groups, being positive and significant on the left but weak on the right in the normal subjects (24) while being similar on both sides in the schizophrenic subjects (10). All of this suggested differences between normal persons and persons with schizophrenia in the neuronal organization of the left and right hippocampus. In this article we present the results of a quantitative study of the size, shape, and orientation of pyramidal neurons in the left and right hippocampus of the same individual. The advantage of left-right comparisons in the same brain is that the two hippocampi reflect the same genetic and environmental influences, as well as the same daily experiences. Treating them identically subsequently increases the ability to detect genuine cytoarchitectural asymmetries. Neuronal size and orientation were measured in order to determine their status in normal individuals, extend current data on individuals with schizophrenia, and ascertain whether or not these measures show left-right differences in schizophrenic subjects. We also measured neuronal shape, since this may index subtle features of the cytoarchitectural organization in both normal persons and those with schizophrenia. Investigating a range of cytoarchitectural parameters will not only clarify the cellular pathology of schizophrenia but also help to determine which parameters are altered, and it may ultimately provide clues to the nature of the disease process itself.

METHOD

We examined postmortem tissue from the left and right hippocampus of 17 normal individuals (10 male and seven female) and 14 individuals with schizophrenia (nine male and five female) who had given written consent for autopsy. Demographic data on the subjects are shown in table 1. The cases met the DSM-III-R criteria for schizophrenia (N=13) or schizoaffective disorder (N=1) as determined by review of psychiatric reports, family practitioners' and other records, and discussion with practitioners involved in the patients' care. None of the subjects had histories of coincidental neurological disorders or substantial substance abuse. All of the schizophrenic subjects had been treated with antipsychotic drugs for intermittent or prolonged periods and were taking medication at the time of death. Causes of death for the normal group were myocardial infarction (N=7), gastrointestinal hemorrhage (N=3), multiple trauma (N=2), asphyxiation (N=2), myocardial fibrosis (N=1), cardiac rupture (N=1), and bronchitis (N=1). Causes of death for the schizophrenic group were myocardial infarction (N=5), left ventricular failure (N=3), bronchopneumonia (N=1), bronchitis (N=1), fibrosing alveolitis (N=1), aortic stenosis (N=1), multiple trauma (N=1), and asphyxiation (N=1).

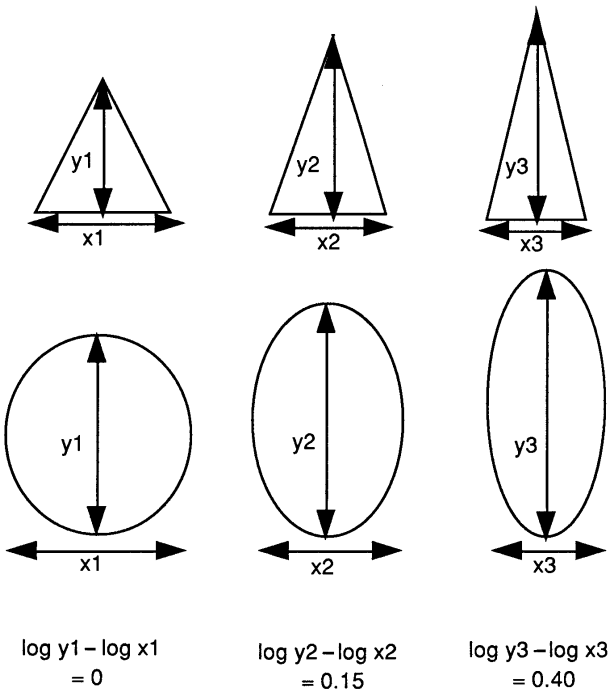
The brains were collected in Oxford, England, and dissected by one of us (P.J.H.). Blocks were taken from the left and right middle hippocampus at the level of the uncal notch (corresponding approximately to figure 21-7 of Amaral and Insausti [25]), fixed in formalin, and embedded in wax. Coronal sections, 10 μm thick, were taken from each block and stained with cresyl violet. Formal neuropathological examination of multiple brain areas (courtesy of Dr. Brendan McDonald) revealed no abnormalities in excess of age-related changes. In particular, a diagnosis of Alzheimer's disease according to the criteria of the Consortium to Establish a Registry for Alzheimer's Disease (26) was excluded.

Procedures

The material was coded and all stages of data collection were conducted blind to diagnosis, cerebral hemisphere, sex, and age. The equipment used for digitizing all of the images from hippocampal sections (on microscope slides) consisted of a color video camera (JVC model KY-F30, 3CCD) attached to an Olympus BH2 microscope that was connected to an IBM-compatible computer and a Kontron Vidas monitor. The camera was calibrated so as to give a clear image of the tissue on the computer monitor, with good contrast and brightness between the cells and the neuropil as judged by the human eye; this calibration was constant throughout the study. A ×10 microscope objective was used to visualize and digitize nucleolated neurons in gray scale. The total magnification was ×250 (objective: ×10; eyepiece: ×20; addition: ×1.25).

Neurons were digitized from the central parts of hippocampal subfields CA4, CA3, CA2, CA1, and the subiculum with the use of the demarcations described by Duvernoy (27). The number of regions captured per subfield was as follows: two regions per subfield in the subiculum, CA4, and CA3; three regions from CA1; and one from the smaller CA2 subfield. Neuronal size, neuronal shape, and the angle of orientation were measured with the NIH-Image software program, version 1.59, on a Macintosh computer. Each digitized region was measured in the following way. First, the spatial scale was calibrated to micrometers with a reticle. Second, in the "options" menu, size, major and minor axes (lengths of the major and minor axes of the best-fitting ellipse), and angle (between the best-fitting ellipse and a line parallel to the x axis of the computer screen) were selected for the measurements by the software program. Third, the background was filtered with 2D Rolling Ball. Fourth, overlapping neurons, neurons where the nucleolus was not visualized on the computer screen, and glia were erased freehand.

FIGURE 1. Schematic Representation of the Neuronal Shape Index Used in a Postmortem Study of the Hippocampus in Subjects With Schizophrenia and Normal Subjects[a]



[a]For each neuron selected, the computer determined its maximum length (y) together with the maximum length of the shorter axis (x), orthogonal to y. Both y and x were converted to logarithms, so that the difference between log y and log x, the shape index, is independent of the size of the object. The figure shows how an increasing value of log y minus log x may reflect either an isosceles triangle becoming more elongated or a circle becoming an ellipse. Clearly, more complex or irregular shapes could also give rise to similar shape index values. However, given that most hippocampal neurons are basically triangular (pyramidal), it is assumed that variation in the shape index most likely reflects variation in triangularity.

Glia were recognized by their shape and size. Fifth, thresholding was enabled, and the wand tool was used to select each neuron manually for measurement.

Experimental Design and Data Analysis

The average value for each neuronal parameter per subfield was computed for each subject separately and entered into the statistical analysis (subject was the random variable). For neuronal size, the means of the areas from the respective regions sampled were analyzed. For neuronal shape, the logarithm of the length of the minor axis was subtracted from the logarithm of the length of the major axis of the best-fitting ellipse (i.e., log [length major] minus log [length minor]) (figure 1), and the means of the difference were entered into the analysis. For variability of the angle of orientation, standard deviations of the angles (measured in degrees, as described above in Procedures) were analyzed. To the data representing the three neuronal parameters (size, shape, and angle) in each subject we applied a separate repeated measures analysis of variance (ANOVA) with a between-subjects factor of diagnosis (normal, schizophrenia) and within-subject factors of hemisphere (left, right) and hippocampal subfield (CA4, CA3, CA2, CA1, subiculum). The number of subjects in each diagnostic group was too small for sex to be entered as a separate factor into the statistical analysis. The main interest was the presence or absence of a statistically significant diagnosis-by-hemisphere-by-subfield interaction. Analyses for simple effects were applied when the triple interaction was obtained. All correlations are Pearson product-moment coefficients.

RESULTS

Neuronal Size

The average number of neurons measured per individual subject was 166 (range=55–349). Figure 2 shows the results for neuronal size. The results of the three-way ANOVA revealed a main effect of diagnosis ($F=6.69$, $df=1, 29$, $p=0.01$), reflecting the overall difference in mean cell size between the two diagnostic groups, with a smaller mean size in the subjects with schizophrenia (286 μm^2) than in the normal subjects (307 μm^2). A significant main effect for subfield ($F=73.58$, $df=4, 116$, $p=0.0001$), reflecting well-known differences in cell size between the hippocampal subfields, regardless of side or diagnosis, was also obtained. The interaction of diagnosis by hemisphere by subfield was significant ($F=2.34$, $df=4, 116$, $p=0.05$). There were no other significant main effects or interactions.

In view of the significant interaction, analyses for simple effects were applied to the data. The group with schizophrenia had significantly smaller neurons than the normal group in the left CA1, the left CA2, and the right CA3 subfields (figure 2). In the normal group, a significant hemisphere-by-subfield interaction ($F=3.15$, $df=4, 64$, $p=0.01$) was obtained, indicating a selective difference between the two sides in the size of neurons in the separate subfields. The left CA2 neurons were significantly larger than the right CA2 neurons ($F=8.43$, $df=1, 16$, $p=0.01$), and statistically nonsignificant asymmetries in the group of normal subjects were revealed in the CA3 neurons and CA4 neurons, which were larger on the right side. In the subjects with schizophrenia there was no significant hemisphere-by-subfield interaction ($p=0.56$), suggesting hippocampal subfield symmetry in neuronal size in the disease.

We found no alteration in neuronal size with aging in either diagnostic group or on either side, as determined by correlational analyses between age and neuronal size in each of the subfields.

Cell size was not confounded by postmortem interval before autopsy, fixation time, or brain pH (a marker of agonal state), as indicated by the correlation values (for postmortem interval: normal subjects, $r=–0.39$; subjects with schizophrenia, $r=–0.38$; for fixation time: normal subjects, $r=–0.19$; subjects with schizophrenia, $r=–0.29$; for pH: normal subjects, $r=–0.03$; subjects with schizophrenia, $r=0.15$; $df=15$ for normal subjects, and $df=12$ for schizophrenic subjects; all p values nonsignificant).

Neuronal Shape

The log of the length of the minor axis was subtracted from the log of the length of the major axis of the best-fitting ellipse around a neuron in order to obtain a quantitative measure of neuronal shape, as illustrated in figure

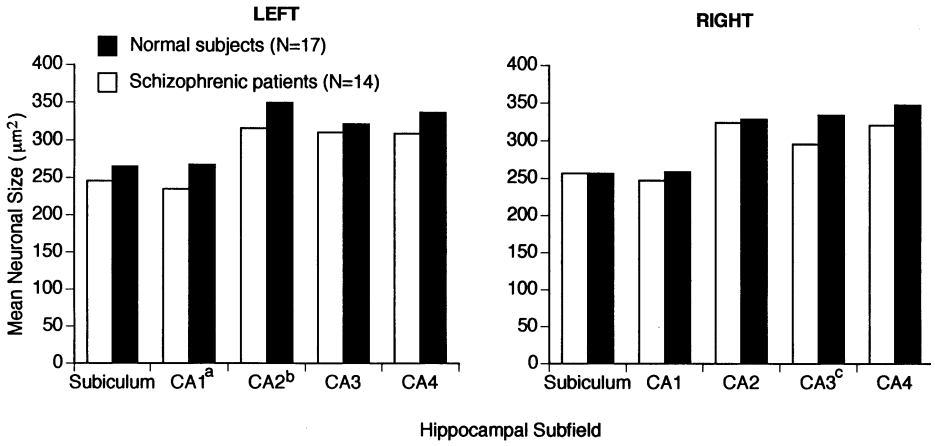
1. The means of the differences between the logarithms of the lengths of the axes in the diagnostic groups are shown in figure 3. The results of the three-way ANOVA revealed a significant overall difference in the shape of neurons between the schizophrenic subjects and the normal subjects (F=4.57, df=1, 29, p=0.04). There was also a main effect of hemisphere (F=4.28, df=1, 29, p=0.04), reflecting an overall difference between the hemispheres. Similarly, there was a significant main effect for subfield (F=15.84, df=4, 116, p=0.00001), reflecting the well-known overall difference in the shape of neurons among hippocampal subfields. The interaction of diagnosis by hemisphere by subfield was significant (F=2.60, df=4, 116, p=0.03).

There were significant differences in cell shape between the normal subjects and the subjects with schizophrenia on the left side in two subfields, CA1 and the subiculum, and on the right side in one subfield, CA3 (figure 3). In the left CA1 and right CA3, the differences reflect greater "elongation" of the neurons in the normal subjects than in the subjects with schizophrenia, whereas in the left subiculum, the neurons in the schizophrenic subjects were elongated in comparison with those of the normal subjects. In the normal subjects there were no statistically significant left-right differences between homologous subfields. In the subjects with schizophrenia, the left CA3 neurons were more elongated than the right CA3 neurons (F=7.74, df=1, 13, p=0.01), and the left subiculum neurons were also more elongated than the neurons in the right subiculum (F=8.62, df=1, 13, p=0.01).

A significant negative correlation between age and neuronal shape occurred only in the normal subjects, in the left CA3 subfield (r=–0.62, df=15, p=0.006).

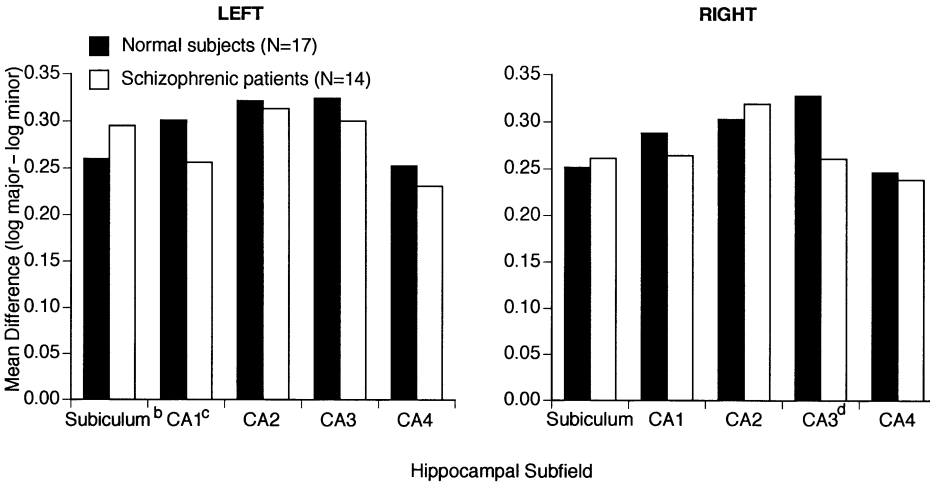
Neuronal shape did not correlate with postmortem interval, fixation time, or pH in the brain (for postmortem interval: normal subjects, r=–0.28; subjects with schizophrenia, r=0.03; for fixation time: normal subjects, r=–0.01; subjects with schizophrenia, r=0.53; for pH: normal subjects, r=–0.32; subjects with schizophrenia, r=0.03; df=15 for normal subjects, and df=12 for schizophrenic subjects; all p values nonsignificant).

FIGURE 2. Mean Neuronal Size in the Left and Right Hippocampus of Subjects With Schizophrenia and Normal Subjects



[a]Significant difference between normal and schizophrenic subjects (F=5.57, df=1, 29, p=0.02).
[b]Significant difference between normal and schizophrenic subjects (F=8.83, df=1, 29, p=0.005).
[c]Significant difference between normal and schizophrenic subjects (F=11.22, df=1, 29, p=0.002).

FIGURE 3. Mean Neuronal Shape[a] in the Left and Right Hippocampus of Subjects With Schizophrenia and Normal Subjects

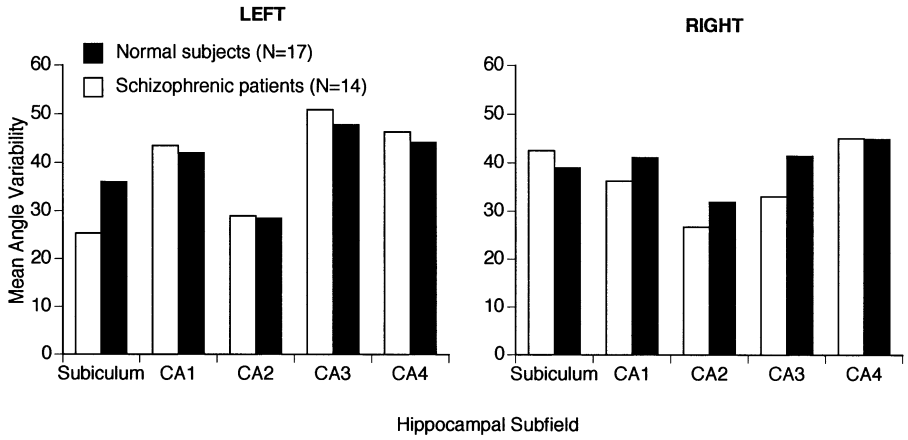


[a]Log of the length of the minor axis minus log of the length of the major axis of the best-fitting ellipse. As the value on the y axis increases, the shape changes.
[b]Significant difference between normal and schizophrenic subjects (F=5.33, df=1, 29, p=0.02).
[c]Significant difference between normal and schizophrenic subjects (F=8.28, df=1, 29, p=0.007).
[d]Significant difference between normal and schizophrenic subjects (F=12.56, df=1, 29, p=0.001).

Neuronal Orientation

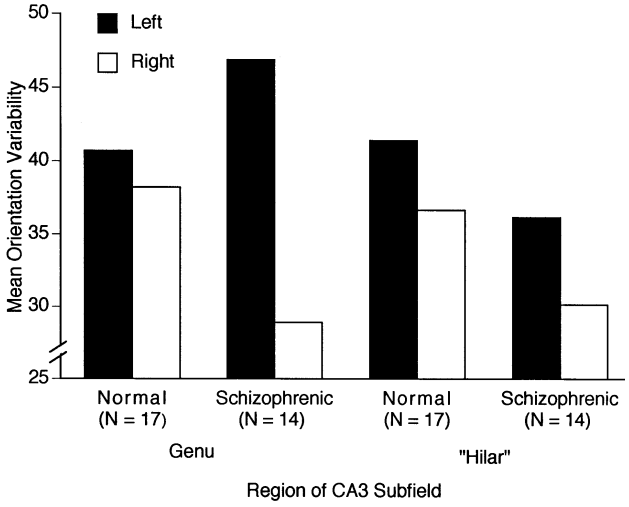
Figure 4 shows the results for variability in neuronal orientation. The three-way ANOVA applied to the standard deviations did not reveal an effect of diagnosis

FIGURE 4. Mean Variability (Standard Deviations) in Orientation of Neurons in the Left and Right Hippocampus of Subjects With Schizophrenia and Normal Subjects[a]



[a]The higher the numerical value on the y axis, the greater the variation.

FIGURE 5. Mean Variability (Standard Deviations) in Neuronal Orientation Within Hippocampal Subfield CA3 (Genu Versus "Hilar" CA3) of Subjects With Schizophrenia and Normal Subjects



or hemisphere, nor was there a significant triple interaction of diagnosis by hemisphere by subfield. There was a main effect for subfield ($F=8.09$, $df=4, 116$, $p=0.00001$), reflecting the already well-recognized variability in orientation among subfields, and a significant interaction between hemisphere and subfield ($F=5.97$, $df=2, 116$, $p=0.0002$).

The source of the two-way interaction was explored with analyses for simple effects, which revealed that within each diagnostic group there was a significant interaction between hemisphere and subfield (normal subjects: $F=5.38$, $df=4, 64$, $p=0.0005$; subjects with schizophrenia: $F=5.66$, $df=4, 52$, $p=0.0007$), indicating a selective hemispheric asymmetry in some subfields regardless of diagnosis. For example, in the normal subjects and subjects with schizophrenia, variability in CA3 neuronal orientation was higher on the left than on the right, with the reverse asymmetry present in the subiculum. This pattern was particularly pronounced in the CA3 subfield in the schizophrenic subjects. To obtain additional insights, we analyzed the data separately in the part of CA3 adjacent to CA4 ("hilar" CA3) and in the part of CA3 where it curves (the genu). The source of the asymmetrical variability of orientation in the subjects with schizophrenia was the genu (left=46.8, right=28.0) ($t=3.55$, $df=13$, $p=0.003$), with no significant asymmetry in the hilar CA3 region (left=36.1, right= 30.1) ($t=0.83$, $df=16$, $p=0.60$). In contrast, in the normal subjects the variability was stable across these two regions of the CA3 subfield and on each of the sides (figure 5).

DISCUSSION

In this study, neuronal size, shape, and variability of orientation were measured in the left and right hippocampus of a series of matched normal individuals and individuals with schizophrenia in order to investigate the possibility that these parameters might be normally asymmetrical or asymmetrically affected by the disease. Neuronal size and shape both showed a significant diagnosis-by-hemisphere-by-subfield interaction, indicating the occurrence of lateralized, localized alterations in schizophrenia: neuronal size was reduced in the left CA1, left CA2, and right CA3 subfields; neuronal shape was altered in the left CA1, left subiculum, and right CA3 subfields. Neuronal orientation variability was not markedly altered in the subjects with schizophrenia (but see figure 5). The main differences between the two diagnostic groups were thus related to the size and shape of neurons.

Our findings in both normal subjects and subjects with schizophrenia were not attributable to possible confounding factors such as age, postmortem interval, fixation time, tissue pH (a marker of agonal state), or coincidental neurodegenerative pathology (the brains had been screened to exclude this). A separate potential confounding factor is the effect on neurons of antipsychotic drugs received by the patients over a prolonged period (28). However, at this time, existing data on humans (4, 5) and rats (29) do not indicate that the size of neurons is affected by the administration of these drugs. We are not aware of any data regarding their effect on neuronal shape, and this must be investigated in drug-naive subjects with schizophrenia, if available, or in patients with other diagnoses

who have received the same medication. In any event, it seems unlikely that medication alone could produce the localized, lateralized abnormalities we observed in the subjects with schizophrenia.

Our observation that neuronal size was decreased in the hippocampus of the schizophrenic subjects (figure 2) confirms the earlier published reports by Benes and colleagues (4) and by Arnold and colleagues (5). We have now added the hemispheric status to the findings on neuronal size. The existence of three positive studies in different brain series makes decreased hippocampal neuronal size the most replicated cytoarchitectural finding in schizophrenia at this time.

For neuronal size in the normal subjects, there was a significant hemisphere-by-subfield interaction, which suggests asymmetry in this parameter of hippocampal morphology. The statistically significant difference between homologous subfields was a bigger cell size in the left CA2 subfield than in the right. The cytoarchitectural asymmetry in the hippocampus of the normal subjects provides the first evidence for what may be a substrate of previously observed functional asymmetries in memory (21–23), although there is currently a paucity of knowledge about the functional contributions of the CA2 subfield to human memory.

The factors determining neuronal size are poorly understood, but certain principles are apparent. Perikaryal size is generally considered to be a reflection of a neuron's axonal and dendritic processes, in which the larger the neuron, the more extensive these processes (15). The largest cells in the cortex are the giant Betz cells of the motor cortex, whose axons project to the spinal cord, and those innervating the lumbosacral region are larger than those projecting to the cervical cord (15, 30). Neuronal size is also a dynamic property, reflecting changes in apparent connectivity and the cell's own axonal projections as found in experimental lesions (14, 31, 32), neuropathological disease (30, 33, 34), or environmental changes (35). A logical inference from our data, then, is that hippocampal neurons in individuals with schizophrenia may have less extensive arborizations and may be making or receiving fewer (or aberrant) connections.

Apart from a small study in the CA1 subfield (16), hippocampal neuronal shape has not previously been investigated in schizophrenia. The present findings provide evidence for the first time from a large study group that the shape of neurons is indeed altered in some subfields of the left and right hippocampus in persons with schizophrenia. Since we cannot at present clearly define the geometrical nature of the shape alteration in schizophrenia (figure 1), we have resisted interpreting the possible biological significance of the findings pending the addition of more informative shape indexes to clarify the issue. In any event, little is known regarding the normal determinants of neuronal shape (as determined morphometrically), although in general the triangularity or "pyramidality" of a neuron is likely to be related to the position of the basal dendrites. The main significance of the present cell shape findings is simply that they provide an additional parameter of cytoarchitectural abnormality in schizophrenia.

Along with other studies (4, 5, 16), we found no remarkable evidence for increased variability of neuronal orientation (neuronal disarray) in subjects with schizophrenia, which Scheibel and colleagues identified (6, 7). This discrepancy from the findings of Scheibel's group may reflect the fact that we sampled neurons from the central part of each subfield, while the changes that Scheibel and colleagues saw were at the boundaries of CA fields. At the same time, we found an asymmetrical pattern in neuronal orientation variability in normal subjects and in subjects with schizophrenia. This was especially true in the CA3 subfield (figure 5). The pattern of variability was remarkable in the subjects with schizophrenia, particularly in the region of CA3 where it bends (the genu), and where the right side was less variable than the left. In principle, then, both high and low variability in neuronal orientation could signal abnormality in the brain. Further analyses of neuronal orientation, motivated by the findings of Scheibel's group (6, 7) and our present localized findings, would be worthwhile in studies of the hippocampi of normal subjects and subjects with schizophrenia.

A striking and novel aspect of the present results was that the alterations observed in the subjects with schizophrenia were localized to particular subfields and were asymmetrically distributed. The data thus provide a histological correlate of brain imaging and macroscopic neuropathological evidence that cerebral asymmetry is altered in the disease (36), and they indicate the value of examining both hemispheres of the same individual in future studies of this kind. Moreover, the abnormalities are not uniform throughout each hippocampus, nor do they all occur in one subfield; in this respect, both a diffuse abnormality and a simple focal hippocampal abnormality in schizophrenia are excluded. When the findings are considered together, attention is drawn to the right CA3 subfield, especially since neuronal density was also increased in this subfield (10). We cannot provide an explanation at this time for a preferential involvement of this subfield in individuals with schizophrenia, nor for its lateralization, although we note that CA3 neurons differ from neurons elsewhere in Ammon's horn in terms of their ontogenesis (37). Furthermore, an alteration in the neuronal characteristics of the CA3 subfield would be predicted to affect hippocampal function substantially, given that these neurons are the recipients of projections from the dentate gyrus subfield and are the source of Schaffer collaterals to the CA1 subfield (25, 27).

In summary, the present study revealed asymmetrical alterations in hippocampal neuronal size and shape in subjects with schizophrenia. These findings extend other recent studies suggesting that cytoarchitectural abnormalities may be part of the histological substrate of the disease, and they lend credence to the possibility that aberrant functional connectivity in schizophrenia has an anatomical basis. The lateralized extent of the changes we found provides further evidence for a disturbed neuro-

anatomical asymmetry. Experimental studies investigating the regulation of the major cytoarchitectural parameters in the hippocampus and cortex (on both sides) will help extend our observations and other related findings.

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