Decreased Somal Size of Deep Layer 3 Pyramidal Neurons in the Prefrontal Cortex of Subjects With Schizophrenia

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Background: Schizophrenia is associated with deficits in working memory, a cognitive function that depends on the connections of the prefrontal cortex (PFC) with the thalamus and other cortical regions. Pyramidal neurons in PFC deep layer 3 play a central role in both thalamocortical and corticocortical circuitry. Given that somal size tends to be associated with both the dendritic and axonal architecture of a neuron, abnormalities in these circuits in schizophrenia may be associated with a change in the somal size of deep layer 3 pyramidal neurons.

Methods: We used design-based stereology to estimate the somal volume of pyramidal neurons in deep layer 3 of PFC area 9 in 28 subjects with schizophrenia, each of whom was matched to 1 normal comparison subject for sex, age, and postmortem interval.

Results: The geometric mean of the somal volume estimates in the subjects with schizophrenia was significantly ($P = .02$) decreased by 9.2%. This decrease was associated with a shift in the distribution of somal volumes toward smaller sizes. Neither antipsychotic medication treatment history nor duration of illness was associated with somal size.

Conclusions: These findings independently replicate previous reports of decreased somal size in the PFC in schizophrenia. The reduction in size of deep layer 3 pyramidal neurons is consistent with abnormalities in thalamocortical and corticocortical circuitry, suggesting that disruption of these circuits may contribute to cognitive abnormalities in schizophrenia.

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Working memory is impaired in persons with schizophrenia, and these abnormalities are associated with altered function of the dorsal prefrontal cortex (dPFC). In addition, studies in nonhuman primates indicate that working memory requires the integrity of dPFC connections with other cortical regions and the thalamus.

Recent studies have reported alterations in layer 3 of the dPFC in schizophrenia. Rajkowska et al described a decrease in the mean somal size of all layer 3 neurons and a decrease in the density of the largest neurons in deep layer 3. The authors interpreted this finding to suggest that large pyramidal neurons in deep layer 3 may be most affected in schizophrenia. Interestingly, the density of dendritic spines, a marker of the number of excitatory inputs to pyramidal neurons, has been found to be significantly decreased on layer 3 pyramidal neurons in subjects with schizophrenia, and this abnormality was reported to be most prominent on pyramidal neurons in deep layer 3 of the dPFC.

Pyramidal neurons in deep layer 3 of the dPFC play a key role in both corticocortical and thalamocortical circuitry. The principal axons of these neurons project to cortical association areas, such as the superior temporal gyrus and the inferior parietal cortex. In addition, intrinsic axon collaterals of layer 3 pyramidal neurons furnish wide-spreading, horizontal excitatory connections within the dPFC. Furthermore, deep layer 3 pyramidal neurons are located in the termination zone of axon projections from the mediodorsal thalamic nucleus, and thus likely receive excitatory input from this nucleus.

Because neuronal size is correlated with the extent of a neuron's dendritic and axonal arbor, a decrease in somal size may reflect decreased afferent and/or efferent connectivity of these neurons in schizophrenia. Consequently, we tested the hypothesis that the somal size of deep layer 3 pyramidal neurons in dPFC area 9 is decreased in individuals with schizophrenia.

The primary MANCOVA model revealed a significant ($F_{1,26} = 5.76; P = .02$) decrease of 9.2% de-
SUBJECTS AND METHODS

SUBJECTS

With the consent of the next of kin and the approval of the Health Sciences Institutional Review Board of the University of Pittsburgh, we obtained brain specimens from 56 subjects during autopsies conducted at the Allegheny County (Pittsburgh) Coroner’s Office (Table). Neuropathological examinations revealed no abnormalities in any of the subjects except for the following: thioflavin-S staining revealed a few neuritic plaques in 3 normal comparison subjects (pairs 3, 4, and 24) and in 1 subject with schizophrenia (pair 6), but they did not meet either clinical or neuropathological criteria for Alzheimer disease.23 Two subjects with schizophrenia died of cerebrovascular events (pair 6, left parietal subdural hematoma; pair 12, intracerebral hemorrhage in the right temporal lobe), but the left dPFC was not affected. An independent panel of experienced clinicians made consensus DSM-III-R diagnoses as described previously.24

Twenty-eight subjects diagnosed as having schizophrenia or schizoaffective disorder (Table) were each matched to 1 comparison subject for sex, age, and postmortem interval (PMI). Individual pairs were completely matched for sex, and the mean ± SD differences in age and PMI within pairs were 3.8 ± 3.0 years and 2.6 ± 2.1 hours, respectively. Mean values for these variables (Table) and percentage of out-of-hospital deaths (comparison group, 96.4%; schizophrenia group, 89.3%) did not differ between the 2 groups. For subjects with schizophrenia, the mean ± SD age of onset was 27.3 ± 9.0 years and the duration of illness was 25.8 ± 11.8 years. Five of these subjects died by suicide, and 13 had a history of an alcohol or substance use–related disorder; these diagnoses were current with a shift in the somal size distribution toward smaller somas.

The distributions of somal sizes (Figure 4) revealed that the subjects with schizophrenia had higher percentages of neurons in the smaller cell size categories and lower percentages in the larger 2 categories compared with the comparison subjects. The MANCOVA model used to compare the cell category percentages between comparison subjects and subjects with schizophrenia showed a significant diagnosis × somal size category interaction (F1,106 = 4.9; P = .02). To determine the differences in the distributions of somal size that accounted for this interaction, we used paired t tests, adjusted to have a simultaneous .05 significance level, to examine the differences in changes in percentages of neurons across size categories for the 2 diagnostic groups. This analysis showed that between the “1001–3000 µm3” and the “3001–5000 µm3” categories, the subjects with schizophrenia exhibited a decrease in the percentage of neurons, whereas the comparison subjects exhibited an increase. The difference in these changes was significant (t108 = 2.8, simultaneous P = .02), and consistent with a shift in the somal size distribution toward smaller cell sizes for the subjects with schizophrenia.

The mean ± SD width of layer 3 did not differ (F1,17 = 0.18; P > .50) between the comparison subjects and those with schizophrenia exhibiting an increase. The difference in these changes was significant (t108 = 2.8, simultaneous P = .02), and consistent with a shift in the somal size distribution toward smaller cell sizes for the subjects with schizophrenia.

MEASUREMENT OF SOMAL SIZE

Quantification was performed without knowledge of diagnosis by one rater (C.L.E.V.). Using a Zeiss Axioplan microscope equipped with Stereo Investigator software27 and a Microvid Monitor (MicroBrightField, Inc, Colchester, Vt), area 9 was identified at low magnification (×50), the border between layers 3 and 4 was located (Figure 1), and a contour outlining the lower third (determined by measuring the width of layer 3) of layer 3 was drawn (Figure 2A). The mean ± SD contour area per section was 1.93 ± 0.33 × 106 µm2 for the comparison subjects and 1.85 ± 0.36 × 106 µm2 for the subjects with schizophrenia. Magnification was then changed to ×1000, using a 1.4 numerical aperture, ×100, oil immersion objective, for cell measurements. To randomly sample cells, we used the optical fractionator28 probe of the Stereo Investigator software, which systematically and randomly placed 18 to 22 sampling boxes throughout the horizontal region of the brain (Figure 2B). Each box was 110 × 75 × 8 µm in the x, y, and z directions, respectively (Figure 2C).

Every tenth section was mounted on slides and stained for thioflavin-S (Figure 1). For somal size estimation, this slide was selected for each subject with schizophrenia. After the slides were dried, they were also placed in phosphate buffer for 48 hours, washed in a graded series of sucrose solutions, and stored in an antifreeze solution at −30°C. Tissue storage time did not differ between the subject groups (Table). From blocks located 2 to 4 cm from the frontal pole, 40-µm coronal sections were cut on a cryostat. Every tenth section was mounted on slides and stained for Nissl substance with thionin. From a series of sections determined by cytoarchitectonic criteria24–26 to contain dPFC area 9 (Figure 1), we selected 4 sections, each separated by 400 µm, for somal size estimation. These slides were placed in random order and coded for blinded quantification.
In this study, subjects with schizophrenia showed a significant 9.2% decrease in the somal volume of pyramidal neurons in deep layer 3 of PFC area 9, with a shift in the somal volume distribution toward smaller cell sizes. Decreased somal size was not related to duration or age of onset of illness, sex, death by suicide, history of alcohol or substance use, or antipsychotic medication treatment at the time of death.

The strengths of this study include (1) the sample size; (2) the use of an optical fractionator design, which enabled systematic random sampling within area 9; and (3) the use of the nucleator, which permitted estimates of somal volume. However, several potential confounds must be considered in interpreting the pathophysiological significance of our observations. First, the stereological design of this study has limitations. Although a relatively large volume of area 9 was sampled, we did not sample throughout the region of interest. Consequently, caution must be used when generalizing findings from our sampling scheme to all deep layer 3 pyramidal neurons in area 9. Also, our method...
Subjects Examined in This Study

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| Mean  | 52.9       | 13.3   | 19.9             |                |             | 52.8      | 14.3   | 15.9             |                |                |
| SD    | 13.8       | 5.3    | 18.7             |                |             | 12.4      | 6.2    | 11.9             |                |                |

* PMI indicates postmortem interval; ASCVD, atherosclerotic coronary vascular disease; CO, carbon monoxide; SA, schizoaffective disorder; CUS, chronic undifferentiated schizophrenia; RS, residual schizophrenia; CPS, chronic paranoid schizophrenia; CDS, chronic disorganized schizophrenia; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; and MCA, middle cerebral artery.

† Superscripts are as follows: a, alcohol dependence; b, alcohol dependence, in remission at time of death; c, alcohol abuse, current at time of death; d, alcohol abuse, in remission at time of death; f, other substance dependence, current at time of death; g, other substance abuse, in remission at time of death; †, schizophrenic subjects not taking medications at time of death; ‡, schizophrenic subject who never received antipsychotic medication.

for estimating somal volume did not take into account the possibility that alterations in the shape or orientation of pyramidal neurons in schizophrenia could lead to underestimates or overestimates of somal volume. However, despite these caveats, the fact that a decrease in somal size of deep layer 3 pyramidal neurons has been reported by another independent group,1 using a different sampling scheme and estimator of cell size, strongly suggests that decreased somal size of deep layer 3 pyramidal neurons in schizophrenia is unlikely to be the result of biased measurement methods.

Second, terminal conditions associated with changes in brain volume, such as prolonged hypoxemia, could result in altered somal size. However, in this study, 92% of the subjects died suddenly, out of hospital, consistent with a limited agonal state.

Third, neuronal size may change as a function of PMI,3,37 as was observed in this study. However, subject pairs were closely matched for PMI, and inclusion of PMI as a covariate revealed that subjects with schizophrenia still showed a significant decrease in somal volume.

Fourth, the duration of brain tissue fixation represents a potential confound since tissue volume shrinks as much as 14% after prolonged fixation.36 In the present study, each specimen was processed following a standard protocol, with a brief fixation time (48 hours), that was identical for both diagnostic groups.

Finally, long-term exposure to antipsychotic medications might confound estimates of somal volume, as dose of antipsychotic medication has been found to be negatively associated with frontal lobe volume in schizophrenia.37 In the present study, the somal volumes of subjects with schizophrenia who were not taking antipsychotic medications at the time of death did not differ from subjects who were (Figure 6D). Moreover, the somal volume of the subject with schizophrenia who had never been treated with antipsychotic medications was less than that of the matched comparison subject.
Decreased somal size is consistent with and possibly related to other reported abnormalities of dPFC layer 3 pyramidal neurons in schizophrenia, such as decreased dendritic spine density.9,10 Specifically, a decrease in the density of basilar dendritic spines on deep layer 3 pyramidal neurons was associated with a decrease in the total length of these dendrites, as well as a nonsignificant decrease in somal size.10

Similar to previous studies of PFC pyramidal neurons,19,20 we also found no relationship between somal size and age at time of death in our subjects, confirming that somal size is stable across adulthood. Furthermore, somal volume in schizophrenia was not related to age of onset or duration of illness, suggesting that reductions in somal volume may not progress with time, and that the events leading to decreased somal size may have occurred during development before illness onset or during a limited progressive phase of the illness.38

Our findings also suggest that a reduction in somal volume may contribute to the subtle reductions in dPFC volume found in neuroimaging studies of schizophrenia.42-47 In addition, our findings may account for the reports of decreased concentrations of dPFC N-acetylaspartate48-51 in schizophrenia, since pyramidal cells make up the majority of neurons in the cortex,8 and since the concentration of N-acetylaspartate may be greatest in these neurons.52

Figure 1. Brightfield photomicrograph of Nissl-stained neurons in prefrontal cortex area 9. Note that pyramidal neurons in deep layer 3 are oriented parallel to the plane of section and perpendicular to the pial surface, consistent with the concept of a local vertical design. The 6 cortical layers and white matter (WM) are identified. The bracket indicates the lower one third of layer 3, where pyramidal neurons were sampled and measured. Scale bar=300 µm.

Figure 2. Schematic of the sampling and somal volume estimation procedure. Panel A shows a camera lucida drawing of the superior frontal gyrus in area 9. The gray area indicates the approximate medial and lateral boundaries of area 9. Within this area, where pyramidal neurons met criteria for a local vertical design, a contour was drawn outlining the lower one third of layer 3. B. A sampling grid was randomly superimposed over this area to designate sampling sites. C. At each sampling site, a 3-dimensional sampling frame was used to identify neurons for measurement according to unbiased inclusion and exclusion rules (broken and solid lines indicate inclusion and exclusion boundaries, respectively). Each neuron was measured at a final magnification of ×1000 using the nucleator principle (D), which involves identifying the nucleolus of each pyramidal neuron by clicking on it with the cursor, and marking (arrow) where each of a set of 5 equidistant (separated by 72°) rays, which randomly overlay the neuron, intersect the boundary of the soma. The photomicrograph depicts a pyramidal neuron undergoing this procedure.

Our findings also suggest that a reduction in somal volume may contribute to the subtle reductions in dPFC volume found in neuroimaging studies of schizophrenia.42-47 In addition, our findings may account for the reports of decreased concentrations of dPFC N-acetylaspartate48-51 in schizophrenia, since pyramidal cells make up the majority of neurons in the cortex,8 and since the concentration of N-acetylaspartate may be greatest in these neurons.52 Interestingly, in subjects with schizophrenia, N-acetylaspartate levels in the dPFC were positively correlated with changes in cortical activation, as measured by regional blood flow, in the prefrontal, temporal, and parietal association cortices during performance of a working memory task.53 This relationship, found only for the dPFC, suggests that activation of the working memory network may be determined by the integrity of cortico-cortically projecting dPFC pyramidal neurons.13,53
Understanding the pathophysiological significance of a decrease in the somal size of pyramidal neurons in deep layer 3 in persons with schizophrenia depends on whether this abnormality reflects a defect intrinsic to deep layer 3 pyramidal neurons or an extrinsic defect in the inputs they receive. An intrinsic defect may be manifest in a decrease in the capacity of these neurons to form and maintain appropriate afferent and efferent connections. For example, in certain neuronal populations, somal size correlates with the extent of a neuron’s dendritic and axonal arbor. If these correlations apply to the findings of the present study, we would expect evidence for decreases in these components of pyramidal neuron architecture. Indeed, this possibility is suggested by reported abnormalities in spine density and total dendritic length. Interestingly, for 12 subjects with schizophrenia in the present study, who were also examined in a previous study of spine density, average total dendritic length, measured in Golgi-stained deep layer 3 pyramidal neurons, and average somal volumes, esti-
mated herein, are significantly correlated \( r = 0.64, P = .02 \). In contrast to measures of a neuron’s dendritic arbor, the axonal arbor of a neuron is much more difficult to measure in the postmortem state. However, given that layer 3 pyramidal neurons participate in reciprocal short- and long-range circuits intrinsic to the dPFC, a proportion of the decrease in pyramidal neuron spine density in schizophrenia may be due to a decrease in axonal arbor.

On the other hand, a decrease in somal size could result from a loss of input from other brain areas, such as the thalamus. Recent studies of the mediodorsal thalamic nucleus, which projects to the dPFC, have reported a decrease in the number of neurons in subjects with schizophrenia. These findings suggest that, in schizophrenia, deep layer 3 pyramidal neurons may receive less excitatory drive from the thalamus, and consequently, they are less active and hypotrophic. This possibility of “denervation atrophy” is supported by experiments in which lesioning a subset of afferent inputs to the PFC induced decreased somal size of layer 3 pyramidal neurons.

Further studies are needed to determine whether abnormalities in dPFC deep layer 3 pyramidal neurons in schizophrenia reflect an intrinsic defect or are the result of altered inputs from other brain regions. Either possibility would support the hypothesis that abnormal thalamocortical and corticocortical circuitry underlie dPFC dysfunction in schizophrenia.

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