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The relationship between callosal axons and cortical neurons in the planum temporale: Alterations in schizophrenia

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ABSTRACT

The relationship between "connectivity" measures such as DTI and the cellular alterations in the cortex that give rise to those connections remains unclear. Cytoarchitectural changes in the planum temporale (PT) suggest impaired layer III feedforward projection neurons in schizophrenia. Altered hemispheric asymmetry of the PT has been reported in patients, along with altered white matter density in the corpus callosum, and there is anomalous activation of the PT during auditory hallucinations. We measured layer III cell density and pyramidal neuron size in PT of both hemispheres of post-mortem brains from patients with schizophrenia ($n = 16$) and control subjects ($n = 16$). We found reduced cell density and the loss of a correlation between magnopyramidal neuron density and axon number in the isthmus of the corpus callosum in schizophrenia. The normal asymmetry indicated that magnopyramidal neurons tend towards being larger and denser in the left PT but this asymmetry is significantly reduced in schizophrenia. The findings offer cytoarchitectural insight into the relationship between PT cortex and callosal white matter abnormalities in schizophrenia.

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1. Introduction

An explosion of interest in cortical connectivity has been encouraged by neuroimaging methods such as DTI (Kubicki et al., 2005). However, the relationship between white matter measures and alterations in the cells that give rise to those connections has not been elucidated. The present study investigated this relationship in the planum temporale (PT) a region affected in schizophrenia and thought to be involved in altered language circuits that may contribute to symptoms. The PT supports auditory language processing, is active during auditory hallucinations (Shergill et al., 2000) and reduced volume in schizophrenia has been shown to correlate with the degree of thought disorder (Shenton et al., 1992). Although neuron density is reported to be unchanged, altered clustering (Beasley et al., 2005) and reduced volume of layer III pyramidal neurons have been found in this area (Sweet et al., 2003). It has been suggested that these findings implicate impaired feed-forward connections in schizophrenia (Sweet et al., 2003). PT inter-hemispheric connections have also been implicated by alterations in callosal white matter (Diwadkar et al., 2004) and abnormal cerebral asymmetry of the PT (Chance et al., 2008) in schizophrenia. We have found that asymmetry of the minicolumnar organisation of cells in PT reflects axonal connectivity through its connecting region – the isthmus – of the corpus callosum (Chance et al., 2006). Greater asymmetry was associated with fewer axons, presumably reflecting more independent hemisphere function. We have also reported disturbed associations between cytoarchitectural minicolumn asymmetry and callosal axon distribution in schizophrenia (Chance et al., 2008).

The goal of the present study was to examine the pyramidal neuron population in PT of post-mortem brain. It was intended to correlate these data with previously collected callosal data. It is known that somal size is related to axon length and that callosally projecting neurons of layer III in monkeys are larger than those that project ipsilaterally. Consequently one may predict that larger neurons will be more sensitive indicators of asymmetric function and disruption.

More axons would be expected to correspond to a larger number of pyramidal neurons. There is a reported asymmetry in the size of magnopyramidal neurons in motor language cortex (Hayes and Lewis, 1993) and one may expect a similar asymmetry in Wernicke's language area (including the PT), which is the sensory equivalent. Also, in the prefrontal cortex, a selective reduction of large pyramidal neurons in schizophrenia was found by Rajkowska

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et al. (1998), which suggests particular vulnerability among the magnopyramidal neurons. We aimed to investigate the largest neurons in the PT, their relationship with callosal axon number, and how they are changed in schizophrenia. The hypothesis predicted abnormal asymmetry of magnopyramidal size and/or density, and altered correlations with callosal axon number in schizophrenia.

2. Material and methods

Brains from 16 patients with schizophrenia (7 men, 9 women) and 16 controls (7 men, 9 women) were fixed in 10% formalin. See Table 1 for demographic details. Patients met the DSM-IV criteria for schizophrenia based on the assessment of clinical notes by a consultant psychiatrist (T.J.C. or Dr S. Cooper, Belfast). Both hemispheres were studied. Tissue was collected in accordance with standard neuropathological practice and registered with UK national investigations on organ retention. Pathological assessment of tissue samples carried out by a consultant neuropathologist (Prof. M. Esiri or Dr B. McDonald, Oxford) used CERAD criteria to exclude brains with evidence of pathology, such as Alzheimer's or cerebrovascular diseases, from the study. Control subjects had no history of neuropsychiatric illness.

The brains had been supported by the basilar artery in 10% formalin for fixation and assigned a randomized code by a third party, so that measurements could be made by persons blind to sex, diagnosis and age. The temporal lobe was cut into 5-mm-thick coronal blocks orthogonal to the long axis of the lobe and sections of PT were cresyl violet Nissl-stained. The PT was identified macroscopically by painting while still intact, and microscopically by light microscope (Olympus BX40). The PT was bounded anteriorly by Heschl's sulcus, including regions TB and TA1, excluding the posterior ascending ramus (see Chance et al. (2008) for more detailed discussion of region definition and tissue extraction).

Cases were selected to yield comparable group mean fixation times and ages at death as far as possible, although pair matching was not possible. No comorbidity of alcohol or illicit drug misuse was detected in our sample's records. Patients had received long-term anti-psychotic medication.

Blocks were cut by hand using a constructed calibrated metal guide and embedded in paraffin wax for sectioning. Cortical tissue volume shrinkage due to embedding in these brains has been estimated by precise measurement of block size before and after embedding, giving a mean of 23.7% with no systematic differential degree of shrinkage found between groups. It must be noted that the shrinkage of these tissues from fresh is unknown since the brains were received in formalin. Shrinkage due to formalin stabilizes after about 3 weeks (Quester and Schroder, 1997) and all of the tissue in this sample had been long fixed for many months so that we would not expect ongoing or differential fixation effects in shrinkage or staining (Nissl staining is relatively robust and less vulnerable to fixation effects unlike many immunohistochemical techniques).

The corpus callosum was not sampled in this study and the data used here were drawn from a previous study on the brains of the same subjects reported in Highley et al. (1999). The material used in the present study was removed from formalin and tissue blocks were placed in embedding medium at the same time as in the previous studies of these brains. Consequently, the comparison between cellular measures in the cortex and axon measures previously reported is not confounded by the time between studies.

2.1. Cell density

The sampling method was designed to be comparable with the approach of Beasley et al. (2005): on each slide at a sample point

Table 1
Demographics and results (means and SDs).

Diagnosis	Sex	Age at death (years)	Fixation time (months)	Fixed brain weight (g)	Post-mortem interval (h)
Control	Female ($n=9$)	71.3 ± 11.5	27.4 ± 14.0	962.2 ± 99.8	36.9 ± 19.0
Schizophrenia	Female ($n=9$)	72.9 ± 13.1	58.4 ± 20.5	889.4 ± 131.5	35.0 ± 23.6
Control	Male ($n=7$)	59.9 ± 11.9	20.9 ± 9.8	1102.5 ± 91.3	36.4 ± 15.9
Schizophrenia	Male ($n=7$)	59.1 ± 14.6	38.1 ± 18.3	1112.1 ± 128.5	35.4 ± 21.2

Diagnosis	Sex	Pyramidal neuron density/0.001 mm^3		Non-pyramidal cell density/0.001 mm^3		Mean pyramidal neuron cross-sectional area (μm^2)		Magnopyramidal neuron mean cross-sectional area (μm^2)		Magnopyramidal neuron density (% pyramidal cell popn.)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Control	Female ($n=9$)	37.8 ± 7.5	43.0 ± 8.1	53.3 ± 9.9	61.6 ± 12.0	168.6 ± 21.7	164.9 ± 19.6	405.2 ± 102.6	361.6 ± 40.5	6.1 ± 3.8	4.8 ± 3.4
Schizophrenia	Female ($n=9$)	36.0* ± 6.8	38.1* ± 6.5	46.0* ± 9.0	53.0* ± 10.8	158.2 ± 12.0	167.2 ± 25.6	385.9** ± 62.6	360.6** ± 27.7	3.7 ± 2.4	7.3 ± 6.0
Control	Male ($n=7$)	37.6 ± 7.4	42.4 ± 12.0	51.9 ± 5.6	56.1 ± 15.0	178.9 ± 20.6	173.6 ± 22.6	409.1 ± 65.0	359.8 ± 25.9	6.7 ± 4.6	5.4 ± 3.2
Schizophrenia	Male ($n=7$)	31.2* ± 7.3	32.6* ± 4.0	45.4* ± 9.0	52.2* ± 16.2	171.2 ± 18.4	166.1 ± 13.4	419.7** ± 56.5	378.0** ± 33.8	5.9 ± 1.8	5.7 ± 1.6

* Significant difference from controls ($p<0.05$) in the mean.
** Significant difference from controls depending on hemisphere ($p<0.05$), therefore affecting asymmetry.

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