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The hippocampus in schizophrenia: lateralized increase in neuronal density and altered cytoarchitectural asymmetry

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ABSTRACT

Background. The histological basis of schizophrenia is unknown, but it appears to affect the hippocampal and neocortical cytoarchitecture. Some cytoarchitectural parameters normally differ between the two cerebral hemispheres. Moreover, schizophrenia is associated with altered structural cerebral asymmetry. However, few cytoarchitectural studies of schizophrenia have taken the question of asymmetry fully into account.

Methods. We performed a morphometric post mortem study of neuronal density in sections from the left and right hippocampus (dentate gyrus, CA4, CA3, CA1 and subiculum) of 22 schizophrenics and 18 normal subjects. We also determined the correlations of neuronal density between pairs of subfields as an index of their inter-relationship; a previous study had found correlations in the left but not the right hippocampus of normal subjects.

Results. There were three differences in the schizophrenics compared to the controls. (1) neuronal density was increased in right CA3 (by 25%) and right CA1 (by 22%); (2) neuronal density correlated strongly between homologous left and right subfields (i.e. inter-hippocampally) for CA4, CA3, CA1 and subiculum, in normals this occurs only for dentate gyrus and CA4; and (3) intra-hippocampal correlations of neuronal density between pairs of subfields were similar in both hippocampi of the schizophrenia cases, unlike their asymmetrical distribution in controls.

Conclusions. The alterations may be part of the histological substrate of schizophrenia. The nature of the findings is consistent with a neurodevelopmental origin, and with a disease process that affects cerebral asymmetry and leaves its imprint upon the hippocampal cytoarchitecture.

INTRODUCTION

Schizophrenia is associated with alterations in the size, shape and proportions of the brain, demonstrable by neuroimaging and by neuropathology (Harrison, 1995*a*). However, the location, nature and significance of the critical changes remain unknown (Shapiro, 1993). There is particular uncertainty about the histological correlates of the macroscopic brain alterations. Several studies have reported cytoarchitectural abnormalities to be common in schizophrenics, especially within the hippocampal formation (medial temporal lobe). Positive findings include aberrant neuronal clusters in entorhinal cortex (Jakob & Beckmann, 1986; Arnold *et al*. 1991) and differences in hippocampal neuronal density, size and orientation (Kovelman & Scheibel, 1984; Falkai & Bogerts, 1986; Jeste & Lohr, 1989; Benes *et al*. 1991; Arnold *et al*. 1995). The characteristics of these changes, occurring in the absence of gliosis, are suggestive of an early neurodevelopmental anomaly (Weinberger, 1995). Nevertheless, the morphometric data are

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inconsistent and there are important negative reports (Christison *et al.* 1989; Heckers *et al.* 1991). Overall, there is still no convincing histological substrate of schizophrenia.

Following a study of neuronal density in the hippocampi of normal adults (Zaidel *et al.* 1995), we wondered whether matters might be complicated by an interaction of the morphometric abnormalities of schizophrenia with the cytoarchitectural asymmetries existing in the normal brain (Harrison, 1995*b*). In the study of Zaidel *et al.* (1995), hippocampal neuronal density itself was not asymmetrical. However, in the left hippocampus, neuronal density correlated positively between several pairs of subfields; that is, an individual with a low neuronal density in one subfield tended to have a low neuronal density in another. No such correlations were seen in the right hippocampus. A similar left–right difference in the pattern of correlations had been noted in hippocampi removed because of temporal lobe epilepsy (Zaidel *et al.* 1993). Although the neurobiological basis of neuronal density correlations is unknown, we interpreted them as indexing the inter-relationships between subfields, akin to the way that correlational analyses have been applied to the distribution of neuropathological lesions (Samuel *et al.* 1994; Nagy *et al.* 1995) and to metabolic coupling between brain regions (Mettler *et al.* 1984; Horwitz *et al.* 1986). Certainly the data implied subtle asymmetry in the cytoarchitecture, and perhaps the circuitry, between the hippocampi. This may contribute to the functional differences in learning and memory between left and right hippocampus (Milner, 1971; Beardsworth & Zaidel, 1994). It may also underlie their possible differential vulnerability to schizophrenia, by analogy with other disorders in which connectivity influences pathology (Pearson *et al.* 1985). Some of the cytoarchitectural alterations reported in schizophrenia seem more apparent in the left than the right hippocampal formation (Jakob & Beckmann, 1986; Jeste & Lohr, 1989; Arnold *et al.* 1991; Falkai & Bogerts, 1993) but the matter has not been well studied. Given the continuing interest in the relationship between schizophrenia and cerebral asymmetry (Southard, 1915; Crow *et al.* 1989; Bogerts *et al.* 1990*a*; Crow, 1990; Bilder *et al.* 1994; Petty *et al.* 1995), we have now investigated whether neuronal density or its correlations differ in left or right hippocampus of schizophrenics compared to normal subjects.

METHOD

Brains from 18 normal subjects and 22 chronic schizophrenics were available for study. Their demographic details are shown in Table 1. The control subjects had no psychiatric or neurological history of note. The controls and 15 of the schizophrenics were collected in Oxford between 1991 and 1995 ('Oxford series'). Brain pH was measured as a marker of agonal state. An additional seven schizophrenic cases, collected between 1972 and 1975, were obtained from the archives of the Corsellis Collection, Runwell Hospital, Essex ('Runwell series'); fresh blocks of tissue were taken from these cases in 1995 for the study. All brains underwent detailed neuropathological examination, courtesy of Dr Brendan McDonald, Oxford, and Dr Clive Bruton, Runwell. None had any abnormalities in excess of age-related features.

Both hemispheres of the cases and controls were dissected and processed uniformly. Matched, coded blocks of left and right hippocampus at the level of the uncal notch (corresponding approximately to Fig. 21.7 of Amaral & Insausti, 1990), were fixed in 10% buffered formalin (for duration see Table 1) before being processed routinely and paraffin-embedded. Then 10 μm coronal sections were cut and Nissl stained with cresyl violet. The left hippocampus from one control, and the right hippocampus from one schizophrenic, were unavailable.

Neuronal density was measured by one of us (D.W.Z.) using standard methods, essentially as described (Zaidel *et al.* 1993). Briefly, an Olympus BH2 microscope was fitted with a 10×10 square eyepiece grid. Nucleolated neurons within the grid, including those which overlapped its left or top border, were counted, on the same section, in the dentate gyrus granule cell layer (magnification $\times 880$), CA4 (hilus), and pyramidal cell layer of CA3, CA1 and subiculum (all $\times 250$). The subfields were delineated according to Duvernoy (1988). Five different zones within each subfield were randomly sampled and the average value entered into the analysis. The only difference from

Zaidel *et al.* (1993) was that the Abercrombie correction was not used; instead, neurons were counted if the nucleolus was visualized at any point through the thickness of the section. The data are, therefore, expressed as neurons per unit volume (grid area × section thickness). Comparisons of neuronal density between schizophrenics and controls were investigated with ANOVA. Correlations of neuronal density between pairs of subfields were determined using the Pearson coefficient.

RESULTS

Neuronal density was higher in most subfields in the schizophrenics from Runwell than in those from Oxford (data not shown). Since this might be due to greater tissue shrinkage because of their much longer fixation time (Table 1), or be the result of other unknown differences in how they were processed, and because we did not have matching control material, we excluded the Runwell series from the comparison of neuronal density between the schizophrenics and controls. They were retained for the neuronal density correlations since the latter are within-individual measures not affected by the hypothetical confounds.

Table 2 shows hippocampal neuronal density in the remaining 15 schizophrenics compared with the controls. In CA3 there was a diagnosis-by-hemisphere interaction ($P < 0{\cdot}02$), with neuronal density selectively increased in right CA3 in schizophrenia ($+25\%$; $P < 0{\cdot}01$). In CA1, there was a significant effect of diagnosis on neuronal density ($P < 0{\cdot}002$) and an equivocal diagnosis-by-hemisphere interaction ($P = 0{\cdot}08$). Notwithstanding the latter trend level of significance, one-way ANOVA revealed an increase in neuronal density in schizophrenics in right ($+22\%$; $P < 0{\cdot}01$) but not left ($+7\%$; $P = 0{\cdot}24$) CA1. No significant differences in neuronal density associated with diagnosis or hemisphere were seen in dentate gyrus, CA4 or subiculum.

The neuronal density correlations between each subfield and its counterpart in the other hemisphere are presented in Table 3. In controls there are positive correlations limited to left and right dentate gyrus and left and right CA4 (both $P < 0{\cdot}02$). In schizophrenics, the correlation between the two dentate gyri becomes non-significant, but CA4, CA3, CA1 and subiculum each show a highly significant positive left–right correlation ($0{\cdot}01 < P < 0{\cdot}0001$).

Table 4 summarizes the neuronal density correlations between subfields within each hippocampus. In the right hippocampus, schizophrenics show three correlations whereas controls show none. In the left hippocampus,

Table 1a. *Demographic details of controls*

Case	Age (years)	Sex	Cause of death	Brain pH	PMI (hours)	Fixation (weeks)
1	70	M	Bronchitis/left ventricular failure	6·36	72	12
2	61	M	Myocardial infarction	nk	84	11
3	67	F	Myocardial infarction	6·76	38	10
4	52	M	Asphyxiation	6·81	20	8
5	75	F	Myocardial fibrosis	6·63	27	7
6	68	M	Myocardial infarction	6·20	27	7
7	79	F	Hypovolaemic shock	6·27	51	12
8	47	M	Myocardial infarction	6·72	21	2
9	84	M	Gastrointestinal haemorrhage	nk	60	2
10	47	M	Myocardial infarction	6·94	38	2
11	75	M	Asphyxiation	6·80	26	9
12	71	F	Myocardial infarction	6·25	27	15
13	22	F	Traumatic aortic rupture	6·20	37	15
14	49	M	Myocardial infarction	6·59	39	12
15	75	F	Cardiac rupture	6·75	27	2
16	72	F	Ruptured aortic aneurysm	6·54	12	13
17	72	M	Gastrointestinal haemorrhage	6·71	35	18
18	92	F	Gastrointestinal haemorrhage	6·45	54	15
Mean	65·4			6·56	38·6	9·6
S.D.	16·6			0·24	19·0	5·1

PMI, Post mortem interval; nk, not known.

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Table 1b. *Demographic details of schizophrenics*

Case	Age (years)	Sex	Cause of death	Brain pH	PMI (hours)	Fixation (weeks)	Subtype[1]	Age at onset[2] (years)	Antipsychotic exposure[3]	ECT[4]	Insulin coma[5]
Oxford series											
1	60	F	Pulmonary embolus	5·90	100	26	Undifferentiated	25	4	Yes	Yes
2	71	F	Bronchopneumonia	6·62	48	25	Disorganized	38	3	Yes	Yes
3	75	M	Left ventricular failure	6·02	56	15	Unknown	32	3	Yes	Yes
4	56	M	Myocardial infarction	6·09	48	20	Paranoid	29	4	Yes	No
5	30	M	Asphyxiation	6·74	92	13	Paranoid	20	3	No	No
6	64	M	Myocardial infarction	6·30	25	8	Paranoid	47	3	No	No
7	43	F	Aortic stenosis	6·52	49	6	Paranoid	29	4	No	No
8	40	M	Left ventricular failure	6·68	76	11	Disorganized	32	4	No	No
9	37	M	Asphyxiation	6·72	72	18	Schizoaffective	31	4	Yes	No
10	67	M	Fibrosing alveolitis	5·70	34	13	Paranoid	43	3	No	No
11	69	M	Bronchopneumonia	6·03	63	8	Unknown	28	4	Yes	No
12	28	F	Multiple injuries	6·67	32	12	Paranoid	20	4	No	No
13	83	M	Bronchopneumonia	6·03	50	7	Undifferentiated	26	3	Yes	Yes
14	44	M	Left ventricular failure	6·72	23	6	Paranoid	25	4	No	No
15	69	F	Bronchitis	6·28	52	6	Disorganized	16	3	Yes	No
Mean	55·7			6·33*	54·7*	12·9		29·4			
S.D.	17·4			0·35	22·8	6·7		8·4			
Runwell series[6]											
16	43	M	Myocardial infarction		44		Paranoid	30		No	No
17	75	F	Left ventricular failure		74		Paranoid	57		Yes	No
18	63	M	Bronchopneumonia		37		Paranoid	37		No	No
19	89	F	Myocardial infarction		23		Paranoid	49		No	No
20	62	M	Cardiac rupture		24		Disorganized	24		No	Yes
21	65	M	Myocardial infarction		12		Undifferentiated	21		No	No
22	59	M	Carcinomatosis		60		Undifferentiated	30		No	No
Mean	65·1				39·1			35·4			
S.D.	14·2				22·0			13·2			
Oxford and Runwell series combined											
Mean	58·7				49·7			31·3			
S.D.	16·7				23·2			10·3			

PMI, post mortem interval; *different from controls, $P < 0{\cdot}05$ (unpaired t test).
[1] DSM-III-R criteria, rated from case notes.
[2] Onset of clearcut psychotic symptoms.
[3] Rated on a scale from 0 (none) to 4 (prolonged, high doses). All cases except case 14 were on medication at death.
[4] Electroconvulsive shock ever administered.
[5] Insulin coma therapy ever administered.
[6] Brain pH and medication history not known for the Runwell series. Their fixation time in formalin was 19–22 years.

Table 2. *Hippocampal neuronal density*

	Left		Right	
	Controls ($N = 17$)	Schizophrenics ($N = 15$)	Controls ($N = 18$)	Schizophrenics ($N = 14$)
Dentate gyrus	73·7 (20·3)	79·6 (18·0)	80·7 (19·9)	85·6 (20·9)
CA4	24·7 (5·3)	26·0 (8·6)	22·6 (4·5)	25·4 (6·5)
CA3	50·2 (11·3)	49·5 (10·5)	44·4 (7·1)	55·4 (15·8)*
CA1	39·6 (8·3)	42·3 (6·6)	35·6 (8·1)	43·6 (8·4)*
Subiculum	18·6 (5·0)	18·0 (4·4)	17·2 (6·1)	18·8 (4·4)

Values are mean (S.D.) neurons per unit volume (0·00042 mm^3 in dentate gyrus and 0·0016 mm^3 in other subfields). *$P < 0{\cdot}01$ compared to controls.

schizophrenics show a similar number of correlations as the controls, albeit affecting different pairs of subfields. In particular, the correlations involving the dentate gyrus which are seen in the controls are lost. They are replaced by positive correlations involving CA4, CA3, CA1 and subiculum. In both hippocampi of the schizophrenics, there is a negative correlation between

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Table 3. *Inter-hippocampal correlations of neuronal density between homolateral subfields*

	Controls ($N = 17$)		Schizophrenics ($N = 21$)	
	R	*P*	*R*	*P*
Left DG–right DG	0·55	< 0·02	0·30	NS
Left CA4–right CA4	0·55	< 0·02	0·66	< 0·001
Left CA3–right CA3	−0·36	NS	0·56	< 0·01
Left CA1–right CA1	0·28	NS	0·85	< 0·0001
Left subiculum–right subiculum	0·01	NS	0·55	< 0·01

R values are Pearson coefficients, *P* values are two-tailed; NS, not significant.

Table 4. *Intra-hippocampal correlations of neuronal density between subfields*

	Left				Right			
	Controls ($N = 17$)		Schizophrenics ($N = 22$)		Controls ($N = 18$)		Schizophrenics ($N = 21$)	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
DG–CA4	0·61	< 0·01	−0·17	NS	−0·30	NS	−0·05	NS
DG–CA3	0·65	< 0·01	0·01	NS	−0·35	NS	0·25	NS
DG–CA1	0·67	< 0·01	−0·28	NS	−0·08	NS	−0·20	NS
DG–subiculum	0·12	NS	−0·45	< 0·05	0·00	NS	−0·59	< 0·005
CA4–CA3	0·36	NS	0·75	< 0·0001	0·28	NS	0·49	< 0·05
CA4–CA1	0·63	< 0·01	0·64	< 0·001	0·20	NS	0·61	< 0·002
CA3–CA1	0·28	NS	0·56	< 0·03	0·03	NS	0·30	NS
CA1–subiculum	0·02	NS	0·51	< 0·02	0·11	NS	0·33	NS

R values are Pearson coefficients, *P* values are two–tailed. Pairs of subfields which showed no significant correlations in any column are omitted. Some data in the controls are taken from Zaidel *et al.* (1995).

dentate gyrus and subiculum which is not seen in controls.

Neuronal density declined with age at death in the left subiculum of controls ($R = -0{\cdot}59$, $N = 17$, $P < 0{\cdot}02$), and in the right dentate gyrus of schizophrenics ($R = -0{\cdot}48$, $N = 14$, $P < 0{\cdot}05$). Neuronal density was not significantly related to agonal state, post mortem interval, fixation time (within the Oxford series), or age of onset of schizophrenia; neither did it differ according to clinical subtype of schizophrenia, or in those with a history of ECT or insulin coma therapy (data not shown). For 10 cases and eight controls we had data on the relative synaptic density of hippocampal subfields as indicated by the abundance of synaptophysin (Eastwood & Harrison, 1995); no relationships were seen between synaptic and neuronal density (data not shown). We did not attempt to relate neuronal density to antipsychotic exposure since this was extensive in all cases (Table 1*b*); previous studies have found no association between cortical neuronal density and medication history (Arnold *et al.* 1995; Selemon *et al.* 1995). We did not inspect our data for possible sex differences given the small sample size and the paucity of female schizophrenics.

DISCUSSION

Involvement of the hippocampal formation in schizophrenia has been advocated on pathological (Kovelman & Scheibel, 1984; Falkai & Bogerts, 1986; Jakob & Beckmann, 1986; Falkai *et al.* 1988; Crow *et al.* 1989; Jeste & Lohr, 1989; Altshuler *et al.* 1990; Arnold *et al.* 1991, 1995; Benes *et al.* 1991; Arnold *et al.* 1995) and other (Roberts, 1963; Kerwin & Murray, 1992; Tamminga *et al.* 1992; Venables, 1992) grounds. This region is also the site where the pathology of schizophrenia appears most asymmetrical, at least with regard to a left-sided enlargement of the temporal horn of the lateral ventricle (Crow *et al.* 1989; Crow, 1990) and possibly in terms of the cytoarchitectural changes (Jakob &

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Beckmann, 1986; Jeste & Lohr, 1989; Arnold *et al.* 1991; Falkai & Bogerts, 1993). Our study focused on the hippocampus for these reasons, and also because its circuitry is unique within the cerebral cortex, with each subfield having a well defined cytoarchitecture and characteristic pattern of connections (Duvernoy 1988; Amaral & Insausti, 1990). This circuitry encouraged us not only to measure neuronal density itself, but also its correlations between ipsilateral and homolateral subfields, as a putative index of the relationships between them (Zaidel *et al.* 1993, 1995). Such correlations are orthogonal to the usual group-wise statistical analyses and may provide novel insights into the relationships between parts of the same structure. We discovered an increase of neuronal density in schizophrenia in the right hippocampus (Table 2) as well as an altered pattern of inter- (Table 3) and intra- (Table 4) hippocampal neuronal density correlations. These findings extend the evidence for hippocampal pathology in schizophrenia, and for a disease process which interacts with and interferes with normal cerebral asymmetries.

Methodological considerations

Like other conventional morphometric methods, our technique allows relative neuronal density to be measured reliably (see Ma *et al.* 1995), but it does not inform about the number of neurons present since we do not know if the hippocampi in our control and schizophrenic groups were of identical size or proportions. Thus, although the increased neuronal density (Table 2) may be indicative of an increased neuronal number, it could instead reflect an unchanged number of neurons in a smaller hippocampus occurring due to shrinkage of the neuropil. These possibilities could be distinguished by a stereological study in which accurate volumetric measurements of each hippocampal subfield were made (West, 1993). Nevertheless, it seems unlikely that a difference in hippocampal size in schizophrenia could entirely explain the present results, since such an artefact would have not only to affect the right hippocampus selectively, but be limited mainly to CA3 and CA1 subfields (Table 2). In fact, two post mortem studies have found no difference in the size of the right hippocampus or its components in schizophrenia (Altshuler *et al.* 1990; Heckers *et al.* 1990); where reductions have been reported they either affect the left hippocampus (Falkai & Bogerts, 1986; Heckers *et al.* 1991) or are bilateral (Jeste & Lohr, 1989; Bogerts *et al.* 1990*b*). Thus, although we cannot establish whether the increased neuronal density is or is not accompanied by a change in neuronal number, we would suggest that our data do indicate that at least one standard cytoarchitectural parameter, the packing density of neurons, is altered in the right hippocampus in schizophrenia. It is also difficult to think of an artefactual explanation for the altered hippocampal neuronal density correlations found in the schizophrenics (Tables 3 and 4), discussed below.

The second potential confounder is that the neurons measured may not be representative of all neurons in that subfield, since the probability of a neuron being sampled is affected by its size and perhaps by its spatial orientation. However, there is no reason why we are likely to have consistently sampled a different population of neurons in the cases compared to the controls, especially since preliminary work on this material shows no correlation between neuronal density and neuronal size or orientation in either hippocampus (Zaidel *et al.* 1996). Regardless, such considerations emphasize that unbiased stereological methods will be valuable for clarifying and extending our findings, and we hope that our data encourage their application despite their considerable tissue and labour requirements.

Apart from the morphometric method employed, neuronal counts in human brain can be affected by age, perimortem factors, concurrent neuropathological changes (which are common in schizophrenics; Bruton *et al.* 1990; Harrison 1995*a*), post mortem interval, and by the mode of fixation and processing (Haug *et al.* 1984; Coleman & Flood, 1987; Benes *et al.* 1991). Hence our decision to exclude the Runwell series from the neuronal density comparisons because we had reason to suspect that the latter factors might confound the data. Within the Oxford series, none of the variables appeared to account for the differences observed in the schizophrenics compared to the controls. Parenthetically, the main conclusions of the study are not significantly affected by the inclusion or exclusion of the Runwell cases: if they are retained for the neuronal density analyses, the

increase in right CA3 and right CA1 in schizophrenics remains, while the trends for a higher neuronal density in right CA4 and right subiculum become significant, as does the small increase in left CA1 (Table 2). If the Runwell cases are omitted, the intra-and inter- hippocampal neuronal density correlations seen when all the schizophrenics are grouped together (Tables 3 and 4) are not markedly altered.

Increased right hippocampal neuronal density in schizophrenia

There have been several previous investigations of hippocampal neuronal density in schizophrenia. In a study of the left hippocampus, Falkai & Bogerts (1986) found that neuronal density was unaltered but that there was a reduced number of neurons in some subfields of their schizophrenic cases. Jeste & Lohr (1989) reported that schizophrenia was associated with decreased neuronal density, more apparent in the left than the right hippocampus. In contrast to these findings, recent papers have concluded that hippocampal neuronal density and/or neuronal number are unchanged in schizophrenia; these comprise a stereological study of left and right hippocampus (Heckers *et al.* 1991), and studies where left and right hippocampal data were pooled (Arnold *et al.* 1995) or where the hemisphere was not stated (Benes *et al.* 1991).

Given the existing findings, our neuronal density data (Table 2) in left hippocampus are in keeping with the majority of the literature and bolster the conclusion that it is not altered in schizophrenia. Conversely, our discovery of higher neuronal density in right CA1 and CA3 in schizophrenics was novel and unexpected. Although our sample was relatively large, replication of the present result in another brain series is clearly needed to confirm its robustness. In support of our finding, however, it is of note that increased neocortical neuronal density has been reported in schizophrenia (Selemon *et al.* 1995) and a similar trend was observed in some hippocampal subfields by Falkai & Bogerts (1986) and Arnold *et al.* (1995). Moreover, several neurodevelopmental disorders, notably autism (Bauman, 1991), dyslexia (Galaburda *et al.* 1985), Rett's syndrome (Bauman *et al.* 1995) and Williams' syndrome (Galaburda *et al.* 1994), demonstrate increased hippocampal or neocortical neuronal density allied with other cytoarchitectural abnormalities. Human neocortical neuronal density is high early in development and then falls (Leuba & Garey, 1987; Amunts *et al.* 1995; Rabinowicz *et al.* 1996). Recent data suggest that the same trajectory applies in the hippocampus (Kuchna 1994; Arnold & Trojanowski, 1996). The decline occurs mainly late in gestation and in infancy, through a combination of neuropil growth and neuronal death (see O'Kusky & Colonnier, 1982; Carlson *et al.* 1988; Granger *et al.* 1995). Given these considerations, our data are consistent with the prevailing theory of an early developmental pathogenesis for schizophrenia, wherein increased hippocampal neuronal density is one manifestation of the failure to complete cortical maturation. Since formation of the hippocampal cytoarchitecture is under both genetic (Vaughn *et al.* 1977; Boss *et al.* 1987; Nowakowski, 1991; Rorke, 1994) and environmental (Madeira *et al.* 1992; Miller *et al.* 1993; Morgane *et al.* 1993) control, our data are neutral with regard to the aetiology of the developmental abnormality underlying schizophrenia. We cannot explain why the neuronal density increase was lateralized to the right hippocampus, merely suggest that it is indicative of a three-way interaction between the schizophrenia disease process, the factors determining neuronal density, and those producing cytoarchictural cerebral asymmetry.

No relationship was seen between the clinical subtype of schizophrenia and neuronal density, neither was there evidence for a bimodal distribution of neuronal density within the schizophrenic group (data not shown). While the number of cases is small once subdivisions are attempted, these negative findings support the view that the structural pathology of schizophrenia differs in severity rather than kind between cases (Roberts & Bruton, 1990).

Altered hippocampal neuronal density correlations in schizophrenia

Human neural circuitry can only be investigated indirectly. A variety of strategies have been adopted for structural imaging (Karbe *et al.* 1995), functional imaging (Mettler *et al.* 1984; Horwitz *et al.* 1986; Friston *et al.* 1993) electrophysiology (Wilson *et al.* 1991), neuroanatomy (Miklossy *et al.* 1991), and neuropathology (Pearson *et al.* 1985; Samuel *et al.*

1994; Nagy *et al.* 1995). We suggest that neuronal density correlations come into a similar category, providing a marker of the inter-relationship or inter-dependence of the areas concerned. However, the correlations are unlikely to reflect the strength of direct anatomical connections, for two reasons. First, since they occur both for pairs of subfields that have large monosynaptic pathways between them (such as dentate gyrus–CA4 and CA3–CA1) and those that do not (such as dentate gyrus–subiculum and CA4–CA1; Table 4). Secondly, we found no consistent correlation between neuronal density in a subfield and the synaptic density, as represented by synaptophysin (Eastwood & Harrison, 1995), in the subfields to which those neurons principally project. Instead, the neuronal density correlations probably reflect factors operating differentially upon the subfields, such as extrinsic afferent connections or persistent patterns of synaptic activity. Whatever the explanation, the clear differences in neuronal density correlations between the left and right hippocampus of normal subjects, and between schizophrenics and controls, indicates that the correlations may be a useful parameter to measure in studies of cytoarchitectural lateralization. They should, however, be viewed as exploratory and subject to the same conceptual and statistical limitations as other correlational analyses (see Ford, 1986; Katz *et al.* 1996). The development of additional approaches to neural circuitry in post mortem human brain research will be valuable (Crick & Jones, 1993).

Table 3 shows that the inter-hippocampal neuronal density correlations are different in the schizophrenics compared with the normal subjects. In the latter, only dentate gyrus and CA4 show these correlations, perhaps reflecting the limited inter-hippocampal connectivity in primates (Amaral *et al.* 1984). Schizophrenics retain the CA4–CA4 correlation and gain them between left and right CA3, CA1 and subiculum. In the respect that the correlations are indicative of the degree of interaction between the hippocampi, these differences are in keeping with theories of altered inter-hemispheric integration in the disease (Doty, 1989; David, 1994). In a similar vein, the right-sided neuronal density increases (Table 2) may be reconciled with suggestions of predominant left-sided involvement in schizophrenia by proposing that the altered inter-hippocampal correlations indicate the existence of aberrant or exuberant commissural connections that interfere with normal left hippocampal functioning (Randall, 1983; Goodman, 1989). An increase in the size or fibre content of the dorsal hippocampal commissure, which is thought to convey most of the residual interhippocampal axons in humans (Gloor et al. 1993), might accompany these findings in schizophrenia.

Two differences were noted in the pattern of intra-hippocampal neuronal density correlations in the schizophrenics (Table 4). First, in normal subjects, correlations are seen between several pairs of subfields in the left hippocampus but not in the right, whereas schizophrenics show correlations bilaterally. Indeed, the correlations are virtually identical in the two hippocampi of the schizophrenics, including the negative one between dentate gyrus and subiculum. This finding implies reduced hippocampal cytoarchitectural asymmetry in schizophrenia. Secondly, although the number of neuronal density correlations in the left hippocampus is similar in schizophrenics as in controls, they relate to different pairs of subfields. Therefore, although overall the changes in the right hippocampus are more striking in this study, the cytoarchitecture of the left hippocampus should not be considered entirely unaffected, at least as indicated by the pattern of neuronal density correlations.

During ontogeny, commissural (Innocenti, 1995) and ipsilateral (Webster *et al.* 1991) cortical connectivity undergoes considerable modifications and pruning. Thus, the altered neuronal density correlations in schizophrenia may, like the increased hippocampal neuronal density discussed above, be indicative of an earlerier neurodevelopmental disturbance.

Finally, the differences in cytoarchitectural organization in schizophrenia implied by the altered neuronal density correlations may be specific to the hippocampus or, as other data suggest (e.g. Selemon *et al.* 1995; Akbarian *et al.* 1996), be part of a widespread change in the cerebral cortex. It will be difficult to distinguish between these possibilities since other cortical regions do not lend themselves readily to correlational analyses. It would be of greatest interest in the entorhinal region, in light of the neuropathological evidence for its involvement

in schizophrenia (Jakob & Beckmann, 1986; Falkai *et al*. 1988; Arnold *et al*. 1991; Falkai & Bogerts, 1993) and because it is normally histologically asymmetrical (Heinsen *et al*. 1994).

Conclusion

Our results extend the evidence for the occurrence of cytoarchitectural hippocampal abnormalities of presumed developmental origin in schizophrenia. Furthermore, the data provide histological support for the view that schizophrenia interacts in a complex fashion with cerebral asymmetries. As well as replication and investigation for possible sex differences (see Zaidel *et al*. 1994), measurement of other parameters such as neuronal size, orientation and clustering, and the application of stereological techniques, are needed to build up a fuller picture of the cytoarchitectural profile of schizophrenia. Utilization of both hemispheres and the full range of morphometric approaches will optimize the speed and the robustness of progress into this most elusive aspect of the disease.

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