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INVITED REVIEW

The neuropathology of schizophrenia
A critical review of the data and their interpretation

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Summary
Despite a hundred years' research, the neuropathology of schizophrenia remains obscure. However, neither can the null hypothesis be sustained—that it is a 'functional' psychosis, a disorder with no structural basis. A number of abnormalities have been identified and confirmed by meta-analysis, including ventricular enlargement and decreased cerebral (cortical and hippocampal) volume. These are characteristic of schizophrenia as a whole, rather than being restricted to a subtype, and are present in first-episode, unmedicated patients. There is considerable evidence for preferential involvement of the temporal lobe and moderate evidence for an alteration in normal cerebral asymmetries. There are several candidates for the histological and molecular correlates of the macroscopic features. The probable proximal explanation for decreased cortical volume is reduced neuropil and neuronal size, rather than a loss of neurons. These morphometric changes are in turn suggestive of alterations in synaptic, dendritic and axonal organization, a view supported by immunocytochemical and ultrastructural findings. Pathology in subcortical structures is not well established, apart from dorsal thalamic nuclei, which are smaller and contain fewer neurons. Other cytoarchitectural features of schizophrenia which are often discussed, notably entorhinal cortex heterotopias and hippocampal neuronal disarray, remain to be confirmed. The phenotype of the affected neuronal and synaptic populations is uncertain. A case can be made for impairment of hippocampal and corticocortical excitatory pathways, but in general the relationship between neurochemical findings (which centre upon dopamine, 5-hydroxytryptamine, glutamate and GABA systems) and the neuropathology of schizophrenia is unclear. Gliosis is not an intrinsic feature; its absence supports, but does not prove, the prevailing hypothesis that schizophrenia is a disorder of prenatal neurodevelopment. The cognitive impairment which frequently accompanies schizophrenia is not due to Alzheimer's disease or any other recognized neurodegenerative disorder. Its basis is unknown. Functional imaging data indicate that the pathophysiology of schizophrenia reflects aberrant activity in, and integration of, the components of distributed circuits involving the prefrontal cortex, hippocampus and certain subcortical structures. It is hypothesized that the neuropathological features represent the anatomical substrate of these functional abnormalities in neural connectivity. Investigation of this proposal is a goal of current neuropathological studies, which must also seek (i) to establish which of the recent histological findings are robust and cardinal, and (ii) to define the relationship of the pathological phenotype with the clinical syndrome, its neurochemistry and its pathogenesis.

Keywords: Alzheimer's disease; cytoarchitecture; morphometry; synapse; psychosis

Abbreviations: DLPFC = dorsolateral prefrontal cortex; 5-HT = 5-hydroxytryptamine; VBR = ventricle : brain ratio

Introduction
A hundred years ago, Kraeplin described the syndrome now called schizophrenia. He was convinced that it was an organic brain disease, and it was his colleague Alzheimer who began the neuropathological investigation before moving to a more fruitful research area. Subsequently the subject has continued to fascinate and exasperate researchers in equal measure, generating more heat than light and being notable for memorable quotes rather than durable data. The most

infamous, that schizophrenia is the 'graveyard of neuropathologists' (Plum, 1972), was a statement which, together with critical reviews of the work up to that time (Corsellis, 1976), marked the nadir of the field.

Over the past 20 years, signs of life have appeared in the graveyard, reflected in the return of schizophrenia to the latest edition of *Greenfield's Neuropathology* (Roberts *et al.*, 1997), having been omitted from the previous two. The significant progress which has been made began with CT findings, followed by MRI and by post-mortem studies using improved methodologies and new techniques. The progress allowed Ron and Harvey (1990) to charge that '[to] have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of twentieth century medicine'. In a similar vein, Weinberger (1995) stated '20 years ago, the principal challenge for schizophrenia research was to gather objective scientific evidence that would implicate the brain. That challenge no longer exists.' On the other hand, it is undoubtedly an overstatement to claim that there is 'an avalanche of consistent . . . evidence of microscopic pathology' (Bloom, 1993); the current challenge is to establish the characteristics of the pathological changes (Shapiro, 1993; Chua and McKenna, 1995). This review summarizes the present state of knowledge, including the issues of hemispheric asymmetry, dementia in schizophrenia, neurodevelopment and neurochemistry. An integration of structure with function is attempted, with elaboration of the proposal that the neuropathology of schizophrenia represents the anatomical substrate of aberrant functional connectivity.

Review coverage and methodology

The review focuses on the key points of agreement and of controversy affecting the robustness of the data and their interpretation. It comprises a comprehensive survey of contemporary (post-1980) neurohistopathological research, with restricted coverage of earlier work and of related fields such as neuroimaging and neurochemistry.

The sources for the review consisted of: (i) papers identified using a range of keywords for on-line searches of Medline, PsycLIT and *Biological Abstracts* (last search, October 1998), (ii) weekly scanning of *Reference Update* (deluxe edition, customized to 350 journals) from 1989 to October 1998 using a similar range of keywords, and (iii) an extensive reprint collection and perusal of each article's reference list. Only data published in full papers in peer-reviewed English-language journals were considered for inclusion.

Clinical features of schizophrenia

Schizophrenia remains a clinical diagnosis, based upon the presence of certain types of delusions, hallucinations and thought disorder (McKenna, 1994; Andreasen, 1995). These 'positive' symptoms are often complemented by the 'negative' symptoms of avolition, alogia and affective flattening. The criteria of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), used for most research studies, require symptoms to have been present for at least 6 months; there must also be impaired personal functioning, and the symptoms must not be secondary to another disorder (e.g. depression, substance abuse). The peak age of onset is in the third decade, occurring a few years earlier in males than in females (Hafner *et al.*, 1998). The course and outcome are remarkably variable, but better than sometimes believed; only a minority of patients have a chronic, deteriorating course, though many others have enduring symptoms or functional deficits (Davidson and McGlashan, 1997; Huber, 1997). There is a significant excess of mortality from suicide and natural causes (Brown, 1997). The lifetime risk of schizophrenia is just under 1% (Cannon and Jones, 1996). It has a predominantly genetic aetiology, but no chromosomal loci or genes have been unequivocally demonstrated (McGuffin *et al.*, 1995).

The diagnosis of schizophrenia is reliable, but as with any other syndromal diagnosis there are problems establishing its validity and debate as to where its external and internal boundaries should be drawn (Jablensky, 1995). These issues have implications for research into its pathological basis just as they do for the search for the causative genes (Kennedy, 1996). For example, is schizophrenia a categorical or dimensional construct? What is the relationship of schizoaffective and schizotypal disorders to schizophrenia? Are there separate pathological counterparts of schizophrenic subsyndromes or specific symptoms, given that each has its own pathophysiological correlates (Liddle *et al.*, 1992; Silbersweig *et al.*, 1995; Sabri *et al.*, 1997)? The delineation of type I and type II schizophrenia was an important, if now rather outmoded, attempt to address this issue (Crow, 1980). As an analogy, is schizophrenia—neuropathologically speaking—comparable to dementia, to a specific dementing disorder or to a domain of memory impairment? Comparisons with epilepsy are also pertinent (Bruton *et al.*, 1994; Stevens, 1997). Clearly, the prospects for success in finding the neuropathology of schizophrenia depend on which of these parallels proves closest. These issues are touched upon later in the review but for the most part, predicated on the design of the studies being discussed, schizophrenia is considered as a single entity.

Structural imaging in schizophrenia

The cardinal findings

Contemporary research into the structural basis of schizophrenia can be traced to the landmark report of Johnstone *et al.* (1976) describing dilatation of the lateral ventricles in a small group of patients with chronic schizophrenia. This CT finding, which was consistent with earlier pneumoencephalographic data (Haug, 1982), has been followed by a large number of CT and MRI studies with ever-improving resolution and sophistication of analysis. The key findings are as follows.

There is enlargement of the lateral and third ventricles in schizophrenia. The magnitude has been estimated in several ways. Comprehensive reviews of lateral ventricle : brain ratio (VBR) indicate an increase of 20–75% (Daniel *et al.*, 1991; van Horn and McManus, 1992), whilst a meta-analysis of CT studies up to 1989 showed a VBR effect size (*d*) of 0.70, corresponding to a 43% non-overlap between cases and controls (Raz and Raz, 1990). A median 40% increase in ventricular size was reported in a recent systematic review of volumetric MRI studies (Lawrie and Abukmeil, 1998). Of note, VBR in schizophrenia follows a single normal distribution, indicating that structural pathology, at least in terms of this parameter, is not restricted to an 'organic' subgroup but is present to a degree in all cases (Daniel *et al.*, 1991). Conversely, despite the group differences, there is a significant overlap between subjects with schizophrenia and controls for every imaging (and neuropathological) parameter to be discussed. For this reason, as well as the fact that changes such as increased VBR and decreased brain size lack diagnostic specificity, it is worth emphasizing that schizophrenia cannot be diagnosed using either a brain scan or a microscope. It remains a moot point whether this situation will change.

The ventricular enlargement is accompanied by a loss of brain tissue averaging 3% (Lawrie and Abukmeil, 1998) with $d = -0.26$ (Ward *et al.*, 1996). However, no consistent correlation has been observed between the degree of ventricular enlargement and that of the decreased brain volume. This may reflect the relative sizes of the ventricles and cerebral cortex, such that a given percentage change in ventricular volumes corresponds to a much smaller percentage change in cortical substance (and hence one which is difficult to measure accurately). Or it may suggest that the ventricular enlargement is due to disproportionate reductions in unidentified, localized periventricular structures, or even that independent pathological processes are at work.

Evidence for regional pathology has emerged from volumetric MRI studies which indicate larger reductions in the temporal lobe overall (~8%) and in medial temporal structures (hippocampus, parahippocampal gyrus and amygdala, 4–12%; Lawrie and Abukmeil, 1998) present after correction for total brain volume (Nelson *et al.*, 1998). In support of this conclusion, the brain size reduction is significantly greater in the axial ($d = -0.60$) than the sagittal ($d = -0.09$) plane (Ward *et al.*, 1996), suggesting a relative decrease in mediolateral breadth and a greater involvement of regions typically included in axial slices, such as the temporal lobes. Grey matter appears to be reduced more than white matter (Lawrie and Abukmeil, 1998; Zipursky *et al.*, 1998).

Valuable information has come from imaging studies of monozygotic twins discordant for schizophrenia. In virtually all pairs the affected twin has the larger ventricles (Reveley *et al.*, 1982; Suddath *et al.*, 1990) and smaller cortical and hippocampal size (Noga *et al.*, 1996). In the MRI study of Suddath *et al.* (1990), the affected twin was distinguishable even more clearly by the smaller size of his or her temporal lobes and hippocampi. The discordant monozygotic twin study design allows two conclusions to be drawn. First, that structural abnormalities are a consistent finding in schizophrenia, their identification being aided by controlling for genetic influences on neuroanatomy (Bartley *et al.*, 1997) and, to a large degree, for variation due to environmental factors. Secondly, that the alterations are associated with expression of the schizophrenia phenotype rather than merely with the underlying, shared genotype. Family studies support this interpretation, in that schizophrenics have bigger ventricles and smaller brains than do their unaffected relatives (Honer *et al.*, 1994; Sharma *et al.*, 1998; Silverman *et al.*, 1998). However, the relatives who are obligate carriers [i.e. unaffected by schizophrenia but transmitting the gene(s)] have larger ventricles than relatives who are not; moreover, both groups of relatives have larger ventricles and smaller brain structures than equivalent control subjects from families without schizophrenia (Lawrie *et al.*, 1999; Sharma *et al.*, 1998). These data indicate that a proportion of the structural pathology of schizophrenia may be a marker of genetic liability to the disorder. (By inference, the same applies to the accompanying histological features, though there have been no post-mortem studies of relatives.)

Imaging of subcortical structures in schizophrenia has produced few clear findings. One firm conclusion is that the striatal enlargement reported in some studies is, unlike the other changes, due to antipsychotic medication (Chakos *et al.*, 1994; Keshavan *et al.*, 1994*b*). Indeed, in unmedicated and first-episode patients, caudate volumes are probably reduced (Keshavan *et al.*, 1998; Shihabuddin *et al.*, 1998). Two MRI studies suggest that the thalamus is smaller in schizophrenia (Andreasen *et al.*, 1994; Buchsbaum *et al.*, 1996); though this evidence is weak (Portas *et al.*, 1998), it is complemented by relatively strong neuropathological data (see below). Finally, reports of structural abnormalities in the cerebellum in schizophrenia (Katsetos *et al.*, 1997) merit further investigation, given accumulating evidence for its pathophysiological involvement in the disorder (Andreasen *et al.*, 1996).

Progression, heterogeneity and clinicopathological correlations

Knowledge of the timing of the brain changes is essential for understanding their aetiological significance. Ventricular enlargement and cortical volume reduction are both present in first-episode cases (Degreef *et al.*, 1992; Lim *et al.*, 1996; Gur *et al.*, 1998; Whitworth *et al.*, 1998; Zipursky *et al.*, 1998), excluding the possibility that they are a consequence of chronic illness or its treatment. Moreover, adolescents and young adults who are at high risk of developing schizophrenia by virtue of their family history show enlarged ventricles (Cannon *et al.*, 1993) and smaller medial temporal lobes (Lawrie *et al.*, 1999), suggesting that the brain pathology

precedes the onset of symptoms (Harrison, 1999*a*) and supporting a neurodevelopmental model of schizophrenia (discussed below).

It is less clear what happens to the structural pathology after symptoms emerge. Neither VBR nor cortical volume reduction, nor the smaller size of the medial temporal lobe (Marsh *et al.*, 1994), correlate with disease duration, suggesting that the alterations are largely static. However, longitudinal studies, which now span 4–8 years, are equivocal. Some support the view that there is no progression (Jaskiw *et al.*, 1994; Vita *et al.*, 1997) whilst others find continuing divergence from controls (DeLisi *et al.*, 1997*a*; Nair *et al.*, 1997; Gur *et al.*, 1998). This may reflect a subgroup of subjects with a deteriorating course (Davis *et al.*, 1998) or who receive high doses of antipsychotics (Madsen *et al.*, 1998), but other studies have not shown such correlations. Overall, the question whether brain pathology in schizophrenia is progressive or static, or even fluctuating, remains controversial, and has an uncertain relationship with the clinical heterogeneity of the syndrome.

It is uncertain whether sex is a confounder. Greater structural abnormalities in men than women with schizophrenia have been reported (Flaum *et al.*, 1990; Nopoulos *et al.*, 1997), perhaps related to sex differences in clinical and aetiological factors (Tamminga, 1997). However, sex differences have not been found consistently (Lauriello *et al.*, 1997) and they were not apparent in the meta-analysis of Lawrie and Abukmeil (1998).

Numerous correlations have been reported between brain structure and the individual subtypes and symptoms of schizophrenia, but they are less well established than those involving cerebral metabolism (e.g. Buchanan *et al.*, 1993; Gur *et al.*, 1994). One of the few reasonably robust correlations is that between decreased superior temporal gyrus size and the severity of thought disorder and auditory hallucinations (Barta *et al.*, 1990; Shenton *et al.*, 1992; Marsh *et al.*, 1997).

In the rare childhood-onset schizophrenia, similar brain and ventricular abnormalities are observed as in adults (Frazier *et al.*, 1996), with progression of the changes during the early phase of the illness (Rapaport *et al.*, 1997; Jacobsen *et al.*, 1998).

Neuropathological findings in schizophrenia

By 1980, the growing evidence for structural brain changes in schizophrenia provided by CT studies had spurred a return to post-mortem investigations. These have focused on three overlapping areas, which I consider in turn. First, attempts have been made to confirm whether the alterations were replicable in direct measurements of the brain. Secondly, research has sought to clarify the frequency and nature of neurodegenerative abnormalities in schizophrenia, especially to ascertain whether gliosis is present and whether Alzheimer's disease occurs at an increased frequency, as earlier authors had suggested. As will be seen, the results indicate strongly that neurodegenerative processes do not represent the neuropathology of schizophrenia and they cannot explain the smaller brain volume. In the context of these negative findings, the third, and largest, area of research has been to investigate the cytoarchitecture of the cerebral cortex.

Contemporary neuropathological investigations of schizophrenia have, unlike their predecessors, been by and large well designed and appropriately analysed. Their renaissance has coincided with the advent of molecular techniques and computerized image analysis, allowing more powerful and quantitative experimental approaches (Harrison, 1996). Nevertheless, it is worth mentioning three limitations which continue to apply, to varying degrees, to most studies. First, few have been carried out according to stereological principles (Howard and Reed, 1998) and hence are subject to errors and biases which may be particularly important in this instance, given the subtlety of the alterations being sought. Secondly, research groups have tended to use differing methods, measuring different parameters, and have studied different regions of the brain. It is therefore difficult to know whether inconsistent results reflect genuine pathological or anatomical heterogeneity or methodological factors, or are simply contradictory. Thirdly, sample sizes have continued to be small, leading inevitably to both false-positive and false-negative results and meaning that potential complexities, such as diagnosis × gender interactions and discrete clinicopathological correlations, have barely been addressed.

Macroscopic features

The CT and MRI findings in schizophrenia are partly but not unequivocally corroborated by measurements of the brain post-mortem. The key positive autopsy studies report a decrease in brain weight (Brown *et al.*, 1986; Pakkenberg, 1987; Bruton *et al.*, 1990), brain length (Bruton *et al.*, 1990) and volume of the cerebral hemispheres (Pakkenberg, 1987). Concerning regional alterations, there are several post-mortem replications of the imaging findings, especially enlargement of the lateral ventricles (Brown *et al.*, 1986; Pakkenberg, 1987; Crow *et al.*, 1989), reduced size of temporal lobe structures (Bogerts *et al.*, 1985, 1990*b*; Brown *et al.*, 1986; Falkai and Bogerts, 1986; Falkai *et al.*, 1988; Jeste and Lohr, 1989; Altshuler *et al.*, 1990; Vogeley *et al.*, 1998), decreased thalamic volume (Pakkenberg, 1990, 1992; Danos *et al.*, 1998) and enlarged basal ganglia (Heckers *et al.*, 1991*a*). Whilst this convergence of autopsy and *in vivo* results is encouraging, there are negative post-mortem reports for each parameter (Rosenthal and Bigelow, 1972; Bogerts *et al.*, 1990*b*; Heckers *et al.*, 1990; Pakkenberg, 1990; Arnold *et al.*, 1995*a*; for further details, see Arnold and Trojanowski, 1996; Dwork, 1997).

As a meta-analysis of the post-mortem studies is not feasible, the robustness of the positive findings and the source of the discrepancies remain unclear. In any event, the reliance upon such measurements has been diminished by MRI, which

allows most of the indices to be measured accurately in life. The real value of neuropathological studies, and hence the primary focus here, is now in elucidating the microscopic and molecular features of schizophrenia which remain beyond the reach of neuroimaging.

Coincidental pathological abnormalities

A high proportion (~50%) of brains from patients with schizophrenia contain non-specific focal degenerative abnormalities, such as small infarcts and white matter changes (Stevens, 1982; Jellinger, 1985; Bruton *et al.*, 1990; Riederer *et al.*, 1995). These are presumably coincidental, in that they are variable in distribution and nature, do not affect the clinical picture (Johnstone *et al.*, 1994) and in some instances are documented as having occurred long after the onset of symptoms. The issue is whether the frequency of lesions is a sign that the brain in schizophrenia is vulnerable to neurodegenerative and vascular impairment, perhaps in conjunction with chronic antipsychotic treatment, or whether the finding is merely a collection artefact (see below). A related point is that ~3–5% of cases diagnosed as schizophrenia turn out to be due to an atypical presentation of a neurological disorder, such as temporal lobe epilepsy, syphilis, Wilson's disease and metachromatic leucodystrophy (Davison, 1983; Johnstone *et al.*, 1987). One school of thought argues that cases in both these categories should be included in neuropathological studies of schizophrenia since there are no grounds a priori for exclusion, and these 'outliers' may provide crucial and unexpected clues—and if not will at least help establish the pathological heterogeneity of the syndrome (Heckers, 1997; Stevens, 1997). On the other hand, the omission of subjects with coincidental pathologies and those with a neurological schizophrenia-like disorder allows 'true' schizophrenia to be examined (Bruton *et al.*, 1990; Dwork, 1997); an argument in favour of the latter strategy is that the excess of miscellaneous lesions in schizophrenia may be an artefact of how tissue is acquired: researchers can afford to pick and choose control brains, but cases with schizophrenia are scarce and hence more likely to be included even if there is a complex or incomplete medical history. Note that the cytoarchitectural findings to be discussed later all come from brain series which were 'purified' to varying extents.

Gliosis

Stevens (1982), in keeping with observations going back as far as Alzheimer (Nieto and Escobar, 1972; Fisman, 1975), found fibrillary gliosis (reactive astrocytosis) in ~70% of her cases of schizophrenia. The gliosis was usually located in periventricular and subependymal regions of the diencephalon or in adjacent basal forebrain structures. As gliosis is a sign of past inflammation (Kreutzberg *et al.*, 1997), this finding supported a number of aetiopathogenic scenarios for schizophrenia involving infective, ischaemic, autoimmune or neurodegenerative processes.

Because of these implications for the nature of the disease and its position as the first major neuropathological study of schizophrenia in the modern era, Stevens' paper has been important and influential. However, many subsequent investigations of schizophrenia have not found gliosis (Roberts *et al.*, 1986, 1987; Stevens *et al.*, 1988*b*; Casanova *et al.*, 1990; Arnold *et al.*, 1996). The illuminating study of Bruton *et al.* (1990) found that, when gliosis was present, it was in the cases exhibiting separate neuropathological abnormalities mentioned above. These findings together suggest strongly that gliosis is not a feature of the disease but is a sign of coincidental or superimposed pathological changes (Harrison, 1997*b*). Though this view is now widely accepted, it is subject to several caveats. First, the recognition and definition of gliosis is not straightforward (Miyake *et al.*, 1988; da Cunha, 1993; Halliday *et al.*, 1996). Secondly, several of the key studies have determined gliosis by GFAP (glial fibrillary acidic protein) immunoreactivity (Roberts *et al.*, 1986, 1987; Arnold *et al.*, 1996), but the sensitivity of this method for detection of chronic gliosis relative to the traditional Holzer technique has been questioned (Stevens *et al.*, 1988*a*, 1992). An alternative method sometimes used, that of counting or sizing glia in Nissl-stained material (Benes *et al.*, 1986; Pakkenberg, 1990; Rajkowska *et al.*, 1998), though reassuringly reaching the same negative conclusion in schizophrenia, has the problem of distinguishing astrocytes from small neurons and other cell types. Thirdly, recent studies have focused on the cerebral cortex rather than on the diencephalic regions where the gliosis of Stevens (1982) were concentrated. Since lesions do not always produce gliosis in distant areas, even those heavily interconnected, it cannot be assumed that a lack of gliosis in the cortex precludes it in other structures (Anezaki *et al.*, 1992; Jones, 1997*a*). Finally, the subgroup of schizophrenics who are demented (see below) do have an increased number of GFAP-positive astrocytes (Arnold *et al.*, 1996). Inclusion of such cases in post-mortem studies, where the cognitive status of individuals is usually unknown, may therefore contribute to the uncertainty concerning gliosis in schizophrenia.

The gliosis debate has been fuelled by the implications it has for the nature of schizophrenia. The gliotic response is said not to occur until the end of the second trimester *in utero* (Friede, 1989). Hence an absence of gliosis is taken as prima facie evidence for an early neurodevelopmental origin of schizophrenia (discussed below), whereas the presence of gliosis would imply that the disease process occurred after that time and raise the possibility that it is a progressive and degenerative disorder. In this respect the lack of gliosis is an important issue. Unfortunately, there are problems with this dichotomous view of the meaning of gliosis. Despite the widely cited time point at which the glial response is said to begin, it has not been well investigated (Roessmann and Gambetti, 1986; Aquino *et al.*, 1996) and may be regionally variable (Ajtai *et al.*, 1997). Hence it is prudent not to time

Table 1 *Neuronal morphometric findings in schizophrenia*

	Cases/ controls	Methods and parameters	Main findings in schizophrenia
(**A**) Temporal lobe			
Kovelman and Scheibel, 1984	10/8	Nissl stain; HC neuron orientation and density	More variability of orientation (disarray) at CA2/CA1 and CA1/subiculum borders. Density unchanged
Jakob and Beckmann, 1986	64/0*	Nissl stain; qualitative neuron organization in ERC and ventral insula	Cytoarchitectonic abnormalities (e.g. abnormal lamina II islands; displaced neurons) in a third of cases†
Falkai and Bogerts, 1986	13/11	Nissl stain; HC neuron number and density	Decreased neuron number. Neuron density unchanged
Altshuler *et al*., 1987	7/6	Nissl stain; HC neuron orientation	No differences
Falkai *et al*., 1988	13/11	Nissl stain; ERC neuron number	Decreased (–37%)
Christison *et al*., 1989	17/32	Nissl stain; neuron orientation; shape and size at CA1/subiculum border	No differences
Jeste and Lohr, 1989	13/16*	Nissl stain; HC neuron density	Decreased (~30%) in CA3 and CA4
Pakkenberg, 1990	12/12	Nissl stain, physical disector, neuron number in basolateral amygdala	No differences
Arnold *et al*., 1991*a*	6/16	Nissl stain; qualitative ERC neuron organization	Neuron disorganization and displacement
Benes *et al*., 1991*b*	14/9	Nissl stain; HC neuron size, density and orientation	Decreased size (~15%). Density and variability of orientation unchanged
Conrad *et al*., 1991	11/7	Nissl stain; HC neuron orientation	More disarray at CA1/CA2 and CA2/CA3 borders
Heckers *et al*., 1991*b*	13/13	Nissl stain, optical disector; HC neuron number and density	No differences
Akbarian *et al*., 1993*b*	7/7	ICC; NADPHd neurons in MTL and BA 21	Decreased (–40%) in MTL and GM of BA 21; increased (>40%) in deep WM of BA 21
Pakkenberg, 1993*b*	8/16	Giemsa stain, optical disector; neuron number and neuron density in temporal lobe	Density increased (29%), number unchanged (as lobar volume reduced)
Arnold *et al*., 1995*a*	14/10	Nissl stain; neuron size, density and orientation in HC and ERC	Decreased size (–10%). Density and variability of orientation unchanged
Akil and Lewis, 1997	10/10	Nissl stain; neuron organization in ERC	No differences
Arnold *et al*., 1997*a*	8/8	Nissl stain, spatial point pattern analyses of ERC neuron organization	Abnormal clustering and higher 'density' in lamina III; lower density in lamina II
Cotter *et al*., 1997	8/11	ICC; number, staining intensity and orientation of MAP-2 HC neurons	Increased staining of non-phosphorylated MAP-2 in subiculum and CA1. Neuron number and orientation unchanged
Jønsson *et al*., 1997	4/8	Nissl stain; neuron density and orientation in HC	Density decreased and correlated with more variable orientation in CA1–CA3
Krimer *et al*., 1997*b*	14/14	Nissl stain, optical disector; neuron number, density and laminar volumes of ERC	No differences. No evidence for cytoarchitectural abnormalities. Trend for decreased neuron number and density
Zaidel *et al*., 1997*a*	14/17	Nissl stain; HC neuron size, shape and orientation	Decreased size (–7%) and altered shape (less pyramidal) in some subfields. Orientation variability unchanged
Zaidel *et al*., 1997*b*	14/18	Nissl stain; HC neuron density	Increased in right CA3 (22%) and CA1 (25%). Altered correlations between subfields
Benes *et al*., 1998	11/10*	Nissl stain; HC neuron number, density and size	Decreased number and density of CA2 interneurons
(**B**) Frontal lobe			
Benes *et al*., 1986	10/9	Nissl stain; neuron density and size in BA 4, 10 and 24	Decreased density (~–25%) in lamina III of BA 4, lamina V of BA 24, deep laminae of BA 10. Size unchanged (laminae III and VI measured)
Benes and Bird, 1987	10/10	Nissl stain, spatial arrangement of neurons in BA 4, 10 and 24	Smaller and more dispersed neuron clusters in lamina II of BA 24
Benes *et al*., 1991*a*	18/12	Nissl stain; neuron density in BA 10 and 24	Small interneurons decreased, mainly lamina II (–30%); pyramidal neurons increased (33%) in lamina V of BA 24

Table 1 *continued*

	Cases/ controls	Methods and parameters	Main findings in schizophrenia
Akbarian *et al*., 1993*a*	5/5	ICC; NADPHd neuron density in BA 9	Decreased in superficial WM, increased in deep WM
Pakkenberg, 1993*b*	8/16	Giemsa stain, optical disector; neuron number in frontal lobe	No differences
Akbarian *et al*., 1995	10/10	Nissl stain; neuron density in BA 9	No differences
Arnold *et al*., 1995*a*	14/10	Nissl stain; neuron density and size in lamina III of BA 4 and lamina V of BA 17	No differences
Daviss and Lewis, 1995	5/5	ICC; CB and CR interneuron density in BA 9/46	Increased (50%) CB neurons
Selemon *et al*., 1995	16/19*	Nissl stain, 3D-counting box; neuron density in BA 9 and 17	Pyramidal and non-pyramidal neuron density increased by 17% in BA 9 and 10% in BA 17
Akbarian *et al*., 1996	20/20	ICC; MAP-2, NADPHd and NPNF neurons in WM of BA 46	All decreased in superficial WM; MAP-2 and NPNF neurons increased in deep WM
Anderson *et al*., 1996	5/5	ICC; MAP-2 neuron density and size in WM of BA 9/46	Increased (44%) density overall; no change in deep WM
Beasley and Reynolds, 1997	18/22	ICC; PV neuron density in BA 10	Decreased, mainly in laminae III and IV (–35%)
Kalus *et al*., 1997	5/5	Nissl stain and PV ICC; neuron density in BA 24	Increased (40%) in lamina V. No change in total neuron density
Rajowska *et al*., 1998	9/10*	Methods as Selemon *et al*., 1995; neuron size, and density × size, in BA 9 and 17	Decreased neuron size (4–9%) in BA 9; large lamina IIIc neurons most affected, and fewer of them. Density of small neurons increased (70–140%). No changes in BA 17
Selemon *et al*., 1998	10/9*	As Selemon *et al*., 1995, in BA 46	Increased (21%). Lamina II thinner (–13%)
(**C**) Subcortical areas			
Thalamus			
Pakkenberg, 1990	12/12	Nissl stain, physical disector; neuron number in mediodorsal nucleus	Fewer (–40%) neurons
Danos *et al*., 1998	12/14	Nissl stain and PV ICC; neuron density in anteroventral nucleus	Decreased (–35%) PV neuron density
Other regions			
Averback, 1981	14/29*	Various stains; neurons in substantia nigra	Swollen, degenerating, lipid-laden neurons
Reyes and Gordon, 1981	12/8	Nissl stain; Purkinje cell density	Decreased (–39%) per unit length; increased (+39%) surface density
Arendt *et al*., 1983	3/14	Nissl stain; neuron density in nucleus basalis and globus pallidus	No differences
Bogerts *et al*., 1983	6/6*	Nissl stain; neuron density in substantia nigra	Decreased in medial part
Lohr and Jeste, 1988	15/13	Nissl stain; neuron density and size in locus coeruleus	No differences
Pakkenberg, 1990	12/12	Nissl stain; physical disector; neuron number in nucleus accumbens and ventral pallidum	Fewer (–48%) neurons in nucleus accumbens. No change in ventral pallidum
Garcia-Rill *et al*., 1995	9/5*	NADPH ICC for cholinergic mesopontine neurons; TH ICC for noradrenergic locus coeruleus neurons	Increased mesopontine neuron number (60%). No change in locus coeruleus
Beckmann and Lauer, 1997	9/9	Nissl stain, optical disector; striatal neuron number	Increased (18%), caudate > putamen
Bernstein *et al*., 1998	10/13*	NOS ICC; optical disector; neuron number and density in hypothalamus	Decreased number (–25%) and density (–31%) in paraventricular nucleus
Briess *et al*., 1998	9/6*	Nissl stain; optical disector; mammillary body size, neuron number and neuron density	Enlarged (+34%); neuron density decreased (–34%); unchanged neuron number
Tran *et al*., 1998	14/13	Nissl stain; Purkinje cell size and density in vermis	Cells smaller (–8%). Unchanged density

BA = Brodmann area; CB = calbindin; CR = calretinin; ERC = entorhinal cortex; GM = grey matter; HC = hippocampus; ICC = immunocytochemistry; MAP = microtubule-associated protein; NADPHd = nicotinamide-adenine dinucleotide phosphate-diaphorase; NOS = nitric oxide synthase; NPNF = non-phosphorylated epitope of 160 and 200 kDa neurofilament; PV = parvalbumin; TH = tyrosine hydroxylase; WM = white matter. *Psychiatric control group(s) also used. †Additional data in Jakob and Beckmann (1989).

Table 2 *Synaptic, axonal and dendritic findings in schizophrenia*[†]

	Cases/ controls	Methods and parameters	Main findings in schizophrenia
(**A**) Hippocampal formation			
Arnold *et al.*, 1991*b*	6/5*	MAP-2 and MAP-5 ICC.	Decreased staining, mainly dendritic, in subiculum and ERC
Browning *et al.*, 1993	7/7	IB for synaptophysin and synapsin I and IIb	Decreased synapsin I (–40%)
Eastwood *et al.*, 1995*a*	7/13	ISH and ICC for synaptophysin	Decreased synaptophysin mRNA (–30%) except in CA1
Eastwood and Harrison, 1995	11/14	IAR for synaptophysin	Decreased (–25%)
Goldsmith and Joyce, 1995	11/8*	Modified Timm's stain for mossy fibres	Decreased intensity of staining
Adams *et al.*, 1995	10/11*	Modified Timm's stain for mossy fibres	No differences
Harrison and Eastwood, 1998	11/11	ISH and IAR for complexin I and II	Both decreased, complexin II > I
Young *et al.*, 1998	13/13	ELISA, IB and ICC for SNAP-25 and synaptophysin	Decreased SNAP-25
(**B**) Frontal and temporal lobe			
Benes *et al.*, 1987	7/7	ICC; NF-labelled axons in BA 24	Increased density (25%) of vertically orientated axons
Aganova and Uranova, 1992	5/7	EM; synaptic density in BA 24	Increased axospinous (225%), decreased axodendritic (–40%) synapses
Perrone-Bizzozero *et al.*, 1996	6/6	IB for synaptophysin in BA 9, 10, 17 and 20	Decreased (30–50%) in BA 9, 10 and 20
Benes *et al.*, 1997	10/15	ICC; TH fibres in BA 10 and 24	Shift of terminals from large to small neurons in lamina II of BA 24
Gabriel *et al.*, 1997	19/16*	IB for synaptophysin, SNAP-25 and syntaxin in BA 7, 8, 20 and 24	All increased in BA 24 (~25%). Unchanged in BA 7, 8 and 20
Honer *et al.,* 1997	18/24	As Gabriel *et al.* (1997) in BA 24	Increased syntaxin (30%)
Glantz and Lewis, 1997	10/10*	ICC for synaptophysin in BA 9, 46 and 17	Decreased (15%) in BA 9, 46. Unchanged in BA 17
Tcherepanov and Sokolov, 1997	22/10	RT-PCR for synaptophysin and synapsin Ia and Ib mRNAs in BA 21 and 22	Unchanged. (Increased, if comparison limited to the nine cases < 75 years old)
Garey *et al.*, 1998	13/9	Golgi stain; dendritic spines on lamina III pyramidal neurons in BA 38	Decreased density (–60%). Similar finding in BA 11
Thompson *et al.*, 1998	5/7*	IB for SNAP-25 in BA 9, 10, 17 and 20	Decreased in BA 10 (–56%) and BA 20 (–33%); increased in BA 9 (32%); unchanged in BA 17
Woo *et al.*, 1998	15/15*	ICC; density of GABAergic axon terminals in BA 9 and 46	Selective decrease (–40%) of chandelier neuron terminals
(**C**) Other regions			
Striatum			
Roberts *et al.*, 1996	6/6	EM; area of dendritic spines	Smaller (–30%)
Uranova *et al.*, 1996	7/7	EM; synaptic size in left caudate	Larger postsynaptic densities in axospinous synapses
Kung *et al.*, 1998	6/7*	EM; proportions, densities and sizes of different synaptic types	Fewer symmetrical, axodendritic and perforated synapses; more axospinous synapses. No size changes
Corpus callosum			
Nasrallah *et al.*, 1983	18/11*	Silver stain; density of myelinated fibres	No differences
Casanova *et al.*, 1989	11/13	Silver stains; fibre counts	No differences
Highley *et al.*, 1999	26/29	Silver stain; fibre number and density	Decreased number and density in female schizophrenics
Thalamus			
Blennow *et al.*, 1996	19/27	IB for rab-3a	Decreased

ELISA = enzyme-linked immunosorbent assay; EM = electron microscopy; IAR = immunoautoradiography; IB = immunoblotting; ISH = *in situ* hybridization; NF = neurofilament (200 kDa subunit); RT-PCR = reverse transcriptase–polymerase chain reaction; SNAP-25 = 25 kDa synaptosome-associated protein. Other abbreviations as in Table 1. *Psychiatric control group(s) also used. [†]Studies using markers of plasticity rather than structure (e.g. GAP-43, N-CAM) omitted.

the pathology of schizophrenia with spurious accuracy or certainty based upon the available data. Additionally, gliosis is not always demonstrable or permanent after (postnatal) neural injury (Kalman *et al.*, 1993; Dell'Anna *et al.*, 1995; Berman *et al.*, 1998), nor does it accompany apoptosis, another process which hypothetically might be involved in

schizophrenia. Furthermore, it is a moot point whether the subtle kinds of morphometric disturbance to be described in schizophrenia, whenever and however they occurred, would be sufficient to trigger gliosis or other signs of ongoing neurodegeneration (Horton *et al.*, 1993). Thus the lack of gliosis does not mean, in isolation, that schizophrenia must be a neurodevelopmental disorder of prenatal origin; it is merely one argument in favour of that conclusion.

Schizophrenia, its dementia and Alzheimer's disease

Cognitive impairment has been a neglected feature of schizophrenia. Its importance is now being appreciated clinically as a major factor contributing to the failure to rehabilitate some patients despite relief of their psychotic symptoms (Green, 1996), and as being a putative therapeutic target (Davidson and Keefe, 1995). Neuropsychological abnormalities are demonstrable in first-episode patients (Hoff *et al.*, 1992; Saykin *et al.*, 1994; Kenny *et al.*, 1997) and premorbidly (Jones, 1997*b*; Russell *et al.*, 1997), and though their progression remains unclear (Bilder *et al.*, 1992; Goldberg *et al.*, 1993; Waddington and Youssef, 1996), in a sizeable minority of chronic schizophrenics their severity warrants the label of dementia (Davidson *et al.*, 1996). There is particular involvement of memory and executive functioning (McKenna *et al.*, 1990; Saykin *et al.*, 1991) against a background of a generalized deficit (Blanchard and Neale, 1994; for review, see David and Cutting, 1994). (As with the neuropathological abnormalities, it is worth pointing out that the mean size of these differences is small. Many individuals with schizophrenia score within the normal range, and some are well above average. On the other hand, there is no evidence that cognitive impairment is limited to a subgroup, and it may be that even in high-functioning subjects there has been a decline from, or failure to attain, their full neuropsychological potential.) The final controversies regarding neurodegenerative processes in schizophrenia concern the neuropathological explanation for the cognitive deficits, and the alleged increased prevalence of Alzheimer's disease in schizophrenia (e.g. Plum, 1972).

The belief that Alzheimer's disease is commoner in schizophrenia, regardless of cognitive status, seems to have originated from two German papers in the 1930s (Corsellis, 1962). It was supported by three retrospective, uncontrolled studies (Buhl and Bojsen-Møller, 1988; Soustek, 1989; Prohovnik *et al.*, 1993) and the suggestion that antipsychotic drugs promote Alzheimer-type changes (Wisniewski *et al.*, 1994). However, corroborating Corsellis' opinion (Corsellis, 1962), a meta-analysis (Baldessarini *et al.*, 1997) and additional methodologically sound studies show conclusively that Alzheimer's disease is not commoner than expected in schizophrenia (Arnold *et al.*, 1998; Murphy *et al.*, 1998; Niizato *et al.*, 1998; Purohit *et al.*, 1998). Even amongst elderly schizophrenics with unequivocal, prospectively assessed dementia (mean Mini-Mental State score = 12), detailed immunocytochemical analyses find no evidence for Alzheimer's disease or any other neurodegenerative disorder (Arnold *et al.*, 1996, 1998). In keeping with this negative conclusion, apolipoprotein E4 allele frequencies are unchanged (Arnold *et al.*, 1997*b*; Powchik *et al.*, 1997; Thibaut *et al.*, 1998) and cholinergic markers are preserved (Arendt *et al.*, 1983; Haroutunian *et al.*, 1994) in schizophrenia. Moreover, the evidence as a whole does not support the view that antipsychotic drugs predispose to neurofibrillary pathology (Baldessarini *et al.*, 1997; Harrison *et al.*, 1997*b*).

How, therefore, is the cognitive impairment of schizophrenia explained? One possibility is that it is a more severe manifestation of whatever substrate underlies schizophrenia itself rather than resulting from the superimposition of a separate process. Or it may be that the brain in schizophrenia is rendered more vulnerable to cognitive impairment in response to a normal age-related amount of neurodegeneration, or even that the pathological findings so far discovered actually relate to the cognitive impairment rather than to the psychotic features by which the disorder is defined. A final, speculative suggestion is that the gliosis observed in demented schizophrenics (Arnold *et al.*, 1996) is a sign of an as yet unrecognized novel neurodegenerative disorder. These possibilities cannot be distinguished at present since few neuropsychologically evaluated patients have been studied neuropathologically; inclusion of subjects with comorbid schizophrenia and mental retardation may be valuable when addressing the issue (Doody *et al.*, 1998).

The cytoarchitecture of schizophrenia

Since neurodegenerative abnormalities are uncommon in, and probably epiphenomenal to, schizophrenia, the question is raised as to what the pathology of the disorder is, and how the macroscopic findings are explained at the microscopic level. This brings us to the heart of recent schizophrenia neuropathology research, which has been the increasingly sophisticated measurement of the cortical cytoarchitecture. The focus has been mainly on the extended limbic system [hippocampus, dorsolateral prefrontal cortex (DLPFC) and cingulate gyrus], encouraged by suggestions that psychotic symptoms originate in these regions (Stevens, 1973; Torrey and Peterson, 1974).

Table 1 summarizes the morphometric investigations in which neuronal parameters such as density, number, size, shape, orientation, location and clustering have been determined. Table 2 summarizes the studies of synapses, dendrites and axons, evaluated either ultrastructurally or indirectly using immunological and molecular markers. Both tables are subdivided by brain region. Only the major findings are listed; details such as laterality effects are omitted. In the following sections the main themes of this literature are discussed, although even the choice of what to highlight is problematic given that controversy surrounds nearly every point.

Studies of neurons

Cytoarchitectural abnormalities in entorhinal cortex. An influential paper reported the presence of various abnormalities in the cytoarchitecture and lamination of the entorhinal cortex (anterior parahippocampal gyrus) in schizophrenia (Jakob and Beckmann, 1986). The changes were prominent in lamina II, with a loss of the normal clustering of the constituent pre-α cells, which appeared shrunken, misshapen and heterotopic. Despite extensions (Jakob and Beckmann, 1989) and partial replications (Arnold *et al.*, 1991*a*), the findings remain questionable for several reasons, which are elaborated because of the importance attributed to them in the neurodevelopmental model of schizophrenia. First, no normal control group was used; the comparisons were made with brains from 10 patients with other psychiatric or neurological disorders. Whilst this criticism does not apply to the study of Arnold *et al.* (1991*a*), both are limited by the lack of objective criteria for the cytoarchitectural disturbance. The later work of Arnold *et al.* (1995*a*, 1997*a*) overcomes this deficiency in different ways and provides some further evidence for a disturbance in the location, clustering and/or size of entorhinal cortex neurons, though of much lesser magnitude and frequency than reported by Jakob and Beckmann. The most serious problem is that none of these studies have fully allowed for the heterogeneous cytoarchitecture of the entorhinal cortex (Beall and Lewis, 1992; Insausti *et al.*, 1995) and its variation between individuals (Heinsen *et al.*, 1996; Krimer *et al.*, 1997*a*; West and Slomianka, 1998). For example, as Akil and Lewis (1997) point out, Jakob and Beckmann (1986) sampled their material based on external landmarks which may shift relative to the entorhinal cortex in schizophrenia, resulting in differences in the rostrocaudal location of the sections, which could account for their findings. Notably, the two studies that most closely attend to the issue of anatomical complexity within the entorhinal cortex found no differences in its cytoarchitecture in schizophrenia (Akil and Lewis, 1997; Krimer *et al.*, 1997*a*).

Disarray of hippocampal pyramidal neurons. A second parameter of cytoarchitectural disturbance in schizophrenia, a disarray of hippocampal pyramidal neurons, has also been given prominence disproportionate to the strength of the data. Normally, pyramidal neurons in Ammon's horn are aligned, as in a palisade, with the apical dendrite orientated towards the stratum radiatum. Kovelman and Scheibel (1984) reported that this orientation was more variable and even reversed in schizophrenia, hence the term 'neuronal disarray'. The disarray was present at the boundaries of CA1 with CA2 and subiculum. The basic finding of greater variability of hippocampal neuronal orientation was extended in subsequent studies from the same group (Altshuler *et al.*, 1987; Conrad *et al.*, 1991) and independently (Jønsson *et al.*, 1997; Zaidel *et al.*, 1997*a*). However, none of these studies constitutes true replication. Conrad *et al.* (1991) came closest, but located the disarray at the boundaries of CA2 rather than CA1; Altshuler *et al.* (1987) found no differences between cases and controls—merely a correlation between the degree of disarray and the severity of psychosis within the schizophrenic group; the disarray in the small study of Jønsson *et al.* (1997) was in the central part of each CA field, and Zaidel *et al.* (1997*a*) found no overall difference in orientation but, in a *post hoc* analysis, found an asymmetrical variability limited to a part of CA3. Furthermore, there are three entirely negative studies (Christison *et al.*, 1989; Benes *et al.*, 1991*b*; Arnold *et al.*, 1995*a*). Thus, even a charitable overview of the data would accept that the site and frequency of hippocampal neuronal disarray in schizophrenia remains uncertain, while a sceptical view would be that the phenomenon has not been unequivocally demonstrated. Certainly, as with the entorhinal cortex abnormalities, it seems inappropriate to place too much interpretative weight on such insecure empirical foundations.

Location of cortical subplate neurons. The subplate is a key structure in the formation of the cortex and the orderly ingrowth of thalamic axons (Allendoerfer and Shatz, 1994). Some of the subplate neurons persist as interstitial neurons in the subcortical white matter and contribute to cortical and corticothalamic circuits. Stimulated by the entorhinal and hippocampal cytoarchitectural findings suggestive of aberrant neuronal migration, subplate neurons have been studied in schizophrenia, since changes in the density and distribution of these neurons would probably be a correlate of such a disturbance. Using nicotinamide-adenine dinucleotide phosphate-diaphorase histochemistry as a marker, these neurons were found to be distributed more deeply in the frontal and temporal cortex white matter in schizophrenics than in controls (Akbarian *et al*., 1993*a*, *b*). A subsequent survey using additional markers and a larger sample confirmed the observation of fewer interstitial neurons in superficial white matter compartments of DLPFC in schizophrenia (Akbarian *et al.*, 1996).

These data are more convincing than the reports of entorhinal cortex dysplasias and hippocampal neuron disarray, and the studies are noteworthy for being embedded in the known cellular biology of cortical development. Nevertheless, it would be premature to consider maldistribution of surviving subplate neurons, and by inference aberrant neuronal migration, to be an established feature of schizophrenia. First, Dwork (1997) has drawn attention to the doubtful statistical significance of the original results (Akbarian *et al*., 1993*a*, *b*). Secondly, in the follow-up study (Akbarian *et al*., 1996) the abnormalities were milder and less prevalent, and their statistical significance was enhanced by the apparent retention of the original cases. Thirdly, considerable variation in the abundance of interstitial neurons has been found between individuals and between frontal and temporal white matter (Rojiani *et al*., 1996), suggesting that sample sizes larger than those employed to date may be necessary to identify clearly any alterations associated with schizophrenia. Finally,

as shown in Table 1B, Anderson *et al.* (1996) found essentially the opposite result from that of Akbarian *et al.* (1996). Further investigations are therefore essential to corroborate the potentially key observations of Akbarian and colleagues.

Hippocampal and cortical neuron density and number. A loss of hippocampal neurons is another oft-stated feature of schizophrenia. In fact only two studies have found reductions in neuron density (Jeste and Lohr, 1989; Jønsson *et al.*, 1997) and one reported a lower number of pyramidal neurons (Falkai and Bogerts, 1986). In contrast, several have found no change in density (Kovelman and Scheibel, 1984; Falkai and Bogerts, 1986; Benes *et al.*, 1991*b*; Arnold *et al.*, 1995*a*) and one found a localized increase (Zaidel *et al.*, 1997*b*). Since none of these studies were stereological, their value is limited by the inherent weaknesses of neuron counts when measured in this way (Mayhew and Gundersen, 1996)—although not to the extent that they should be discounted (Guillery and Herrup, 1997). Nevertheless, the fact that the single stereological study that has been carried out found no difference in neuronal number or density in any subfield (Heckers *et al.*, 1991*a*) supports the view that there is no overall change in the neuron content of the hippocampus in schizophrenia. In this context, single reports of altered neuronal density restricted to a specific neuronal type or subfield (Zaidel *et al.*, 1997*a*; Benes *et al.*, 1998) must be replicated before discussion is warranted.

The prefrontal cortex has also been examined. A careful stereologically based study found an increased neuronal density in DLPFC (Selemon *et al.*, 1995, 1998), and a similar trend was seen for the whole frontal lobe by Pakkenberg (1993*b*). The higher packing density identified by Selemon and colleagues affected small and medium-sized neurons more than large pyramidal ones. Other neuronal density studies in the prefrontal cortex have not produced consistent findings (Table 1B). For example, Benes *et al.* (1986, 1991*a*) identified a variety of lamina-, area- and cell type-specific differences, whilst unaltered neuronal density has been reported in the motor cortex (Arnold *et al.*, 1995*a*) and DLPFC (Akbarian *et al.*, 1995). These discrepancies may be due to anatomical heterogeneity or may be the consequence of differences in the stereological purity of the studies. The total number of neurons in the frontal cortex is not altered in schizophrenia (Pakkenberg, 1993*b*), which probably reflects the net effect of anatomical variation in the neuronal density changes within the frontal lobe and/or the trend for cortical grey matter to be thinner in schizophrenia, which compensates for the increased packing density of neurons therein (Pakkenberg, 1987; Selemon *et al.*, 1998; Woo *et al.*, 1998).

Hippocampal and cortical neuronal size. With the advent of user-friendly image analysis it has become relatively straightforward to measure the size of the cell body of neurons, either by tracing around the perikaryal outline or by measuring the smallest circle within which the soma fits. Three studies, each counting large numbers of neurons, have now identified a smaller mean size of hippocampal pyramidal neurons in schizophrenia (Benes *et al.*, 1991*a*; Arnold *et al.*, 1995*a*; Zaidel *et al.*, 1997*a*). Although different individual subfields reached significance in the latter two studies, the same downward trend was present in all CA fields and in the subiculum. The non-replications comprise Christison *et al.* (1989) and Benes *et al.* (1998), perhaps because measurements were limited to a restricted subset of neurons. Smaller neuronal size has also been reported in DLPFC, especially affecting large lamina IIIc neurons (Rajkowska *et al.*, 1998). A degree of anatomical specificity to the size reductions is apparent, since this study found no differences in the visual cortex of the same cases, in agreement with the unchanged cell size found in that region as well as in the motor cortex by Arnold *et al.* (1995*a*) and Benes *et al.* (1986).

Neuronal morphometric changes in other regions. Outside the cerebral cortex, consistent cyto-architectural data are limited to the thalamus (Table 1C). Pakkenberg (1990) found markedly lower numbers of neurons in the dorsomedial nucleus, which projects mainly to the prefrontal cortex. A similar finding was observed in the anteroventral nucleus, which also has primarily prefrontal connections, the significant deficit affecting parvalbumin-immunoreactive cells, a marker for thalamocortical neurons (Danos *et al.*, 1998). Whether similar changes occur in thalamic nuclei not intimately related to cortical regions implicated in schizophrenia remains to be determined.

In summary, a range of differences in neuronal parameters have been reported to occur in schizophrenia. The abnormalities most often taken to be characteristic of the disorder—disarray, displacement and paucity of hippocampal and cortical neurons—are in fact features which have not been clearly demonstrated. This undermines attempts to date the pathology of schizophrenia to the second trimester *in utero* based on their presence (see below). In contrast, decreased neuron size, especially affecting neurons in the hippocampus and DLPFC, has been shown fairly convincingly; some studies suggest that the size reduction is accompanied by increased neuron density. The other relatively robust cytoarchitectural abnormality in schizophrenia is in the dorsal thalamus, which is smaller and contains fewer neurons.

Studies of synapses and dendrites. Synaptic abnormalities represent a potential site for significant pathology in schizophrenia which would be undetectable using standard histological approaches. The term 'synaptic pathology' is used here to denote abnormalities in axons and dendrites in addition to those affecting the synaptic terminals themselves.

Practical issues. Qualitative studies identified a range of ultrastructural abnormalities of neuronal and synaptic elements in schizophrenia (Tatetsu *et al.*, 1964; Miyakawa *et al.*, 1972; Averback, 1981; Soustek, 1989; Ong and Garey,

1993). However, because of the difficulties and limitations of electron microscopy in post-mortem human brain tissue, especially for quantitative analysis, much contemporary research into synaptic pathology in schizophrenia has adopted a complementary approach whereby the expression and abundance of proteins concentrated in presynaptic terminals, such as synaptophysin, are used as proxies for synapses. This approach has been validated in several experimental and disease states (Masliah and Terry, 1993; Eastwood *et al.*, 1994*a*). For example, in Alzheimer's disease, synaptophysin mRNA and protein levels correlate inversely with the clinical and pathological severity of dementia (Terry *et al.*, 1991; Heffernan *et al.*, 1998). Note, however, that although synaptic protein measurements are widely interpreted as reflecting synaptic density, an assumption almost certainly true in neurodegenerative disorders, in principle changes in synaptic protein expression could instead be due to alterations in synaptic size or number of vesicles per terminal, or to a structural abnormality of the presynaptic region. Such possibilities should not be ignored in schizophrenia, given that ultrastructural features of this kind were suggested by some of the electron microscopy studies mentioned above.

Hippocampal formation. Synaptic protein determinations in the hippocampal formation (hippocampus and parahippocampal gyrus) in schizophrenia have fairly consistently found levels to be reduced (Table 2A), although not all reach statistical significance for reasons other than just inadequate sample size. First, subfields may be differentially affected (Eastwood and Harrison, 1995; Eastwood *et al.*, 1995*a*), and localized changes may be masked if homogenized tissue is used. Secondly, the synaptic proteins studied change to varying degrees, probably reflecting their concentration in differentially affected synaptic populations. For example, synaptophysin, which is present in all synapses, shows only slight reductions (Browning *et al.*, 1993; Eastwood and Harrison, 1995; Eastwood *et al.*, 1995*a*), whereas SNAP-25 (Young *et al.*, 1998) and complexin II (Harrison and Eastwood, 1998), which are both concentrated in subsets of synapses, show greater decrements. Furthermore, complexin II is primarily expressed by excitatory neurons, unlike complexin I, which is mainly present in inhibitory neurons and is less affected in schizophrenia (Harrison and Eastwood, 1998). Thus, these data suggest a particular involvement of excitatory pathways in this region, a conclusion in keeping with neurochemical studies of the glutamatergic system (see below). A final example of current attempts to dissect out the nature of hippocampal synaptic involvement in schizophrenia is provided by a study of the expression of the neuronal growth-associated protein-43 (GAP-43), a marker of synaptic plasticity (Benowitz and Routtenberg, 1997). A loss of hippocampal GAP-43 mRNA was found, suggesting that hippocampal synapses may be remodelled less actively in schizophrenia (Eastwood and Harrison, 1998).

Less attention has been paid to postsynaptic elements of the hippocampal circuitry. However, dendritic abnormalities have been reported, with decreased and aberrant expression of the dendritic microtubule-associated protein MAP-2 in some subfields (Arnold *et al.*, 1991*b*; Cotter *et al.*, 1997).

Neocortex. Two studies have found synaptophysin to be reduced in DLPFC in schizophrenia (Perrone-Bizzozero *et al.*, 1996; Glantz and Lewis, 1997). The inferred decrease of presynaptic terminals is complemented by a lower density of dendritic spines (to which many of the synapses are apposed) on layer III pyramidal neurons (Garey *et al.*, 1998). The pattern of synaptophysin alteration is not uniform throughout the cortex, since levels are unchanged in the visual cortex (Perrone-Bizzozero *et al.*, 1996; Glantz and Lewis, 1997) and increased in the cingulate gyrus (Gabriel *et al.*, 1997). The suggestion that there is a discrete profile of synaptic pathology in the cingulate gyrus is noteworthy given the other cytoarchitectural and ultrastructural findings in that region (Tables 1B and 2B), such as increased glutamatergic axons (Benes *et al.*, 1987, 1992*a*) and axospinous synapses (Aganova and Uranova, 1992), and deficits in inhibitory interneurons (Benes *et al.*, 1991*a*) which have not been reported elsewhere. However, further direct comparisons are needed before it can be concluded that the cingulate exhibits a different pattern of pathology.

Thalamus. A marked reduction of the synaptic protein rab3a from the thalamus was found in a large group of schizophrenics compared with controls (Blennow *et al.*, 1996). These data, in concert with the morphometric and imaging findings (Table 1C), highlight the thalamus as meriting active investigation in schizophrenia (Jones, 1997*a*), a somewhat belated return to the one brain region for which the earlier generation of studies had produced potentially meaningful findings (David, 1957).

Striatum. In the striatum, electron microscopy rather than immunocytochemical measurements has continued to be used to investigate synaptic pathology in schizophrenia. Altered sizes and proportions of synapses in the caudate nucleus have been found compared with controls (Table 2C). It is difficult to interpret these findings and integrate them with those in other regions because of the methodological differences and the greater concern about confounding effects of antipsychotic medication in basal ganglia (see below). Nevertheless, they broadly support the view that synaptic organization is altered in schizophrenia.

In summary, synaptic studies in the hippocampus and DLPFC in schizophrenia show decrements in presynaptic markers and, though less extensively studied, in postsynaptic markers too. The simplest interpretation is that these changes reflect a reduction in the number of synaptic contacts formed and received in these areas, bearing in mind the caveat about alternative possibilities such as abnormal synaptic vesicle composition or even dysregulation of synaptic protein gene transcription. In pathogenic terms, the direction of the

synaptic alterations in the hippocampus and DLPFC supports hypotheses of excessive (Keshavan *et al.*, 1994*a*) rather than inadequate (Feinberg, 1982) synaptic pruning in schizophrenia. Since the reductions are not uniform in magnitude or location, it is likely that certain synaptic populations are more affected than others; preliminary evidence suggests glutamatergic synapses may be especially vulnerable in the hippocampus and perhaps the DLPFC, with predominantly GABAergic involvement in the cingulate gyrus. There is a need not only to extend the work (e.g. to include confocal microscopy and to measure additional synaptic proteins) but to integrate it with further Golgi staining and electron microscope investigations directly visualizing synapses and dendrites.

Integrating the neuronal and synaptic pathological findings

Despite the limitations of the neuronal (Table 1) and synaptic (Table 2) data in schizophrenia, there is an encouraging convergence between the two, at least in the hippocampus and DLPFC, from where most data have been obtained (Fig. 1). In particular, the fact that presynaptic and dendritic markers are generally decreased in schizophrenia is in keeping with the finding of smaller neuronal cell bodies, since perikaryal size is proportional to the extent of the dendritic (Hayes and Lewis, 1996; Elston and Rosa, 1998) and axonal (Ho *et al.*, 1992; Pierce and Lewin, 1994) tree. It is also consistent with the findings of increased neuron density, in that dendrites, axons and synapses are the major component of the neuropil and, if the latter is reduced, neurons will pack more closely together (Schlaug *et al.*, 1993). Moreover, there is a correspondence with the results of proton MRS (magnetic resonance spectroscopy) and MRS-imaging studies of the hippocampus and DLPFC in schizophrenia, which have shown reductions in signal for the neuronal marker NAA (*N*-acetyl-aspartate) (Maier *et al.*, 1995; Bertolino *et al.*, 1996; Deicken *et al.*, 1997, 1998), as one would predict if the constituent neurons are on average smaller and have less extensive axonal arborizations. (Given the morphometric findings in schizophrenia, this is a more plausible explanation than attributing the NAA reduction to a lower neuronal density.) Parenthetically, the lowered NAA signal is seen in unmedicated (Bertolino *et al.*, 1998) and first-episode (Renshaw *et al.*, 1995) schizophrenia, as are alterations in ^{31}P-MRS phosphoester signals suggestive of synaptic pathology (Kegeles *et al.*, 1998). These findings imply that the cytoarchitectural abnormalities seen in post-mortem studies, which inevitably are limited to chronic schizophrenia, may also be present at this early stage.

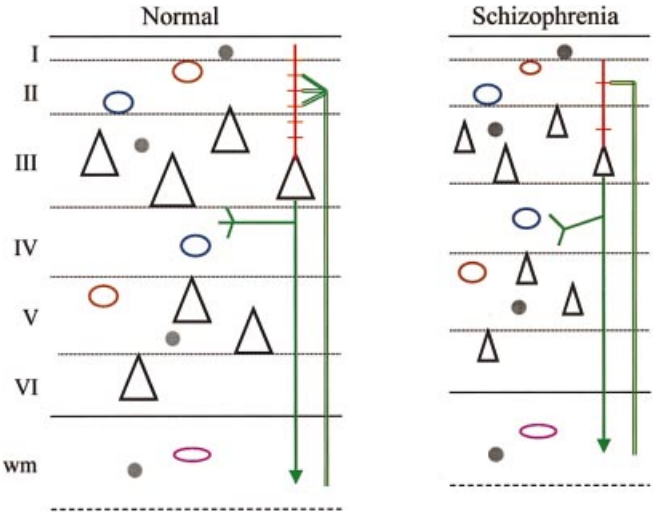

Fig. 1 Schematic cartoon exaggerating the putative cytoarchitectural features of schizophrenia. The grey matter contains an unchanged number of neurons, but the pyramidal neurons (black triangles) are smaller and more densely packed. The cortex is thinner, especially in laminae II and III. The reduced neuron size and increased neuron density are both correlates of a reduced neuropil volume, which in turn reflects abnormalities affecting the axonal (green) and dendritic (red) arborizations of some neurons. For example, there may be less extensive, or otherwise aberrant, synaptic connections formed by incoming corticocortical fibres (hollow green lines, shown as having restricted terminations on dendritic spines, denoted by thin red lines) and by axon collaterals (solid green lines, shown as being shorter and in a different position) of efferent pyramidal neurons. Glia (grey filled circles) are unaffected. Although the figure illustrates the situation in the prefrontal neocortex, a similar diagram could be drawn for the hippocampus. For clarity, possible differences in the distribution and synaptic organization of interneuron subpopulations (blue and brown) and white matter (wm) neurons (purple), as well as the pattern of changes in the cingulate gyrus and subcortical structures, are omitted.

Schizophrenia and cerebral asymmetry

Neuropathological findings have been prominent in maintaining the persistent belief that there is an important interaction between schizophrenia and cerebral asymmetry (Crichton-Browne, 1879). Interest in this question was rekindled by the report that schizophrenia-like psychosis is commoner in temporal lobe epilepsy when the focus is in the left hemisphere (Flor-Henry, 1969), and has been reinforced by the observations in schizophrenia of decreased left parahippocampal width (Brown *et al.*, 1986) and ventricular enlargement limited to the left temporal horn (Crow *et al.*, 1989). Several other recent reports indicate that normal asymmetries are reduced or even reversed in schizophrenia, and that the pathological findings—as well as neuropsychological, neurochemical and electrophysiological abnormalities—are more pronounced in the left hemisphere (Crow, 1997).

Key studies which have been able to address the issue of lateralized pathology in schizophrenia are summarized in Table 3. Though no firm conclusion can be drawn, alterations in normal asymmetries, and a left-sided 'preference' of the pathology, are findings that seem to be more common than one would expect by chance. Insofar as there is a phenomenon

Table 3 *Cerebral asymmetry and the neuropathology of schizophrenia*

	Key positive reports*	Relevant negative reports†
Macroscopic features		
Decreased fronto-occipital torque	Bilder *et al*., 1994; DeLisi *et al*., 1997*b*	DeLisi *et al*., 1997*b*
Decreased size of left superior temporal gyrus	Shenton *et al*., 1992	Flaum *et al*., 1995
Reversal of left > right planum temporale size asymmetry	Falkai *et al*., 1995; Barta *et al*., 1997‡	Kulynych *et al*., 1996
Loss of left > right sylvian fissure length	Falkai *et al*., 1992	
Left parahippocampal thinning	Brown *et al*., 1986§	
Left temporal horn enlargement	Crow *et al*., 1989	
Left medial temporal lobe reductions	Bogerts *et al*., 1990*a*; Pearlson *et al*., 1997	Altshuler *et al*., 1990; Bogerts *et al*., 1990*b*; Nelson *et al*, 1998
Progressive left ventricular enlargement in severe cases	Davis *et al*., 1998	
Cytoarchitectural asymmetries		
Asymmetrical size and shape changes in hippocampal neurons	Zaidel *et al*., 1997*a*	
Increased right hippocampal neuron density	Zaidel *et al*., 1997*b*	
Loss of synaptic protein from left thalamus	Blennow *et al*., 1996	

For additional references see Falkai and Bogerts (1993) and Crow (1997). *With clear evidence for lateralised change (e.g. diagnosis × side interaction on ANOVA). †Studies where the change was found bilaterally. ‡Planum temporale area reduced unilaterally, but volume reduced bilaterally. §Relative to affective disorder controls.

to be explained, two hypotheses exist. Crow's evolving and evolutionary theory is that schizophrenia, cerebral dominance, handedness and language are inextricably and causally linked to each other and to a single gene (Crow, 1990, 1997). Alternatively, altered asymmetry in schizophrenia is viewed as an epiphenomenon of its *in utero* origins, a process which interferes with subsequent brain lateralization (Bracha, 1991; Roberts, 1991). Clarifying how the neuropathology interacts with cerebral asymmetry thus requires not only additional, appropriately designed studies of schizophrenia and other neurodevelopmental disorders, but also a better understanding of the causes and consequences of histological asymmetries *per se* (Galaburda, 1994; Hayes and Lewis, 1996; Anderson and Rutledge, 1996). Interactions between asymmetry, gender and schizophrenia introduce further complexity to the issue (Highley *et al.*, 1998, 1999; Vogeley *et al.*, 1998).

Interpretation of the neuropathology of schizophrenia

Neuropathology and the neurodevelopmental model

The concept of developmental insanity was proposed by Clouston in 1891 (Murray and Woodruff, 1995) and elaborated in neuropathological terms early this century (Southard, 1915). However, it is only in the past decade that a neurodevelopmental origin for schizophrenia has become the prevailing pathogenic hypothesis for the disorder; indeed the principle is now largely unchallenged (Murray and Lewis, 1987; Weinberger, 1987, 1995). The model receives support from various sources, the neuropathological data forming an important component of the evidence (Table 4) (Harrison, 1997*a*; Raedler *et al.*, 1998).

The most influential and specific form of the theory is that the pathology of schizophrenia originates in the middle stage of intrauterine life (Roberts, 1991; Bloom, 1993; Roberts *et al.*, 1997). An earlier timing is excluded since overt abnormalities in the structure and cellular content of the cerebral cortex would be expected if neurogenesis were affected, whilst the absence of gliosis is taken to mean that the changes must have occurred prior to the third trimester. The conclusion that, by default, the pathological process originates in the second trimester is bolstered by reference to certain of the cytoarchitectural abnormalities of schizophrenia. However, this 'strong' form of the neurodevelopmental model is weak on two grounds. First, because of the limitations of the absence-of-gliosis argument mentioned earlier. Secondly, the types of cytoarchitectural disturbance adduced in favour are those of neuronal disarray, heterotopias and malpositioning suggestive of aberrant migration (Kovelman and Scheibel, 1984; Jakob and Beckmann, 1986; Arnold *et al.*, 1991*a*; Akbarian *et al.*, 1993*a*, *b*), processes which occur at the appropriate gestational period; yet, as described above, none of these cytoarchitectural abnormalities has been unequivocally established to be a feature of schizophrenia. By comparison, the other cytoarchitectural findings, such as alterations in neuronal size and synaptic and dendritic organization, could well originate much later, being susceptible to ongoing environmental influences (Jones and Schallert, 1994; Moser *et al.*, 1994; Saito *et al.*, 1994; Andrade *et al.*, 1996; Kolb and Whishaw, 1998), ageing (Huttenlocher, 1979; Braak and Braak, 1986; Masliah *et al.*, 1993; de Brabander *et al.*, 1998) and perhaps also to genetic factors (Vaughn *et al.*, 1977; Williams *et al.*, 1998).

Other versions of the neurodevelopmental theory of

Table 4 *Key points of evidence for a neurodevelopmental origin of schizophrenia*

Neuropathological evidence
Ventricular enlargement and decreased cortical volume present at onset of symptoms, if not earlier
Presence and nature of cytoarchitectural abnormalities
Absence of gliosis and other neurodegenerative features
Increased prevalence of abnormal septum pellucidum (Shioiri *et al*., 1996; Kwon *et al*., 1998)
Other evidence
The environmental risk factors are mostly obstetric complications (Geddes and Lawrie, 1995)
Children destined to develop schizophrenia in adulthood show neuromotor, behavioural and intellectual impairment (Jones, 1997*b*)
Increased prevalence of abnormal dermatoglyphics and minor physical anomalies (Buckley, 1998)
Experimental neonatal lesions have delayed effects on relevant behavioural and neurochemical indices

For additional references see text.

schizophrenia postulate additional or alternative abnormalities in processes such as cell adhesion, myelination and synaptic pruning (e.g. Keshavan *et al.*, 1994*a*; Benes *et al.*, 1994; Akbarian *et al.*, 1996; Arnold and Trojanowski, 1996; Lewis, 1997) or allow for a mixture of maturational and degenerative processes (e.g. Murray *et al.*, 1992; Garver, 1997). Overall, a parsimonious view is that the extant cytoarchitectural abnormalities and lack of gliosis are indicative merely of an essentially neurodevelopmental as opposed to neurodegenerative disease process, rather than as pointing directly to a particular mechanism or timing. It is only by consideration of the pathological features in conjunction with the other evidence (Table 4) that a strong case for a significant early childhood, including foetal, component to schizophrenia can be made. Even then, it is unknown whether neurodevelopmental deviance is either necessary or sufficient. Moreover, any such model has a problem explaining the onset and outcome of the disorder: how is an abnormality in the cortical cytoarchitecture, present since early in life and presumably persistent, reconciled with the onset of symptoms in adulthood and a typically relapsing and remitting course thereafter? Regarding the explanation for the timing of psychosis, one can take refuge in the similar difficulties in explaining some epilepsies, and point to the fact that pathological and behavioural effects can clearly be long delayed after relevant neonatal lesions (Beauregard *et al.*, 1995; Lipska and Weinberger, 1995; Saunders *et al.*, 1998). It can also be argued that the expression of psychotic symptoms requires a brain which has reached a certain stage of biochemical and anatomical maturation. Explaining the course of the disorder is more difficult and entirely speculative. It may be hypothesized that the aberrant circuitry is rendered 'unstable' (e.g. is more susceptible to neurochemical fluctuations which precipitate recurrence) or is unable to undergo normal plasticity in response to age-related and environmental factors (Stevens, 1992; DeLisi, 1997; Lieberman *et al.*, 1997).

Neuropathology and neurochemistry

The neurochemical pathology of schizophrenia is outside the scope of this review, but it is pertinent to summarize some key recent findings (Table 5) and their relationship to the neuropathology. For more extensive coverage see Owen and Simpson (1995) and Reynolds (1995).

Dopamine

The dopamine hypothesis proposes that the symptoms of schizophrenia are due to dopaminergic overactivity. This might arise due to excess dopamine itself or to an elevated sensitivity to it, e.g. because of increased numbers of dopamine receptors. The hypothesis originated with the discovery that all effective antipsychotic drugs are dopamine (D_2) receptor antagonists, and that dopamine-releasing agents such as amphetamine can produce a paranoid psychosis. It received support from findings of increased dopamine content and higher densities of D_2 receptors in schizophrenia (summarized in Roberts *et al.*, 1997). However, despite the longevity of this hypothesis there is still no consensus as to the nature of the supposed abnormality or any evidence that dopamine has a causal role in the disorder (Davis *et al.*, 1991; Joyce and Meador-Woodruff, 1997). There are two main difficulties. First, antipsychotics have marked effects on the dopamine system, seriously confounding all studies of medicated subjects. Secondly, the molecular characterization of the dopamine receptor family has greatly increased the number of potential sites of dysfunction and the mechanisms by which it might occur in schizophrenia.

There is no doubt that D_2 receptor densities are increased in schizophrenia, but considerable doubt as to what proportion is not attributable to antipsychotic treatment (Zakzanis and Hansen, 1998), especially given that PET studies of D_2 receptors in drug-naive, first-episode cases are largely negative (Nordstrom *et al.*, 1995). There are reports of altered D_1 (Okubo *et al.*, 1997) and D_3 (Gurevich *et al.*, 1997) receptors in schizophrenia, but these are either unconfirmed or contradicted by other studies (see Harrison, 1999*b*). The D_4 receptor has proved particularly controversial following a report that its density was increased several-fold in schizophrenia, seemingly independently of medication (Seeman *et al.*, 1993). However, it appears that the result was due to a 'D_4-like site' rather than the true D_4 receptor (Reynolds, 1996; Seeman *et al.*, 1997). In summary, the status

Table 5 *Summary of recent neurochemical findings in schizophrenia*

	Strength of evidence
Dopamine	
Increased striatal D_2 receptors	++++*
Increased dopamine content or metabolism	+++*
Increased amphetamine-stimulated dopamine transmission	+++
Decreased cortical D_1 receptors	+
Increased cortical D_3 receptors	+
Increased D_4 receptors	+/–
Abnormal configuration of D_2 receptors	+/–
Altered dopamine receptor–G protein coupling	+/–
5-HT	
Decreased cortical 5-HT_{2A} receptors	+++
Increased cortical 5-HT_{1A} receptors	++
CSF 5-HIAA concentrations related to negative symptoms	+
Glutamate	
Decreased expression of hippocampal non-NMDA receptors	++
Increased cortical expression of some NMDA receptor subunits	++
Increased glutamate reuptake in frontal cortex	+
Decreased cortical glutamate release	+
Altered concentrations of glutamate and metabolites	+/–

+/– = weak ; + = moderate; ++ = good; +++ = strong; ++++ = shown by meta-analysis. *Though much of the increase is due to antipsychotic medication (see text).

of dopamine receptors in schizophrenia is still contentious. In contrast, there is emerging evidence for a presynaptic dopaminergic abnormality in schizophrenia, with PET and single photon emission tomography displacement studies indicating an elevated dopamine release in response to amphetamine (Laruelle *et al.*, 1996; Breier *et al.*, 1997; Abi-Dargham *et al.*, 1998), implying a dysregulation and hyper-responsiveness of dopaminergic neurons. This is a potentially important finding which needs further investigation.

5-Hydroxytryptamine (5-HT; serotonin)

The idea that 5-HT is involved in schizophrenia has long been advocated because the hallucinogen LSD is a 5-HT agonist. Current interest centres on the role of the 5-HT_{2A} receptor (Harrison and Burnet, 1997) because a high affinity for the receptor may explain the different therapeutic and side-effect profile of novel antipsychotics (Meltzer, 1996), and polymorphisms of the gene are reported to be a minor risk factor for schizophrenia (Williams *et al.*, 1997) and response to the atypical antipsychotic drug clozapine (Arranz *et al.*, 1998). Neurochemically, many studies have found lowered 5-HT_{2A} receptor expression in the frontal cortex in schizophrenia (Harrison, 1999*b*), and there is a blunted neuroendocrine response to 5-HT_2 agonists (Abi-Dargham *et al.*, 1997). An elevated number of cortical 5-HT_{1A} receptors is also a replicated finding (Burnet *et al.*, 1997). Both the 5-HT_{1A} and 5-HT_{2A} receptor alterations are seen in unmedicated subjects post-mortem, but a preliminary PET study has not shown any change in 5-HT_{2A} receptors in younger, medication-free patients (Trichard *et al.*, 1998), suggesting that the abnormalities may emerge during the course of the illness.

Hypotheses to explain 5-HT involvement in schizophrenia include alterations in the trophic role of 5-HT in neurodevelopment, impaired 5-HT_{2A} receptor-mediated activation of the prefrontal cortex, and interactions between 5-HT and dopamine (Kapur and Remington, 1996).

Glutamate

Phencyclidine and other non-competitive antagonists of the NMDA (N-methyl-D-aspartate) subtype of glutamate receptor produce a psychosis closely resembling schizophrenia (Javitt and Zukin, 1991). This has driven the hypothesis of glutamatergic dysfunction in schizophrenia. In support, there is now considerable evidence for abnormalities in pre- and postsynaptic glutamate indices (Table 5). For example, in the medial temporal lobe, glutamatergic markers are decreased and there is reduced expression of non-NMDA subtypes of glutamate receptor (Kerwin *et al.*, 1990; Eastwood *et al.*, 1995*b*, 1997*b*; Porter *et al.*, 1997). However, a different pattern is seen in other brain regions, affecting other glutamate receptor subtypes (Roberts *et al.*, 1997), precluding any simple conclusion regarding the nature of glutamatergic abnormality in schizophrenia (Tamminga, 1998).

Mechanisms proposed to explain glutamatergic involvement in schizophrenia centre on its interactions with dopamine (Carlsson and Carlsson, 1990), subtle forms of excitotoxicity (Olney and Farber, 1995) and a developmental abnormality of corticocortical connections (Deakin and Simpson, 1997).

Relationship between neurochemical and neuropathological findings

Even from this brief, selective review it is apparent that there is still no clear picture as to the cardinal neurochemical features of schizophrenia or their position in the pathogenesis of the disorder. The main point, *vis a vis* neuropathology, is that the presence of structural abnormalities, however slight, must be taken into account. That is, a change in the level of a neurotransmitter, receptor or any other molecule may be due to dysfunction in the cells producing it or a change in the cellular constituents of the tissue being evaluated, rather than being indicative of a molecularly specific abnormality. This applies to *in vivo* functional imaging as well to neurochemistry, and affects discussions as to the putative causes and consequences of any alteration. Whilst an obvious point to make, it has not always been appreciated in schizophrenia research, perhaps because of the belief that the brain is entirely normal, structurally speaking. As an example, consider the case of 5-HT receptors. In the prefrontal cortex in schizophrenia, we and others have found a loss of 5-HT_{2A} receptors and an accompanying increase of 5-HT_{1A} receptors (Burnet *et al.*, 1996, 1997). In this region, the 5-HT_{2A} receptor is expressed by pyramidal neurons, interneurons and perhaps glia (Burnet *et al.*, 1995; Jakab and Goldman-Rakic, 1998), whilst the 5-HT_{1A} receptor is expressed exclusively, or virtually so, by pyramidal neurons (Burnet *et al.*, 1995). Thus it is unclear whether the 5-HT receptor changes seen in schizophrenia arise from differential involvement of the cell types concerned or from opposing abnormalities in the regulation of expression of each receptor subtype. Similarly, it is difficult to interpret unambiguously the various glutamatergic and dopaminergic abnormalities reported in schizophrenia, or the deficits in GABA which are also apparent (Simpson *et al.*, 1989; Benes *et al.*, 1992*b*; Akbarian *et al.*, 1995), independently of the morphometric alterations in excitatory and inhibitory neurons and their synapses discussed above. More sophisticated analyses are needed in order to establish when a neurochemical finding in schizophrenia is really that, and when it is a reflection of neuropathology.

Neuropathology and aberrant functional connectivity

Bleuler, who coined the term schizophrenia, stated 'the thousands of associations guiding our thought are interrupted by this disease . . . The thought processes, as a result, become strange and illogical, and the associations find new paths' (Bleuler, 1950). His view that the key symptoms of schizophrenia were those of 'psychic splitting' now have their counterparts in neuropsychological models and in imaging studies which have implicated aberrant functional connectivity between different brain regions as the pathophysiological mechanism of psychosis (Friston and Frith, 1995; McGuire and Frith, 1996; Andreasen *et al.*, 1996; Bullmore *et al.*, 1998). Although the evidence in favour of altered connectivity in schizophrenia remains circumstantial and its details poorly specified, the concept has been widely promulgated. Examples are shown in Table 6.

Here the specific hypothesis is elaborated that aberrant connectivity in schizophrenia has neuroanatomical roots: the neuropathology of the disorder is that of a miswiring of the neural circuitry within and between certain brain regions. This 'hard-wiring' theme (Mesulam, 1990), which can be traced back to Wernicke, is apparent in a number of experimental and theoretical perspectives (Table 6). However, aberrant functional connectivity does not presuppose or require an anatomical substrate, and neither is it synonymous with regional brain dysfunction (Friston, 1998). Hence the pathological evidence in schizophrenia must be considered on its own merits before attempts are made to integrate structure with function. Certainly, schizophrenia is not a disconnectivity syndrome akin to Alzheimer's disease, in which there is frank loss of connections due to neuronal and synaptic degeneration (Pearson and Powell, 1989; De Lacoste and White, 1993), but it is argued here that schizophrenia is a dysconnectivity or misconnectivity syndrome which affects the precise organization of the neural circuitry, and perhaps its plasticity characteristics (Randall, 1983; Haracz, 1985; Goodman, 1989; Walker and Diforio, 1997). It is in such terms that the cytoarchitectural abnormalities reported in schizophrenia can reasonably be interpreted as being a putative basis for at least a proportion of the aberrant connectivity. That is, the types of neuronal, synaptic and dendritic findings reviewed above are entirely consistent with aberrant functional connectivity. For example (Fig. 1), in DLPFC, lamina III pyramidal neurons are smaller (Rajkowska *et al.*, 1998), have fewer dendritic spines (Garey *et al.*, 1998) and receive fewer inhibitory inputs (Woo *et al.*, 1998); moreover there is a reduction in synaptophysin in this region (Glantz and Lewis, 1997). Since the layer III pyramidal neurons are the origin of corticocortical projections, it is reasonable to propose that this combination of abnormalities will result in dysfunction of pathways to and from the DLPFC, in keeping with the many neuropsychological and functional imaging data attesting to the involvement of this region in the pathophysiology of schizophrenia (Weinberger, 1987; Andreasen *et al.*, 1996; Pantelis *et al.*, 1997).

Much remains to be done before the hypothesized association between structure and function can be confirmed and shown to be causal. It will not be easy to falsify or to clarify its detail, and the overriding need at present is still to improve the robustness of the contributory data. Nevertheless, the goal should be kept firmly in mind when designing neuropathological investigations into schizophrenia.

Methodological issues

It is all too evident that schizophrenia pushes neuropathology to its technical and conceptual limit. As well as sharing the

Table 6 *Concepts of dysconnectivity in schizophrenia*

Approach	Comments and examples of findings in schizophrenia
Experimental	
Patterns of correlations	
of regional cerebral blood flow	Inverted temporal lobe activity correlation during frontal lobe tasks (Frith *et al*., 1995)
of regional glucose metabolism	Fewer corticothalamic correlations (Katz *et al*., 1996)
of regional brain volumes	Frontotemporal (Woodruff *et al*., 1997) or thalamocortical (Portas *et al*., 1998) dissociation
of volume with rCBF	Hippocampal size correlates with frontal rCBF (Weinberger *et al*., 1992)
of volume with function	Hippocampal size correlates with frontal test performance (Bilder *et al*., 1995)
of neuron density	Asymmetrical change in subfield correlations within and between hippocampi (Zaidel *et al*., 1997*b*)
of gene expression	Increased inter-areal correlations of GAP-43 mRNA (Eastwood and Harrison, 1998)
Distribution of abnormalities	
Cytoarchitectural	Hippocampal (Arnold *et al*., 1995*a*) and corticocortical (Rajkowska *et al*., 1998) pathways
Neurochemical	Frontotemporal glutamatergic circuitry (Deakin and Simpson, 1997)
Profile of neuropsychological deficits	Frontostriatal dysfunction (Pantelis *et al*., 1997)
Theoretical	
Comparison with other disorders affecting connectivity	Inattention syndromes (Mesulam and Geschwind, 1978); metachromatic leucodystrophy (Hyde *et al*., 1992)
Anatomical considerations	Intrinsic DLPFC circuitry (Lewis, 1997); heteromodal association cortex (Pearlson *et al*., 1996)
Pharmacoanatomical considerations	Corticostriatal glutamatergic dysfunction (Carlsson and Carlsson, 1990)
Evolutionary	Myelination (Randall, 1983); callosal pathways and language representation (Crow, 1998)
Modelling	Dopamine system (Cohen and Servan-Schreiber, 1992); synaptic pruning (Hoffman and Dobscha, 1989)
Other	Functional clustering (Tononi *et al.*, 1998)

Table 7 *Methodological problems in schizophrenia neuropathology*

Issues especially pertinent to neuropathological studies
Availability of enough cases, with adequate documentation
Duration of disease prior to death
Dealing with other pathologies which may have produced a schizophrenia-like psychosis
Confounding by concurrent illnesses
Confounding by perimortem factors (e.g. mode of death, autopsy delay, tissue processing)
Hemispheric structural asymmetries
Is the neuropathology a result of schizophrenia? (e.g. caused by persistent symptoms, or a poor environment?)
Selecting which brain areas to study
Adherence to stereological principles
Issues common to all schizophrenia research
Validity of the diagnosis
Does the variable being measured relate to the syndrome of schizophrenia, or to a symptom? Is it categorical or dimensional?
Is there heterogeneity?
Is the variable affected by antipsychotic drugs or other treatments?
Are subjects included in research representative?
Use of a psychiatric control group

For further discussion of the methodological issues affecting neuropathological studies of schizophrenia, see Kleinman *et al*. (1995), Harrison (1996) and Hill *et al*. (1996).

difficulties inherent in schizophrenia research, neuropathological investigations are faced with additional problems, some of which have already been alluded to (Table 7). None are unique to schizophrenia, but they take on disproportionate importance given the nature of the pathology and the low signal-to-noise ratio.

Confounding by antipsychotic medication is almost unavoidable. However, it is a somewhat overemphasized problem, certainly for cortical cytoarchitectural studies, in that no correlations have been found with treatment exposure in any of the studies mentioned, and little or no effect of the drugs upon similar parameters has been found in the rat brain (Harrison, 1993). Though reassuring, these approaches cannot wholly eliminate medication as a confounder; study of brains

Table 8 *Certainty and doubt in schizophrenia neuropathology*

	Strength of evidence
Macroscopic findings	
Enlarged lateral and third ventricles	++++
Decreased cortical volume	++++
The above changes present in first-episode patients	+++
Disproportionate volume loss from temporal lobe (incl. hippocampus)	+++
Decreased thalamic volume	++
Cortical volume loss affects grey rather than white matter	++
Enlarged basal ganglia secondary to antipsychotic medication	+++
Histological findings	
Absence of gliosis as an intrinsic feature	+++
Smaller cortical and hippocampal neurons	+++
Fewer neurons in dorsal thalamus	+++
Reduced synaptic and dendritic markers in hippocampus	++
Maldistribution of white matter neurons	+
Entorhinal cortex dysplasia	+/–
Cortical or hippocampal neuron loss	+/–
Disarray of hippocampal neurons	+/–
Miscellaneous	
Alzheimer's disease is not commoner in schizophrenia	++++
Pathology interacts with cerebral asymmetries	++

+/– = weak ; + = moderate; ++ = good; +++ = strong; ++++ = shown by meta-analysis.

collected in the pre-antipsychotic era does (e.g. Altshuler *et al.*, 1987; Falkai *et al.*, 1988; Arnold *et al.*, 1991*b*), but has its own limitations such as the age of the material, changes in diagnostic practice, and the frequent occurrence of leucotomy, insulin coma and other potentially neurotoxic therapies (e.g. Lohr and Jeste, 1988; Pakkenberg, 1993*a*). In the striatum and substantia nigra there is greater evidence for antipsychotic drug-induced neuronal and synaptic changes, both in animals (Harrison, 1993; Eastwood *et al.*, 1994*b*, 1997*a*; Kelley *et al.*, 1997) and in post-mortem series (Christensen *et al.*, 1970; Jellinger, 1977). Investigations in these regions must therefore continue to take particular care to distinguish the effects of disease from those of medication.

Of all the factors listed in Table 7, the main one affecting the design and execution of neuropathological studies of schizophrenia is simply the collection of brains. This problem has worsened with the fall in autopsy rates, and is exaggerated by community care, which means that most deaths occur outside hospital and are frequently referred to the coroner, making acquisition of tissue for research practically and legally difficult. The decreased supply is compounded by exclusion of some potentially suitable subjects because of a lack of sufficient information about the clinical history or other confounders. A significant effort is needed to overcome these problems and allow continuing collection of brain tissue of adequate quality and quantity from subjects with schizophrenia and suitable controls, both healthy and those with other psychiatric disorders. This is not an undertaking to be embarked on lightly, nor is it easily funded, but it has been productively implemented in several centres (Arnold *et al.*, 1995*b*; Johnston *et al.*, 1997; Garey *et al.*, 1998).

A final issue to consider is how the types of neuropathological abnormality described in schizophrenia relate to the clinical phenotype, whether defined in terms of psychotic symptoms or neuropsychological profile (Elliott and Sahakian, 1995). Features such as decreased cortical volume and cytoarchitectural abnormalities are diagnostically non-specific, overlapping with those observed in other psychiatric and neurological conditions. There could be a diagnostic lesion characteristic of schizophrenia still going unrecognized, though this is increasingly implausible. Or it could be the precise combination of alterations and their location and timing which produces schizophrenia. Some clarification will emerge as other idiopathic, putatively neurodevelopmental conditions such as bipolar disorder (Benes *et al.*, 1998; Drevets *et al.*, 1998), autism (Raymond *et al.*, 1996; Bailey *et al.*, 1998) and Rett's syndrome (Belichenko *et al.*, 1997) begin to be investigated in the same fashion. A complete answer, however, will also probably require identification of the causative genes and a better understanding of the pathogenesis, not just the pathology, of schizophrenia. At this point, one re-encounters the circular problem: the goal of the research is to find a valid endophenotype, yet without one the goal may be unattainable.

Conclusions

Despite the many controversies and contradictions, there are now established facts about the neuropathology of schizophrenia (Table 8). The disorder is associated with ventricular enlargement and decreased cortical volume. The pathology is neither focal nor uniform, being most convincingly demonstrated in the hippocampus, prefrontal cortex and dorsal thalamus. The pattern of abnormalities is

suggestive of a disturbance of connectivity within and between these regions, most likely originating during brain development. At the cellular level, the changes are manifested as abnormalities, mainly decrements, in perikaryal, presynaptic and dendritic parameters (Tables 1 and 2; Fig. 1). The phenotype of the affected neurons and synapses is unclear, though there is some evidence for preferential glutamatergic involvement in the hippocampus. The sorts of cytoarchitectural changes being proposed, whilst still speculative and perhaps better viewed as aberrant neuroanatomy rather than neuropathology *per se*, are in keeping with the clinical complexity of the syndrome which they are being invoked to explain, as well as with the results of various functional imaging, neurochemical and neuropsychological findings. Progress is now constrained more by the subtlety of the target pathology than by methodological limitations of the work; indeed, the best contemporary studies are prime examples of innovative, quantitative neuropathology research.

In 1915 the neuropathologist Southard boldly stated that 'structural (visible or invisible) changes of a mal-developmental nature lie at the bottom of the [schizophrenia] disease process . . . Aside from the left-sidedness of the lesions and internal hydrocephalus, very striking is the preference of these changes to occupy the association centres of Fleschig'. A positive view of the field today is that empirical data are belatedly proving the correctness of these assertions. Conversely, a cynic might suggest that it is the invisibility which has proved the most robustly demonstrable, or that the current histological findings remain sufficiently vague and numerous to cover all possibilities, ensuring that one will turn out, with hindsight, to be similarly prescient. Certainly it is time to implement still better research, driven by specific hypotheses (e.g. Benes, 1998; Weickert and Weinberger, 1998). In this way the small but increasingly steady steps which are finally being taken can proceed to a clear identification of the pathological substrate(s) of schizophrenia.

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