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Review Article

Schizophrenia: A Neuropathological Perspective

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It is probable that all schizophrenics have abnormalities in the medial temporal lobe, which differ in degree but not in kind. The structures of the medial temporal lobe are believed to have a crucial role in the integration and processing of the output from the association cortex. Dysfunction of this system could result in the clinical symptoms that form the core of the schizophrenia syndrome. The structural differences appear to fit the profile of a disturbance in the normal pattern of brain development. The asymmetrical patterns of normal brain development explain how such a disturbance simultaneously affecting both hemispheres could, disproportionately, affect the left (dominant) hemisphere. Epidemiological and pathological evidence points to aberrant genetic mechanisms as being the cause of the developmental anomaly in the majority of cases; environmental factors probably play a minor role. Despite the great progress made in solving the enigma of the structural changes in the brains of schizophrenics, the cause(s) of the changes – the aberrant genetic mechanism controlling brain development – may prove difficult to define.

Schizophrenia is still generally viewed as a 'functional' psychosis, a label implying a condition arising from disordered cognition with no basis in structural or pathological alteration of brain substance. Clinically, considerable emphasis is laid on the differential diagnosis of 'functional' psychoses from the dementias (chronic organic psychoses) in which cognitive and intellectual impairment are known to be related to structural changes in the brain.

Despite clinical evidence of brain dysfunction in schizophrenia, little progress was made in determining its organic parameters for most of this century and early neuropathological studies were conflicting and controversial (Corsellis, 1976; Roberts & Crow, 1987; Roberts, 1990). In a valedictory review, Corsellis (1976) sorrowfully summed up the lack of direction in the field and concluded that progress lay in the use of carefully matched samples and quantitative techniques to define the brain abnormalities underlying psychosis.

The current Lazarus-like state of research into the neuropathology of schizophrenia dates from the study of Johnstone *et al* (1976) which used the emerging technology of computerised tomography (CT) to re-examine the ventricular system in schizophrenics. They reported ventricular enlargement in schizophrenics which correlated with cognitive impairment but was unrelated to physical treatment. This study replicated earlier pneumoencephalographic studies (e.g. Lemke, 1935; Haug, 1962). The resultant flood of CT and, more recently, magnetic resonance imaging (MRI) studies have confirmed the finding (see Crow & Johnstone, 1987; Shelton & Weinberger, 1986) and lent credence to the idea of an underlying structural abnormality in the brains of many schizophrenic subjects, although the degree of ventricular enlargement observed is variable and not diagnostic.

This replicable evidence of structural abnormalities in the brains of schizophrenic subjects encouraged pathologists to adopt experimental approaches necessary for their detection (i.e. statistical comparison of quantitative data obtained from matched groups). Enough neuropathological data have now accumulated to attempt a synthesis with the epidemiological and genetic literature, which could provide a useful perspective for future research.

Brain structure in schizophrenia

Brain weight in schizophrenia has been studied since the beginning of the century, although the earlier studies are open to criticism on many grounds (Brown *et al*, 1986). Three recent studies have produced consistent results. Each found a significant decrease in brain weight in schizophrenic patients compared with controls after accounting for such factors as height, weight, sex, and year of birth. Brown *et al* (1986) reported an average reduction of some 100 g (6%), Pakkenberg (1987) a loss of 109 g (8%) and Bruton *et al* (1990), in a large prospective study, reported a 30 g loss from *each* hemisphere (approximately 5% of brain weight), and both male and female schizophrenics had reductions of a similar magnitude.

Other parameters of gross brain structure are also altered. Bruton *et al* (1990) found significant (4%) reductions (about 7 mm) in brain length (maximum

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anteroposterior length of formalin-fixed cerebral hemispheres) in both male and female schizophrenics. A separate analysis indicated that *both* left and right hemispheres were shorter. Pakkenberg (1987) found significant reductions in volume of the cerebral hemispheres (8% loss), cerebral cortex (12% loss), and central grey matter (6% loss). No loss in volume of white matter was found. No separate analysis of sex or laterality was made.

Post-mortem studies have also found evidence of ventricular enlargement. Brown *et al* (1986) reported a significant increase in the cross-sectional area of the anterior horn (by 19%) and temporal horn (by 97%) of the lateral ventricles, and Pakkenberg (1987) found an increase of 33% (10 ml) in the total volume of the ventricular system. Bruton *et al* (1990) in a blind semiquantitative study also noted a significantly increased incidence of ventricular enlargement in their schizophrenic sample.

While these data confirm structural abnormalities in the brains of schizophrenics, they provide little guidance as to which brain regions are particularly affected and how the structural abnormalities arise. The study of Pakkenberg (1987) indicates that cortical regions may be preferentially affected and data from Brown *et al* (1986) suggest that the ventricular enlargement may be regional in that the temporal horn is particularly affected. The enlargement of the temporal horn is lateralised, the left hemisphere being particularly affected (Crow *et al*, 1989).

Abnormalities in the gyral patterns of the temporal lobe have been described in schizophrenics (Jakob & Beckman, 1986) but the extent and precise nature of these sulcogyral abnormalities is uncertain and no such abnormalities were seen in the brains of schizophrenics in a larger, well controlled study (Bruton *et al*, 1990).

Brain regions affected

While CT and MRI studies are extremely useful for demonstrating structural changes in brains and allow 'fishing expeditions' for correlates of ventricular enlargement in schizophrenia, it should be remembered that larger ventricles are only an *indication* of pathology (an indirect one at that). The resolving power of such techniques is limited and detailed studies to pin-point specific regions and types of pathological change require painstaking and reproducible measurements on post-mortem tissue.

A planimetric study of archival material (the Vogt collection) revealed considerable volume reductions of temporal lobe structures (hippocampal formation, amygdala, parahippocampal gyrus) and a moderate reduction of the inner pallidal segment (by 20%) in schizophrenic subjects (Bogerts *et al*, 1985). The outer pallidal segment, caudate, putamen and nucleus accumbens did not show significant differences in volume.

In the largest planimetric study to date, Brown *et al* (1986) used subjects with affective disorder as a control group. All subjects (41 schizophrenics and 29 with affective disorder) were screened for senile or vascular change, and the findings were controlled for age, sex and year of birth. The brains of schizophrenics were 6% lighter (see above) and had enlarged ventricles. The schizophrenic group also had a significantly thinner parahippocampal cortex (11% reduction). No significant differences were noted in the areas of basal ganglia structures, third ventricle, cingulate cortex and insula opercula cortex. The thinning of the parahippocampal gyrus was significantly correlated with the increased area of the ventricular temporal horn (Colter, personal communication).

Thus both planimetric studies found evidence of structural change in the brains of schizophrenics, although to a lesser degree than that found in Alzheimer's disease or Huntington's chorea. Neither study provides support for the notion of homogeneous cortical atrophy or that the basal ganglia are particularly affected. Both conclude that the temporal lobe, specifically the medial temporal lobe structures (hippocampus and parahippocampal gyrus), are preferentially affected. The post-mortem studies are supported by a recent MRI study (Suddath *et al*, 1989) which used image analysis to measure the size of the temporal lobe and the amounts of grey and white matter in schizophrenics. Significant reductions were seen in the amount of temporal lobe grey matter (reduced by 18% in the right hemisphere and by 21% in the left hemisphere) in schizophrenics, particularly at the level of the amygdala and anterior hippocampus. These reductions correlated inversely with ventricular enlargement in the same sample. No differences were seen in the amount of temporal lobe white matter.

Medial temporal lobe structures (particularly the hippocampus) have been the subject of intensive study. Structural disorganisation of the hippocampal pyramidal cells has been reported (Kovelman & Scheibel, 1984). Disruption was maximal in the anterior and middle portions of the hippocampus (cf. Suddath *et al*, 1989, mentioned above) particularly at the interface between the entorhinal cortex and the hippocampus proper. These changes were considered suggestive of a defective pattern of neuronal migration. However, this finding of

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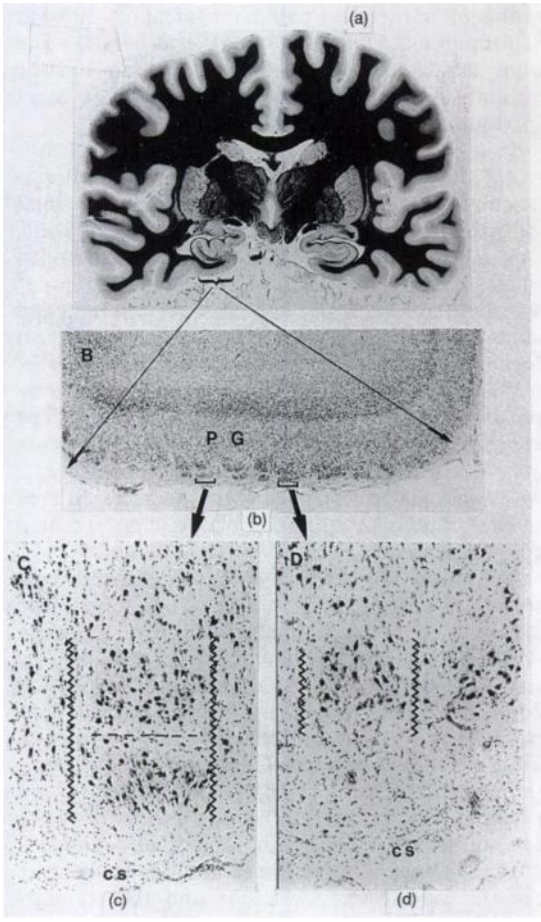


Fig. 1 Aberrant development in the parahippocampal gyrus in schizophrenia. The parahippocampal gyrus (PG) located close to the hippocampus (a) has a characteristic pattern of cell formations (b). In this region of cortex 'pre-αclouds' of neurons (cortical layer II, bracketed) lie close to the cortical surface. A high-power view (c) of one of the 'clouds' in a control (staggered line) shows it to be formed of two cell clusters separated by a cellular gap (dashed line). In schizophrenics (d) the pre-clouds are poorly developed, separate cell cluster not being discernible, and the whole formation lies deeper from the cortical surface (CS).

disorganisation has not been replicated in a more recent study (Christison *et al*, 1989).

Falkai & Bogerts (1986) reported that volumes of the hippocampal formation, pyramidal cell bands and hippocampal segments were decreased in the brains of schizophrenics. The absolute number of pyramidal cells was reduced and the loss of pyramidal cells was more noticeable in paranoid that in catatonic patients. The reduction of hippocampal nerve cells was not accompanied by gliosis (as indicated by counts of glial cells). In a further study on the same material (Falkai *et al*, 1988*a*) a reduction in both the area and neuron content of entorhinal cortex was found and, once again, the loss of neurons was not accompanied by increases in numbers of glial cells. These findings of decreased volume of the hippocampus and pyramidal band have recently been replicated (Jeste & Lohr, 1989). The decreased volume was most marked in the anterior hippocampus of the left hemisphere (cf. Crow *et al*, 1989).

A qualitative description of morphological changes in the temporal lobe of schizophrenics has been presented by Jakob & Beckman (1986). The changes include alterations to and cell loss from cortical lamina of the ventral insula (claustrocortex) and parahippocampal gyrus. The medial and central portions of the parahippocampal gyrus were most disturbed, with the lateral (transitional) region less affected (Fig. 1). These changes did not extend anteriorly to the pre-piriform cortex nor posteriorly to the occipital level of the temporal cortex (cf. Kovelman & Scheibel, 1984; Suddath *et al*, 1989). The cytoarchitecture of the remaining temporal neocortex was normal. The cytoarchitectural abnormalities were present in *both* hemispheres but more conspicuous in the left hemisphere. Of interest was the tendency for patients with marked pathological abnormalities to have an earlier age of onset of psychotic symptoms. These findings were considered to indicate abnormal ontogenetic development of a small part of the entorhinal cortex. This study is open to some criticism; it was not blind, not quantitative and only ten control cases (as opposed to 64 schizophrenic cases) were assessed. However, a preliminary quantitative study of the cytoarchitecture of the pre-alpha cells of the parahippocampal gyrus revealed evidence of putative migration anomalies (Falkai *et al*, 1988*a*; Fig. 1c,d).

Other brain regions can be affected to a lesser degree (see Roberts & Crow, 1987; Roberts, 1990; Roberts & Bruton, 1990).

Neuropathological studies of structural changes and clinical symptoms

Cognitive impairment (and associated negative symptoms) and measurements of poor pre-morbid and social functioning appear to be best related to loss of brain weight, decrease in brain length, increased ventricular size and abnormalities in cytoarchitecture (Jakob & Beckman, 1986; Pakkenberg, 1987, Bruton *et al*, 1990). In general, the greater the structural changes, the greater the cognitive impairment and the poorer the pre-morbid function. Cognitive impairment and poor pre-morbid function are

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associated with early onset of the illness and a poor prognosis (Shelton & Weinberger, 1986; Crow & Johnstone, 1987).

While the correlations between measures related to cognitive impairment (negative, or type II symptoms (Crow, 1980)) and structural changes is discernible, it should be remembered that many of these patients also have delusions, hallucinations and incongruity of affect (positive, or type I symptoms). Thus, studies in this field are at an early stage and the conclusions concerning the clinical correlates of altered morphology should be regarded as preliminary.

The clinical state of schizophrenia has been viewed as a common endpoint for a number of discrete aetiological factors. Various studies have sought to relate measures of structural abnormality (usually ventricular enlargement) to subgroups of schizophrenics defined on the basis of symptoms or presumed aetiological factors (Crow, 1980; Murray *et al*, 1985; Lewis & Murray, 1987; Lewis, 1989*a,b*). None of these attempts has been entirely convincing. Despite the proposal that ventricular enlargement might be confined to patients with negative symptoms or a history of birth difficulties, it has in fact been found in patients with or without positive symptoms, negative symptoms, and with varying degrees of assumed genetic loading (Farmer *et al*, 1987; Nimgaonkar *et al*, 1988; Owen *et al*, 1989).

Murray & Forester (1987) hoped that psychiatrists of the future would be able to define subgroups or types of schizophrenia "according to aetiological principles rather than on the quicksands of symptomatology and course". At present there is no consistent evidence that a rationale subgrouping schizophrenics on the basis of the presence or absence of structural change or other aetiological factors can be made. Thus, it seems simpler to assume that *all* schizophrenics have a degree of structural abnormality and that, neuropathologically, schizophrenia is best viewed as a homogeneous condition: the symptoms of schizophrenia arise from a type of lesion which differs in degree but not kind.

The origin of the structural changes

Kraepelin (1919) originally conceived of schizophrenia as a degenerative process. This was modified in later years by others to a series of variations of stress–diathesis models and psychobiological theories. The early CT findings were regarded as evidence for an underlying degenerative process and focused attention back to Kraepelin's early ideas. Schizophrenia was again viewed as a degenerative process (possibly caused by an acquired pathogen) (e.g. Crow, 1983). This view fitted with the correlation between ventricular enlargement and cognitive impairment, a finding to be expected in a neurodegenerative condition. The report of increased periventricular gliosis (Stevens, 1982 – but see below) was also in accord with a "low-level of viral infection". However, the correlation between length of illness and increasing ventricular size seen in other neurodegenerative diseases failed to emerge (see Weinberger, 1984, 1987; Crow & Johnstone, 1987). Furthermore, changes of a similar degree were found in patients only weeks or months after the onset of their first psychotic episode. In view of this background it was hypothesised that schizophrenia was of multifactorial aetiology, with family history (genetic factor) and obstetric or perinatal complications (environmental factor) being regarded as the most prominent (Murray *et al*, 1985, 1988).

Several recent studies have attempted to obtain evidence of the 'smoking gun' which might implicate one of these factors directly. However, identifying aetiological constants in schizophrenics in pathological studies is made more difficult by the findings from neuropathological surveys, which show that, as a group, schizophrenics have a high incidence of pathological changes (e.g. infarcts, vascular disease, Alzheimer-type changes, Parkinson's disease, etc.): Stevens (1982) had found pathology in 50% of cases, Jellinger (1985) in 51%, and Bruton *et al* (1990) in 43%. In the latter study, the incidence was significantly greater ($P>0.01$) than the 21% incidence found in age- and sex-matched controls, although the *types* of pathology found are qualitatively indistinguishable. The explanation for these observations is unclear, although several possibilities have been canvassed (Bruton *et al*, 1990), such as lifestyle, drug treatment, selection bias and, more interestingly, a secondary vulnerability to damage due to underlying structural changes.

Many neuropathological studies have focused on gathering evidence for the presence of a neurodegenerative process and ascertaining when the structural changes occurred. All types of disease process which cause neuronal damage result in glial reaction, which is marked by proliferation of glial cells and rises in associated glial proteins and enzymes (such as glial fibrillary acidic protein and monoamine oxidase-B) (Roberts *et al*, 1987). Finding a constant pattern of such reactivity in schizophrenic brains would signal a neurodegenerative process and indicate the location of the damage.

Stevens (1982) reported periventricular gliosis in schizophrenics. However, as noted above, some 50% of her cases had evidence of identifiable pathology. Bruton *et al* (1990) also noted an increased incidence

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of gliosis in the schizophrenics, but this was significantly associated with the various types of pathology present in the sample. Further analysis showed that the application of a neuropathological 'sieve' to the total sample (removing cases with identifiable pathology excluding gliosis) gave a 'purified' group which still showed reduced brain weight, brain length, and increased ventricular size but no significant gliosis. Recent quantitative studies using similar selection criteria and a variety of methods report similar results (see Roberts & Bruton, 1990). The available pathological evidence indicates that the structural changes in the brains of schizophrenics are not the result of a neurodegenerative process or a destructive lesion. Rather the data fit the profile of a disturbance in brain development (Roberts *et al*, 1987). Although ideas of maldevelopment in schizophrenia have a long history (see Lewis, 1989) it is only recently that such a concept has been firmly rooted in data obtained from direct observation of the neuropathology of the condition.

The idea of schizophrenia as a neurodevelopmental anomaly of the medial temporal lobe gives rise to several predictions (Roberts *et al*, 1987). The lesion would be present from birth, preceding the onset of clinical symptoms and may be constant and not progressive. Only a few studies have addressed these questions. Ventricular enlargement has been reported in a ten-year-old diagnosed as schizophrenic (Woody *et al*, 1987) and in two teenagers scanned *before* the onset of schizophrenic symptoms (O'Callaghan *et al*, 1988; Weinberger, 1988). There is little or no evidence of progressive structural changes. In the first such study to examine the problem only 20% of patients were reported as showing progressive ventricular enlargement over four years (Lemke, 1935) and three recent studies show no evidence of progression in groups of patients scanned over eight years (Illowsky *et al*, 1988), and five years (Vita *et al*, 1988; Reveley *et al*, 1988).

Neuropathological studies and suggested aetiological factors

Are the neuropathological data compatible with the intrusion of external environmental events (such as those caused by obstetric complications or infection) on brain development around the time of birth?

Foetal brain tissue does not show an adult glial response until after six months (Larroche, 1984) and an early destructive lesion might not leave a gliotic trace. However, the type of changes to the cytoarchitecture reported in the schizophrenic brain (Jakob & Beckman, 1986) indicate that they originate in the last trimester before birth, a period when an adult-like glial response to injury does occur (Larroche, 1984; Volpe, 1989). Birth difficulties can give rise to intraventricular haemorrhages and infarcts which lead to enlarged ventricles and small brains (Gilles & Green, 1985; Volpe, 1989). Such pathologies *are* accompanied by gliosis and periventricular leucomalacia. However, neuropathological studies report no excess gliosis and an absence of inflammation (Roberts *et al*, 1986, 1987; Bruton *et al*, 1990) and there is little evidence of trauma (Bruton *et al*, 1990). These data do not suggest that brain damage due to birth injury or perinatal infection is a major factor in the genesis of the structural abnormalities in schizophrenia. Thus, direct evidence for the involvement of external environmental events in the genesis of schizophrenia is lacking.

The argument that external environmental events cause the changes in brain structure in a majority or significant minority of schizophrenic cases rests on a number of pillars: (a) the lack of 100% concordance for schizophrenia in monozygotic twins, (b) the excess of winter births in schizophrenics, (c) the increased incidence of birth complications in schizophrenics, and (d) the occurrence of schizophrenic symptoms in various neurological conditions. This evidence has been extensively reviewed (Davison & Bagley, 1969; Murray *et al*, 1985; Crow & Johnstone, 1987; McGuffin *et al*, 1987*b*; Lewis, 1989; Roberts *et al*, 1990). However, most of these pillars have recently met their experimental Samson and the details of these encounters are worth briefly noting.

The determination of heritability based on monozygotic or dizygotic concordance rates may no longer be valid in general (Burn & Corney, 1988) and may only represent the lower limit of heritability in schizophrenia in particular (Gottesman & Bertelsen, 1989). Monozygotic twins discordant for the expression of Duchenne muscular dystrophy have been reported (Burn *et al*, 1986). To explain this phenomenon it has been proposed that a single egg can form clones at the blastocyst stage and that these clones (the twin pair), although genetically identical, will differ in their expression of the aberrant gene (Burn *et al*, 1986). Such a phenomenon could explain some of the discordance for schizophrenia in monozygotic twins (see Gottesman & Bertelsen, 1989). The excess of winter births accounts for about 5% of cases and this may be an overestimate since it has been argued that reanalysis of the original data on winter births reveals the possibility of an ascertainment artefact which might diminish the significance of the effect (Lewis, 1989,*a*,*b*). On the basis of current data, birth complications might represent a significant aetiological factor in 1–2% of

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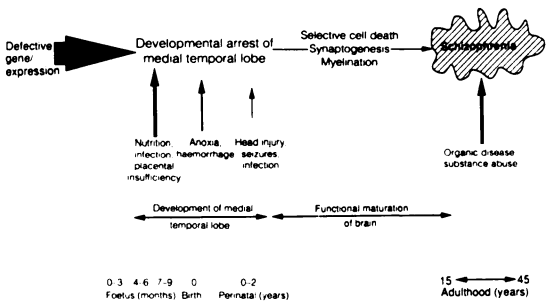


Fig. 2 The relative importance of different factors in the aetiology of schizophrenia (size of arrow reflects relative importance of factor).

cases of schizophrenia. However, the robustness of this finding and the direction of causality (i.e. do birth complications cause schizophrenia or does the expression of the schizophrenia genotype cause birth complications?) has been questioned on epidemiological grounds (Goodman, 1988). Psychotic symptoms indistinguishable from schizophrenia occur during various kinds of neurodegenerative disease (Johnstone *et al*, 1988), notably Alzheimer's disease (Drevets & Rubin, 1989) which particularly affects pre-alpha cells in the medial temporal lobe. However, the incidence of unsuspected organic disease in schizophrenics is only about 5% (Johnstone *et al*, 1987).

Even if taken at face value, the identified environmental factors could account for some 15% of schizophrenia cases. However, bearing in mind the criticisms noted above, 15% may well be an overestimate of cases resulting from environmental factors. Overall the evidence from neuropathological and epidemiological studies supports the view that a developmental anomaly causing structural changes in the brains of schizophrenics is likely to be *genetic* in origin in the majority of cases. Environmental factors such as birth complications or other organic disease which could give rise to phenocopies of schizophrenia are probably responsible for a small, possibly insignificant, number of cases (Fig. 2).

Normal brain development and structural changes in schizophrenia

The human brain develops asymmetrically (Chi *et al*, 1977). The gyral pattern of the temporal lobe develops from the 31st week to term, with the left hemisphere developing one to two weeks *later* than the right. The hippocampus appears during the latter half of pregnancy and reaches approximately 50% of the adult volume by birth. The adult volume is reached at about two years of age. The hippocampi in each hemisphere are symmetrical both in size and pattern of growth (Kretschman *et al*, 1986). The hippocampus forms the medial wall of the temporal horn of the ventricular system. During brain development ventricular size (as a percentage of brain area) is *reduced* (Koop *et al*, 1986). This is particularly noticeable in the temporal horn, whose cross-sectional area is halved between birth and nine years of age (Kurihara *et al*, 1986). So the volumetric growth of the medial temporal lobe causes a compression of the ventricular system, particularly the temporal horn.

The development of the parahippocampal gyrus is asymmetrical and earlier than the development of the hippocampus. The two structures are functionally connected by the perforant path, an excitatory projection from the parahippocampal gyrus/entorhinal cortex into the hippocampus. Loss of or alteration to projection systems during *development* can result in aplasia or dystrophy in the target structure (in this case the hippocampus) (see Roberts, 1990).

The pattern of normal brain development provides an explanation for the structural changes seen in the brains of schizophrenics. The mechanism causing the aberration in brain development is effective during the third trimester, it affects both hemispheres, and it alters the development of the temporal cortex, particularly the parahippocampal gyrus. Since development of the left temporal cortex lags behind the right, any factor which simultaneously arrests both will inevitably affect the left more than the right.

Thus the asymmetric changes in the parahippocampal gyrus will give rise to asymmetrical effects on the (usually symmetrical) development of the hippocampus. This in turn could produce asymmetry of the temporal horn. Suddath *et al* (1989) presented evidence for reduced volume of the temporal lobe, which was inversely correlated to the area of the temporal horn (cf. thinning of parahippocampal gyrus and increased temporal horn area from study of Brown *et al* (1986), discussed above). They argue that changes in the volume of the temporal lobe are translated into relatively larger changes in ventricular volume. Thus ventricular volume acts as a sensitive indicator of reduced brain volume.

Anatomical significance of the parahippocampal gyrus

Information from the association cortex (temporal, cingulate and frontal cortices) converges on the entorhinal cortex and reaches the hippocampus via

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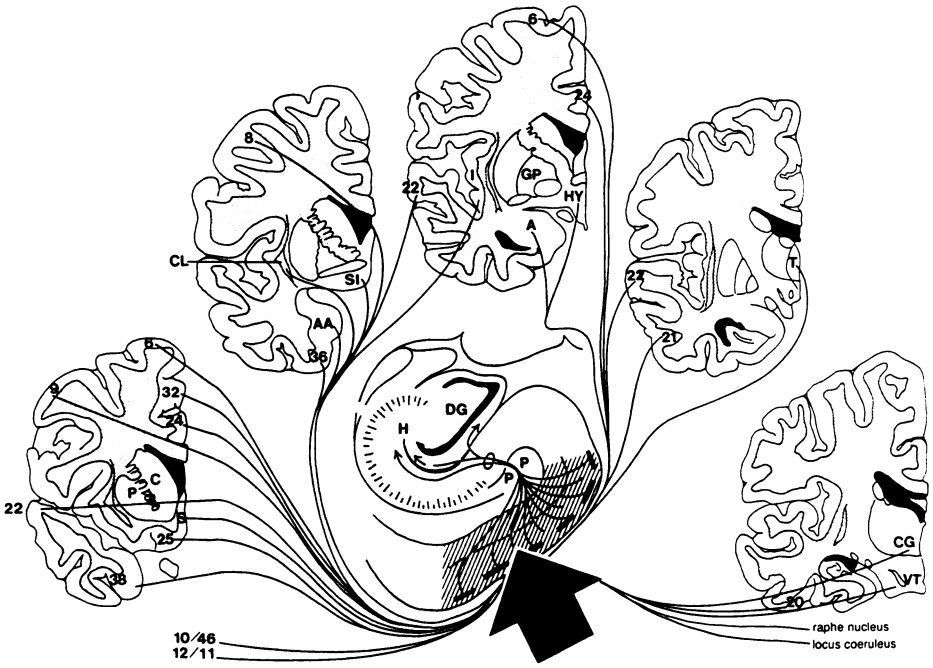


Fig. 3 Projections to the parahippocampal gyrus. The links between various cortical and subcortical areas and the parahippocampal gyrus are shown diagrammatically. The projections shown are those from the same hemisphere but it should be noted that similar (but smaller) projections from the *opposite* hemisphere are also present. The terminal regions of the projections are topographically organised and often separate projections arise from subdivisions of one region (e.g. amygdala). The diagram is a synthesis of data obtained from Van Hoesen (1982), Amaral *et al* (1987) and Insausti *et al* (1987*a*,*b*). (■ parahippocampal gyrus, ▨ white matter, ■ ventricle, A, amygdala, AA, anterior amygdala, C, caudate, CG, central grey, CL, claustrum, DG, dentate gyrus, GP, globus pallidus, H, hippocampus, HY, hypothalamus, I, insula, P, putamen, PP, perforant path, S, septum, SI, substantia inominata, T, thalamus, VT, ventral tegmentum, 6–46, Brodman areas.)

polysynaptic relays in the parahippocampal gyrus and subiculum (Van Hoesen, 1982; Insausti *et al*, 1987*a*,*b*)) (Fig 3). Hippocampal output is organised in a similar fashion. By virtue of this arrangement the parahippocampal gyrus and subiculum serve to 'gate' all information entering and leaving the hippocampus. Direct connections link the medical temporal cortex and the frontal cortex, striatum and amygdala. Temporal cortex, hippocampus and amygdala are thought to be central in the integration of affect and intellect (Frith & Done, 1988). Changes in the functional ('gating') capabilities of the parahippocampal gyrus could have a significant effect on such integrative processes and have large effects on the functioning of many other systems (e.g. dorsolateral pre-frontal cortex) (Weinberger, 1987; Frith & Done, 1988). Changes in the structure and function caused by the developmental abnormalities will inevitably alter the neurochemistry of other brain regions. Neurochemical changes in the brains of schizophrenics are lateralised to a certain extent and have been reviewed (Reynolds, 1989).

The brain in schizophrenia – a summary

Neuropathological studies indicate that the brains of schizophrenics suffer from a developmental abnormality which preferentially, but not exclusively, affects the medial temporal lobe (parahippocampal gyrus, hippocampus and amygdala). Medial temporal lobe structures are believed to have a crucial role in the integration and processing of the input from association cortex. Dysfunction of this system could result in the clinical symptoms that form the core of the schizophrenia syndrome. The cause of the anomaly is probably genetic in the overwhelming majority of cases and affects brain development in the third trimester. The asymmetrical pattern of development in the normal human brain explains why such a defect affecting both hemispheres

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simultaneously will disproportionately affect the left (dominant) hemisphere.

Despite the great progress made in determining the nature of the structural changes in the brains of schizophrenics, the cause of the changes – its mechanism – is still the subject of speculation.

Factors relating to the mechanism of structural change

The evidence for a genetic component of schizophrenia has been exhaustively reviewed (e.g. McGuffin *et al*, 1987*b*) and it is accepted that while there is a genetic component of schizophrenia, its nature (single gene with variable penetrance, polygenic, etc.) is obscure.

Discrete possibilities about genetic mechanisms are difficult to discern. Two classes of genes have been proposed to be involved in cortical development (Rakic, 1988). One class is thought to regulate the number of radial units (columns) in the cortex. A failure here would reduce the number of columns but the neuronal content *within* each column would remain normal. These defects would be early events in corticogenesis (in humans within six weeks of gestation); reduced numbers of proliferative radial units are established in the ventricular zone but each unit can produce the normal (genetic) number of neurons. Cortex suffering from such defects would have a smaller surface area in spite of normal or enlarged thickness and significant neuronal ectopias (as seen in lissencephaly and pachygyria). This is *not* seen in schizophrenics.

A second class of genes is responsible for the control of neuronal proliferation within radial units. Defects in these genes might cause diminished neuronal production within radial units, giving fewer neurons in ontogenetic columns and therefore a thinner cortex. Neuronal number in ontogenetic columns could also be affected by programmed cell death or migrational failure. Thinning of the parahippocampal gyrus is seen in schizophrenia and this second class of genes may repay close study.

Despite this pointer, the complexity of the genetic regulation of brain development is only just becoming apparent (Nowakowski, 1987; McConnell, 1988; Rakic, 1988). Genes on different chromosomes affect the same cell types, other single genes affect widely different cell types and feedback mechanisms exist between afferent and target cells which determine cell survival and regulate synaptogenesis. Overlaying these mechanisms is the crucial factor in development – that of timing. Widely disparate mechanisms (different genes or perturbations in gene expression) operating at the same stage of development produce similar results. Epidemiologically, few cerebral malformations appear to be caused by simple Mendelian inheritance (Larroche, 1984). The fine processes that shape brain development could be viewed as an example of a chaotic phenomenon, where minor changes in any one of dozens of genes will have unpredictable effects. In such circumstances arrest or curtailment of cellular migration is more frequent than complete failure and such phenomena may be more common than previously realised in normal human brains (e.g. see Kaufman & Galaburda, 1989).

In schizophrenia the focus of the abnormality is the parahippocampal cortex and this stone in the developmental pond causes ripples which can spread to affect other brain areas. The magnitude of the genetic defect and the timing of its expression are the vector that determines the size and spread of the ripples. The ripples affect the dynamics of development and cause long-term defects in intellectual function as the brain completes its processes of maturation via mechanisms of programmed cell death, synaptogenesis and myelination (Schneider, 1979; Weinberger, 1987; Goodman, 1989) (Fig. 2). Thus a chaotic parahippocampal tail grows up to wag the temporal dog.

The magnitude of the task of untangling the mechanisms that contribute to the schizophrenogenic brain is only now becoming apparent. Many genes could contribute to the structural abnormalities outlined above and none may be more important than the others. Future studies to locate the gene for schizophrenia might find it useful to bear in mind this background and recall the hard-won lessons on the multifactorial genetics of predisposition to coronary heart disease and thus avoid schizophrenia becoming the mausoleum of molecular biology (see Lander, 1988; Mullan & Murray, 1989; Robertson, 1989).

However, the speed of progress in neuropathological investigations allied to the expansion in our understanding of the genetics of developmental neurobiology augurs well for the future and offers a way ahead. Neuropathological studies should aim to define the essentials and limits of structural changes (e.g. cell types affected and altered patterns of neuronal connections) and relate these to the data on factors and mechanisms responsible for the regulation of such phenomena derived from basic studies of brain development. In this way the complexities of genetic regulation can be reduced to postulate mechanisms (target genes) and suggest practical ways of pin-pointing which aberrant genetic structures or regulatory mechanisms generate the brain abnormalities that cause schizophrenia.

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