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Review Article

Is the Concept of Frontal–Subcortical Dementia Relevant to Schizophrenia?

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A syndrome of subcortical dementia has been described in conditions predominantly affecting the basal ganglia or thalamus, structures that have also been implicated in the pathogenesis of schizophrenia. There are similarities between subcortical dementia and the type II syndrome of schizophrenia, in terms of clinical features, pattern of neuropsychological deficits, pathology, biochemistry and data from brain-imaging studies. These similarities raise the possibility that certain schizophrenic symptoms, particularly negative symptoms and disturbance of movement, may reflect subcortical pathology. Neuropsychological deficits of presumed frontal lobe origin have been reported in some schizophrenic subjects. The occurrence of such deficits in a condition in which frontal lobe pathology has not been clearly demonstrated may be explicable in terms of a subcortical deafferentation of the pre-frontal cortex.

The concept of subcortical dementia

Subcortical dementia refers to the behavioural symptoms, including changes in mood and cognition, that are associated with, and which may be directly or indirectly attributable to, lesions in the subcortical structures of the brain. The term was brought to prominence by Albert *et al* (1974), who used it to describe a distinctive pattern of neuropsychological deficits in patients with progressive supranuclear palsy (PSP), comprising forgetfulness, slowness of thought processes, alterations of mood and personality, and an impaired ability to manipulate acquired knowledge. McHugh & Folstein (1975) identified a similar pattern of symptoms in Huntington's disease, with abnormalities of problem solving, insight, judgement, abstraction, attention, concentration and motivation. Thus defined, subcortical dementia has been described in other disorders with pathology predominantly involving subcortical grey matter, particularly the basal ganglia and thalamus (Cummings, 1986, 1990). The operational definitions of cortical and subcortical dementia used by Cummings (1986) derive their authority from a claim by Benson (1983) that the clinical features alone provide a clear distinction between the two types of dementia, although the validity and reliability of these as operational criteria have not been established (Whitehouse, 1986; Mayeux & Stern, 1987; Ron, 1988).

In his review of subcortical dementia, Cummings (1986) argues that in cortical dementia, primarily involving the association areas of the cerebral hemispheres and medial temporal lobes, there is intellectual decline with loss of abilities such as language, learning, perception, calculation and praxis. Thus, cortical dementia is characterised by aphasia, amnesia, agnosia, acalculia, and apraxia. In contrast, the gradual decline in intellectual and memory functions seen in conditions with lesions in the basal ganglia, thalamus and brain-stem structures, is characterised by marked slowness of thinking (bradyphrenia) and action, and impaired motivation, attention and arousal, often accompanied by depressed mood and sometimes by psychotic disturbance.

Cummings (1986) considers that the evidence supporting a distinction between the two types of dementia is not limited to the clinical features alone. Evidence from studies of cortical and subcortical disorders suggests differences in cognitive deficits and motor abnormalities as well as topographical and neurochemical changes. Brown & Marsden (1988) have provided a thorough review of the neuropsychological evidence for a distinction and are more circumspect about the validity of the concept. They have emphasised the need for sensitive tests to clarify the situation, echoing the suggestions of others, such as Mayeux *et al* (1983) and Freedman & Oscar-Berman (1986*b*).

In this review we explore the relationship between some patients with schizophrenia and those with subcortical dementia and discuss the likely implications. In particular, similarities exist with type II schizophrenia (Crow, 1980). Comparisons are made between the two conditions in terms of clinical features, pattern of neuropsychological deficits, pathology, and biochemistry, as well as evidence from computerised tomography (CT) and positron emission tomography (PET). That frontal lobe deficits have been demonstrated in both conditions implicates frontal–subcortical pathways, particularly those involving basal ganglia and thalamus.

Clinical features of subcortical dementia and schizophrenia

The clinical features of subcortical dementia, especially slowness, apathy, and loss of motivation, closely resemble the negative symptoms of schizophrenia. Negative symptoms are an essential feature of the type II syndrome (Crow, 1980) and include flattening of affect, poverty of speech, and loss of drive and volition. Other symptoms and behavioural disturbances, including social withdrawal, apathy and anergia, have also been described in this context (Barnes & Liddle, 1990) and may be likened to the apathy and motivational difficulties described in patients with subcortical dementia.

Depression, an integral feature of subcortical dementia, has been considered by some as an integral part of schizophrenia (Knights & Hirsch, 1981; Hirsch *et al*, 1990). Slowed cognitive functioning in schizophrenia has been reported over the last 60 years (Babcock, 1930, 1933), being consistently corroborated in numerous investigations, although the term 'bradyphrenia' has never been applied to this phenomenon. The frontal-type deficits which are observed in both subcortical dementia and in schizophrenia provide further parallels between the two conditions. Other parallels can be drawn between disorders with subcortical pathology and schizophrenia, including the presence of abnormal involuntary movements, and psychosis with a predominance of positive symptoms, such as delusions and hallucinations.

Abnormal involuntary movements

The conditions manifesting subcortical dementia are characterised by abnormal movements, usually considered to be a manifestation of basal ganglia pathology (Jeste *et al*, 1984*b*; Cummings, 1986). There is an overlap here with schizophrenia, in which involuntary movements are common. Although much of the abnormal movement seen, such as tardive dyskinesia, can be at least partly attributed to medication, there is evidence that motor disturbance can be an integral part of the schizophrenic illness. For example, abnormal movements were consistently reported in schizophrenic patients before the introduction of antipsychotic medication (Kahlbaum, 1874; Kraepelin, 1913) and have also been observed in contemporary studies of untreated patients (Owens *et al*, 1982; Rogers, 1985; Waddington & Crow, 1988).

Several studies in schizophrenia have found an association between abnormal involuntary movements and both cognitive deficits and negative symptoms (Waddington, 1989*a*). For example, Owens & Johnstone (1980) found significant inter-relationships between negative symptoms, poor behavioural performance, and neurological signs, including disorders of movement. Jeste *et al* (1984*a*,*b*) found an association between tardive dyskinesia and negative symptoms, and concluded that "the apparent similarity with the reported subcortical dementias raises a possibility that subcortical (e.g. basal ganglia) damage might be related to certain major clinical manifestations of our persistent tardive dyskinesia patients". Barnes (1988) concluded that the observed associations between tardive dyskinesia, negative symptoms and cognitive deficits might be explained by a shared pathophysiology within the basal ganglia.

Psychosis

A number of neuropsychiatric disturbances have been described in those conditions exhibiting subcortical dementia. These include a high reported incidence of neurotic symptoms, depression, dementia and schizophrenia-like psychoses, which may precede other manifestations of the disease (Jeste *et al*, 1984*b*; Cummings, 1985*c*, 1986). The association with psychosis further suggests a link between subcortical dementia and schizophrenia. For example, Huntington's disease, a condition which produces dramatic striatal degeneration, is often misdiagnosed in the early stages as schizophrenia. In one series of patients with Huntington's disease (Dewhurst *et al*, 1969), half had delusions at the time of admission to hospital. When the entire course of the disease is taken into account, the majority of patients with Huntington's disease will manifest psychotic ideation (Cummings, 1986).

Psychosis is uncommon in idiopathic Parkinsonism, although it has been reported in conditions such as post-encephalitic Parkinson's disease (Crow *et al*, 1976), Wilson's disease, spinocerebellar degenerations, and subcortical neoplasms and infarctions (Jackson & Immerman, 1919; Keddie, 1969; Trimble & Cummings, 1981; Cummings, 1985*a*,*b*), although the association with Wilson's disease has been disputed (Dening & Berrios, 1989).

Subcortical involvement in schizophrenia

Frontal lobe connections with subcortical structures

Recent work on the structure and fibre connections of the basal ganglia indicate that these structures are highly organised, with segregated circuits throughout their course (Alexander *et al*, 1986; DeLong *et al*,

1990). Their role is now understood to extend beyond the control of movement, with cognitive and limbic functions being influenced by inputs from association and limbic cortical areas. Five distinct basal ganglia–thalamocortical circuits have been identified: the motor and oculomotor circuits are both associated with sensorimotor functions; two segregated pathways, the dorsolateral pre-frontal and orbitofrontal, are associated with cognitive functions; and finally, the anterior cingulate circuit is associated with limbic mechanisms (DeLong *et al*, 1990).

Nauta (1986) has proposed an alternative system for the organisation of the pathways connecting cortical and subcortical structures. The key element of this proposal is that the afferent pathways from the allocortex and neocortex funnel into the basal ganglia, so that there is a diminution in the number of neurons. DeLong *et al* (1990) have applied this notion to each of the five circuits, which have a broadly similar organisation, while remaining separate from each other.

The organisation of these pathways, with their close proximity in the basal ganglia, provides a model for understanding how pathology in that region might generate a range of symptoms, including disorders of movement, affect, and cognition. While outside the basal ganglia, these pathways are not so closely aligned and lesions would be expected to produce more limited and discrete impairment of cognitive, limbic or motor function; disruption occurring within the basal ganglia would be more likely to produce symptoms involving all of these functions. Thus, the topographical arrangement of these pathways would seem to be consistent with evidence of cognitive, psychiatric, and motor disturbance occurring together in disorders of the basal ganglia, such as Huntington's disease and Parkinson's disease. The implication of similar disturbances coexisting in schizophrenia is that basal ganglia pathology is relevant in this condition. Interestingly, Rapoport (1990) and Wise & Rapoport (1989) have presented a similar argument to suggest that obsessive–compulsive disorder may be explained as a disorder of the basal ganglia, particularly involving the orbitofrontal–striatal–thalamic loop.

The role of the basal ganglia and thalamus in schizophrenia

The notion that a disorder of the basal ganglia or thalamus is important in the pathogenesis of schizophrenia is not new (Mettler, 1955; Lidsky *et al*, 1979) but there has been a resurgence of interest in it (Patterson, 1987; Oke & Adams, 1987; Crosson & Hughes, 1987; Barnes, 1988; McKenna, 1990; Robbins, 1990, 1991; McGrath, 1991). Although the evidence is inconclusive, the association with disorders of movement and the results of various lines of investigation, including neuropathology and scan studies, have implicated the basal ganglia and thalamus as possible sites of involvement in schizophrenia. For example, Bowman & Lewis (1980) attempted to identify the site of damage in schizophrenia by examining 22 neurological disorders which had symptoms in common with schizophrenia (apathy, dementia, attentional deficits, auditory hallucinations, "jargon speech" aphasia, and catatonia) as well as known sites of neural damage, and comparing them with neurological disorders with no symptoms of schizophrenia. They found that the basal ganglia were the most commonly involved structures in those conditions which had shared symptoms with schizophrenia.

Other studies and case reports have noted an association between the negative as well as positive symptoms of schizophrenia and conditions with subcortical pathology. These involve the basal ganglia predominantly, with sparing of the cortex. Laplane *et al* (1984) described three patients with lesions of the basal ganglia in which the predominant symptom was 'psychic akinesia', with a severe reduction of both mental and behavioural activities. Casanova *et al* (1989) and Francis & Freeman (1984) reported cases of familial non-arteriosclerotic mineralisation of the basal ganglia in which affected members exhibited schizophreniform psychosis. Prasad *et al* (1989) identified 17 patients with basal ganglia mineralisation on CT scan from a total of 725 consecutive scans from a psychiatric population. Eight had a diagnosis of schizophrenia while nine had other diagnoses, mostly dementia. Jones *et al* (1989) describe brief psychotic reactions in clear sensorium post-operatively in Parkinsonian patients who underwent autograft of adrenal medullary tissue to their right caudate nucleus. Cummings *et al* (1983) described a patient with idiopathic calcification of the basal ganglia presenting with a schizophrenia-like psychosis who later developed movement disorder and mild dementia. The latter authors conclude that "the occurrence of schizophrenia-like psychoses in subcortical disorders may provide a heuristic link between the idiopathic and symptomatic schizophrenias and present an important avenue for investigating the psychobiology of schizophrenic psychoses".

Neuropathological findings

Post-mortem investigations of schizophrenic patients have provided some clues as to the underlying processes involved, though a number of structures have been implicated, including temporal lobes, frontal lobes, and subcortical as well as other structures (Lantos, 1988). The CT findings of ventricular enlargement have been corroborated by post-mortem findings (Brown *et al*, 1986).

Early developmental pathology may be instrumental in the later manifestation of illness, as the abnormal brain matures (Weinberger, 1987; Murray & Lewis, 1987; Murray *et al*, 1988; Lewis, 1989; Crow *et al*, 1989) and may result from aberrant neuronal migration (Jakob & Beckmann, 1986). Such hypotheses receive some support from animal work (Goldman-Rakic *et al*, 1983).

The pathological findings to date are confused by various methodological difficulties and the lack of clinical correlates. The latter issue has been addressed only recently by the team at Northwick Park (Crow *et al*, 1989; Bruton *et al*, 1990). In their study of post-mortem brain tissue, comparing normal controls, patients with 'Feighner-positive' schizophrenia, and patients with Alzheimer's disease, Crow *et al* (1989) demonstrated enlargement of the temporal horn of the lateral ventricle mainly on the left side, in the patients with schizophrenia. They suggest that the lack of demonstrable gliosis in this area is explicable in terms of developmental arrest.

A further paper by the same group (Bruton *et al*, 1990) reported that schizophrenic patients had reduced brain weight and length, as well as ventricular enlargement, these features most strongly distinguishing patients from normal controls. As well as changes suggesting abnormalities of brain development in these patients, there were vascular lesions, particularly of the caudate and putamen and fibrosis in cortex and white matter; these features were considered to be acquired, and the authors suggested that the structurally abnormal brain may be vulnerable to damage later in life. Alternatively, they suggested that schizophrenia may be a final common pathway for either developmental or acquired brain damage. The clinicopathological correlates presented suggested that although clinical findings correlated with abnormalities there was no consistent pattern, and it was not possible to draw conclusions about the relative importance of presumed developmental as compared with acquired brain abnormalities.

Pathological changes in various subcortical structures have been reported in schizophrenia. In their review of the neuropathological findings in this condition, Kleinman *et al* (1988) concluded that the basal ganglia require further investigation, particularly their connections with other structures. In a post-mortem study investigating changes in basal ganglia and limbic system of 13 patients with schizophrenia, Bogerts *et al* (1985) found that the medial aspect of the globus pallidus was reduced in volume compared with controls. Lesch & Bogerts (1984) studied diencephalic and mesencephalic structures, including thalamic and extrathalamic brain areas. The only significant finding was loss of periventricular grey matter in the region of the third ventricle. Similarly, Stevens (1982) found gliosis in this region, the diencephalon and peri-aqueductal structures. However, others have detected significant changes in the thalamus which has intimate connections with the basal ganglia and cortex. Pakkenberg & Gundersen (1989) reported a 40% reduction in total neuron number in the mediodorsal nucleus of the thalamus in brains of chronic schizophrenic patients compared with controls.

The available evidence would suggest both neurodevelopmental and acquired pathologies in schizophrenia, affecting a number of structures including subcortical grey matter. Further work is necessary to establish the relationship between pathological findings, cognitive deficits, and symptoms.

Neurotransmitter systems

A number of neurotransmitter systems have been implicated in both schizophrenia (Meltzer, 1987; Deakin, 1988; Reynolds, 1989) and subcortical dementia (Cummings, 1986). In particular, the dopaminergic pathways have been implicated as the most important systems affected in both conditions. In the subcortical dementias, dopamine neurotransmission is affected in a number of conditions; most notably, idiopathic Parkinson's disease involves losses of dopamine, although other neurotransmitter systems are also affected. In PSP there is marked deficiency of dopamine in the basal ganglia (Kish *et al*, 1985; Ruberg *et al*, 1985) and cognitive impairments of PSP are thought to correlate best with reduced levels of dopamine (Cummings, 1986). In Huntington's disease the GABAergic system is preferentially affected, resulting in hyperinnervation by the dopaminergic system (Afifi & Bergman, 1986).

The neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) destroys the zona compacta of the substantia nigra, the area principally affected in Parkinson's disease (Langston, 1987). This results

in a hypodopaminergic state (Langston & Tetrud, 1988), although other neurotransmitters are also affected; in particular, depletion of cortical noradrenalin may result from damage to the locus coeruleus (Crossman, 1987). When compared with controls, patients with MPTP-induced Parkinsonism show subtle deficits on neuropsychological tests which assess predominantly frontal cortical function, including impairment on visuospatial and sequencing tasks, as is also seen in patients with idiopathic Parkinson's disease (Stern & Langston, 1985). As the MPTP lesion affects subcortical rather than cortical structures, one explanation for the neuropsychological deficits may be a deafferentation of the subcortical connections to the frontal lobe.

Hornykiewicz (1973) considers that hypokinetic-rigid syndromes predictably reflect striatal dopamine deficiency, and Bachman & Albert (1984) postulate that the associated dementias result from such dopamine loss. Comparison with the cortical dementias has suggested use of the terms 'dopaminergic' and 'cholinergic' dementias as roughly corresponding with subcortical and cortical dementia respectively, although such a distinction is simplistic and unsatisfactory (Tagliavini *et al*, 1984; Ruberg *et al*, 1985; Kish *et al*, 1985).

In schizophrenia, the most consistent finding in post-mortem studies is of increased numbers of dopamine D2 receptors in the striatum, putamen and nucleus accumbens (Owen *et al*, 1978; Lee & Seeman, 1980; Mackay *et al*, 1980) and this has been proposed as being of aetiological importance (Lee & Seeman, 1980). Although the work of Wong *et al* (1986), using PET in drug-naive patients, supports these post-mortem findings, the Karolinska group found no such increase in these receptors in drug-naive patients (Sedvall *et al*, 1987; Farde *et al*, 1990). Post-mortem studies of dopamine content and levels of homovanillic acid have produced inconsistent results. Mackay *et al* (1980) found increases of dopamine in the nucleus accumbens, while Crow *et al* (1979) found increases in the caudate and putamen. Reynolds (1983, 1987) reported increased dopamine levels in the left amygdala, with no changes in the caudate, and Deakin *et al* (1989) postulated that this may result from loss of glutamate afferents to the amygdala. Gray *et al* (1991) also suggested that glutamatergic pathways are important mediators of dopaminergic function. Others have focused on GABAergic systems, cholecystokinin and neurotensin, particularly because of their effects on modifying dopamine neurotransmission (Reynolds, 1989). On the basis of the neurochemical evidence, Reynolds (1989) hypothesises that the amygdala, a subcortical structure, is actually the focus of abnormality in schizophrenia.

The limbic system and temporal lobes have been a focus of attention as important sites in the development of psychosis because of the association of pathology in this region, such as temporal lobe epilepsy, and schizophreniform and affective psychoses (Slater *et al*, 1963; Flor Henry, 1969; Davison & Bagley, 1969). However, such psychoses may result from secondary effects in areas close to the temporal lobe rather than as a direct effect. Stevens (1990) discusses possible mechanisms in patients with temporal lobe epilepsy; for instance, the phenomenon of 'surround inhibition' may act to suppress the epileptic focus and may involve enhanced dopaminergic and possibly other inhibitory transmitters. It is postulated that such overactivity is important in the pathogenesis of psychosis.

In keeping with this hypothesis, Reynolds' (1983) report of increased dopamine in the left amygdala of patients with schizophrenia may result from the effects of a glutamatergic impairment affecting the neighbouring hippocampus, which may be specific to the left hemisphere (Reynolds, 1989). Thus, whether as a primary effect or a secondary effect of other neurotransmitter systems, evidence continues to implicate the dopaminergic system in the manifestation of schizophrenic symptoms.

Cummings (1985*c*) suggests that limbic and extrapyramidal structures form a unified system mediating motivation, mood and motion. Cognition must be included in view of the anatomical evidence discussed earlier. Both systems are heavily invested with dopamine projections, and this may account for the coexisting motor, cognitive and behavioural abnormalities in conditions where there is a disturbance of dopamine systems, such as the spontaneous movement disorders and schizophrenia.

If subcortical dementia does result from a hypodopaminergic state, how does this bear upon the question posed in the title of this review? It has been suggested that negative symptoms could represent a decrease in dopaminergic function (Chouinard & Jones, 1978; Mackay, 1980; Lecrubier *et al*, 1980), and this suggestion receives some support from clinical studies. The investigations testing dopamine agonists as a potential treatment for negative symptoms have yielded inconsistent results, although generally the findings suggest limited benefit (Angrist *et al*, 1980; Van Kammen & Boronow, 1988). However, the expectation that dopamine antagonists would exacerbate negative symptoms is not consistently supported (Barnes & Liddle, 1990). Indeed, an improvement in negative symptoms after antipsychotic medication is commenced, and a worsening on drug withdrawal, have been reported (Goldberg, 1985; Brier *et al*, 1987),

while Pogue-Geile & Harrow (1985) found no differences when comparing ratings of negative symptoms in young schizophrenic patients on and off medication.

Andreasen (1989) proposes a model for schizophrenia which takes account of the coexistence of positive and negative symptoms. She draws on evidence from PET studies in schizophrenia, together with animal work indicating a reciprocal relationship (Pycock *et al*, 1980) between frontal and subcortical dopamine function. She suggests that there is an imbalance in the relationship between cortical and subcortical areas and proposes that this relationship changes over time. In this way there is a progression of symptoms from a 'positive', floridly psychotic onset, to an end-stage defect state characterised by a predominance of negative symptoms. Her model therefore suggests that the symptoms in schizophrenia are explicable by a single underlying process, rather than implicating pathologies at different sites. This would necessarily imply a reciprocal relationship between positive and negative symptoms, which is only partially supported by evidence (Lenzenweger *et al*, 1989). Crow's model of type I and type II schizophrenia, on the other hand, suggests that positive and negative symptoms represent separate underlying processes. Liddle (1987*a*,*b*; Liddle & Barnes, 1990) advocates separate but overlapping pathologies, a model which unifies the formulations of Crow and Andreasen, and may explain the observed coexistence of the syndromes.

Andreasen (1987) has emphasised the similarity of negative symptoms to frontal lobe deficits. This would seem to be in keeping with the observed similarity to the symptoms of subcortical dementia when the frontal–striatal connections are considered; thus, proponents of subcortical dementia have suggested that the more appropriate term of 'frontal–subcortical dementia' be applied (Albert, 1978; Cummings, 1986), while Robbins (1990, 1991) suggested the term 'fronto–striatal dementia'.

The relationship between the frontal lobes, the basal ganglia and dopamine has been investigated in studies of the cognitive deficits of Parkinson's disease (Agid *et al*, 1984; Gotham *et al*, 1988). The model proposed to explain frontal lobe dysfunction in Parkinson's disease is subcortical deafferentation of frontal projection areas (Taylor *et al*, 1986; Sagar & Sullivan, 1988; Gibb, 1989). A similar notion has been applied to MPTP lesions and PSP (D'Antona *et al*, 1985; Agid *et al*, 1987). That is, there is a primary degeneration of subcortical areas with a loss of activating subcortical afferents to the frontal cortex, resulting in secondary frontal hypometabolism and the manifestation of the frontal lobe syndrome. Weinberger and his colleagues (Weinberger *et al*, 1986; Berman *et al*, 1986) proposed that frontal cortical dopamine release is reduced in schizophrenia resulting in an avolitional frontal lobe syndrome. Again, impaired dopamine transmission frontally may be explained by deafferentation of frontal cortex from subcortical areas.

The role of the D1 and D2 dopamine receptors may be important here; these may act independently or have antagonistic and synergistic actions to each other (Waddington, 1989*b*, 1990). Meltzer (1987) suggests that in this way both increased and decreased dopaminergic function may occur at different sites. D1 dopamine receptors are found in mesolimbic, striatal and frontal cortex (Seeman, 1980; DeKeyser *et al*, 1988), whereas D2 receptors are not found in human cortex (Farde *et al*, 1988; Hall *et al*, 1988), implying that antipsychotics act subcortically. Crow *et al* (1980) found a high correlation between the number of D2 receptors in the basal ganglia and the presence of delusions and hallucinations. That no increase in D1 receptor numbers has been reported (Cross *et al*, 1981; Pimoule *et al*, 1985; Czudek & Reynolds, 1988) compared with D2 receptor numbers may indicate a relative hypofunctioning of the D1 receptor system, with a consequent frontal hypodopaminergic state. Indeed, Hess *et al* (1987) have reported a significant decrease of the D1 receptor in the striatum, although this has not been replicated (Reynolds, 1989). Such a reciprocal relationship between frontal and subcortical dopaminergic functioning would support the hypotheses suggested (Weinberger *et al*, 1986; Andreasen, 1987; Liddle, 1990), and implicate the fronto–subcortical system as important in the pathogenesis of both positive and negative symptoms. Indeed, Iversen (1988) has suggested that schizophrenia may result from progressive degeneration of cortical–subcortical neurotransmitter neurons.

Brain-imaging studies of schizophrenia

Main findings in schizophrenia and the subcortical dementias

The results of CT investigation of brain structure in schizophrenia have been variable, with reports of lower density in the anterior left hemisphere (Golden *et al*, 1981) and laterality differences in white matter density (Largen *et al*, 1984; Rossi *et al*, 1989). The most consistent finding has been lateral ventricular enlargement, although the cause of this remains unclear (Weinberger *et al*, 1979).

There have been relatively few CT studies in

schizophrenia that have demonstrated abnormalities in subcortical structures. Vita (1989) examined CT densities of brain nuclei in 39 patients with DSM-III-R diagnosed schizophrenia and 14 control subjects. Significantly increased tissue densities were found in the anterior region of the thalamus and in the right putamen of the schizophrenic subjects. There was also a significant interhemispheric asymmetry of density of the caudate nucleus, with relative left hypodensity. Similar abnormalities of subcortical nuclei have been found by Dewan *et al* (1983) and Stevens (1982). In a CT study comparing 29 patients with tardive dyskinesia (TD), most of whom had a diagnosis of residual schizophrenia, with a similar number of age- and sex-matched controls, Bartels & Themelis (1983) found that patients with TD had significantly wider third ventricles, a larger bicaudate distance, smaller heads of the caudate nuclei, and smaller lenticular nuclei, suggesting structural abnormalities in the basal ganglia in TD. In a magnetic resonance imaging (MRI) study of schizophrenia, Besson *et al* (1987) found that TD was associated with increased regional spin-lattice relaxation times (T1) in the basal ganglia, suggesting pathological changes. These findings support the role of these subcortical areas in schizophrenia, although other areas are also implicated. Further work is required to investigate the association between these various findings and both clinical and neuropsychological features.

In patients with PSP, in which pathology is limited to subcortical structures, PET has revealed cortical hypometabolism affecting the frontal lobe (D'Antona *et al*, 1985). There is a parallel here with reports of frontal hypometabolism detected by PET in patients with chronic schizophrenia (Buchsbaum *et al*, 1984; Farkas *et al*, 1984; Wolkin *et al*, 1985), and this hypofrontality was not found to be affected by antipsychotic medication over 3-14 months (Buchsbaum *et al*, 1987). However, other workers such as Early *et al* (1987) and Szechtman *et al* (1988) have not confirmed hypofrontality when investigating groups of acute drug-naive schizophrenics. Indeed, Szechtman *et al* (1988) found hyperactivity in frontal areas relative to posterior cortical areas, and suggested that several years of exposure to antipsychotic medication may contribute to the hypofrontality reported by others. This may, however, relate to chronicity of illness rather than effects of medication.

Studies that have looked at the basal ganglia have generally reported reduced metabolism in these regions (Buchsbaum *et al*, 1982, 1987; Sheppard *et al*, 1983), which show an increase in metabolic rate in response to antipsychotic medication (Buchsbaum *et al*, 1987; Szechtman *et al*, 1988) and which may reflect "normalisation of the low rates observed" (Buchsbaum & Haier, 1987). Again, there have been opposing findings in drug-naive patients, with abnormally high blood flow reported in the left globus pallidus of such patients with schizophrenia (Early *et al*, 1987).

Cortical/subcortical imbalance

In PET studies comparing cerebral glucose utilisation by initially unmedicated schizophrenic patients and matched controls, Gur *et al* (1987*a*,*b*) found differences in the cortical-subcortical gradient. Although the schizophrenic subjects had comparatively lowered metabolism both cortically and subcortically, there was evidence for a relative hypocortical and hypersubcortical metabolism, indicating a steeper subcortical to cortical gradient for schizophrenics. Surprisingly, there was no change in this gradient when neuroleptics were introduced, and the authors felt this observation warrants further investigation, particularly as dopaminergic pathways may be implicated.

Although these findings require clarification, they imply that these areas are important in the pathogenesis of schizophrenia. A possible mechanism to explain the frontal-subcortical gradient is deafferentation of the frontal lobe. Although Weinberger *et al* (1986) hypothesise that a pre-frontal cortical deafferentation lesion would explain some of the features of schizophrenia, the possibility of a subcortical deafferentation lesion would also be in keeping with the evidence. Subcortical hypermetabolism would also be consistent with the idea that positive symptoms are due to excess dopamine subcortically (Weinberger *et al*, 1986), while relative hypometabolism of frontal areas would be a possible explanation for negative symptoms.

Neuropsychological aspects of schizophrenia and subcortical dementia

Central to the notion of subcortical dementia is the premise that the profile of cognitive deficits described distinguish it from a cortical dementing process. However, the presumed anatomical interdependence of cortical and subcortical areas would predict some overlap in the cognitive deficits exhibited between the two dementias. Such overlap would also be expected where the cognitive functions mediated by the cortex are dependent on the integrity of the cognitive functions mediated by the subcortex, and vice versa. In view of the anatomical connections between frontal and subcortical areas, features of frontal lobe dysfunction might be expected in both

cortical and subcortical disorders; however, more posterior deficits, such as apraxia or acalculia, would not be expected in the subcortical disorders.

This hypothesis is supported by animal studies showing similar effects of lesions of frontal cortical areas compared with lesions of corresponding striatal areas (Divac, 1984). In the subcortical dementias, similarities with the pattern observed in frontal lobe dysfunction reinforce the appropriateness of the description 'frontal–subcortical' dementia. In the discussions to follow, the terms 'cortical' and 'subcortical' dementia will refer to dementias with a predominantly cortical or predominantly subcortical origin.

Several studies have examined the neuropsychological deficits of conditions associated with predominantly subcortical and cortical pathologies. One of the major problems in summarising the results of these different studies is that the different patient groups are rarely equivalent in overall severity of dementia, patients with subcortical dementia being generally less demented than those with cortical involvement. Even in studies directly comparing cognitive functioning in subcortical and cortical groups, the results have often been confounded by the failure to match appropriately for extent of dementia. For example, when Mayeux *et al* (1983) reanalysed their results from an earlier study (Mayeux *et al*, 1981) they found that when their groups of patients with Parkinson's, Huntington's and Alzheimer's disease were equated on overall intellectual impairment, the distinctive patterns of cognitive deficits previously reported disappeared. Similarly, while a study showing different patterns of cognitive deficits in patients with Alzheimer's and Parkinson's disease was interpreted by the authors as evidence for a distinction between cortical and subcortical dementia (Huber *et al*, 1986), it has been argued that if differences in overall levels of dementia were taken into account then the results would be compatible with a single dementing process affecting both groups but to a different extent (Rosen, 1987).

In their extensive review of the neuropsychological evidence for a discrete subcortical dementia, Brown & Marsden (1988) concluded that such a distinction has yet to be proven. However, as they point out, although there are a large number of studies showing similarities between Alzheimer's disease, Parkinson's disease and Huntington's disease, there are also a handful of studies showing clear differences (Sagar *et al*, 1985; Freedman & Oscar-Berman, 1986*a*, 1987; Heindel *et al*, 1987, 1988; Sahakian *et al*, 1988). Studies such as these, that show a double dissociation of deficits, are generally interpreted as evidence for the involvement of different underlying processes, although strictly speaking this interpretation is valid only if the subjects being compared are originally from the same population with respect to the functions being assessed (Shallice, 1979; Brown & Marsden, 1988).

The fact that there is a large overlap in the neuropsychological dysfunctions of cortical and subcortical dementia is not surprising in view of the anatomical and functional interrelatedness of these brain areas. Viewed within this context, the albeit small number of studies to date that have shown dissociable deficits may be of particular interest in directing attention to what will most likely represent subtle differences in patterns of cognitive impairments. The use of detailed and highly selective tests in the future will help to elucidate these distinctions further (Brown & Marsden, 1988).

So how do the neuropsychological deficits that suggest a distinction between the two types of dementia relate to schizophrenia? Bradyphrenia has been considered the cardinal feature of subcortical dementia and it is possible to draw close parallels with schizophrenia. The two dementias are also reported to show differences between procedural and declarative knowledge, recall and recognition memory as well as other more subtle aspects of memory function. The evidence for such dysfunction is presented, although more work is required in these areas for schizophrenia.

Bradyphrenia

The term 'bradyphrenia' was introduced by Naville (1922) to describe patients with Parkinsonism secondary to encephalitis lethargica. Other terms have also been applied, such as 'psychic akinesia' (Hassler, 1953; Laplane *et al*, 1984; Rogers, 1986). Cummings (1986) considers that slowing of cognitive functioning remains the most compelling feature, providing a distinction between dementia of subcortical origin and cortical dementia. Rogers (1986), preferring to avoid nomenclature that implies a particular topography, has argued that subcortical dementia is a more recent synonym for bradyphrenia. Robbins (1991) considers that the distinction between the two dementias provides a means of understanding the slowness apparent in some patients who are nevertheless able to complete a task accurately.

The measurement of cognitive speed presents a number of challenges. Earlier workers emphasised the need for error-free cognitive tasks (see Eysenck, 1968). Also it is important to separate motor speed from cognitive speed. Various tests have been devised to attempt such a separation, and have included

simple cancellation and other tests (see Eysenck, 1968; Coughlan & Hollows, 1985; Dubois *et al*, 1988; Nelson *et al*, 1990) as well as computerised test procedures (Rogers *et al*, 1987; Morris *et al*, 1987, 1988; Owen *et al*, 1990). For example, Morris *et al* (1987) developed a sophisticated computerised version of Shallice's 'Tower of London' task (Shallice, 1982), which incorporates a yoked control. The latter allows motor and therefore cognitive speeds to be estimated. Such an assessment has revealed differences between subjects with frontal lobe lesions and patients with Parkinson's disease (Morris *et al*, 1988; Owen *et al*, 1990) in planning (time taken to make the first move) and subsequent thinking times.

These two components of bradyphrenia have also been supported by the study of Dubois *et al* (1988) in their comparison of patients with Parkinson's disease and PSP with matched normal controls. They concluded from their findings that slowness in decision making related to basal ganglia dysfunction, while slowing of (subsequent) thought processes resulted from frontal dysfunction. Such a distinction has not yet been demonstrated in patients with schizophrenia, although it is presently under investigation by the present authors, employing the same computerised tests developed by Morris *et al* (1987).

Bradyphrenia in schizophrenia and other psychiatric disorders

Recent work on bradyphrenia in psychiatric disorders has focused on depressive illness (Rogers *et al*, 1987; Rogers, 1988). Rogers *et al* (1987) suggested that psychomotor retardation in depression may result from dopaminergic dysfunction. However, this notion remains a controversial area (Goodwin *et al*, 1970; Matussek *et al*, 1970; Rafal *et al*, 1984; Gibb, 1989).

Parallels may also be drawn between bradyphrenia and schizophrenia. Babcock (1930, 1933, 1941) hypothesised that abnormal slowness among psychotics could account almost entirely for the general intellectual deterioration observed, and she believed that much of their general behaviour, now often conceived in terms of negative symptoms, could be explained by this specific cognitive deficit. She demonstrated that a number of tests of motor and mental speed differentiated well between normal individuals and psychotic patients. Twenty years later, Babcock's findings were further investigated in studies by Shapiro & Nelson (1955) in which 20 normal subjects, 20 schizophrenics, 20 manic depressives, and 20 'organics' were assessed using the Babcock test and other measures of intellectual speed, such as the Nufferno test. All the cognitive measures differentiated between the groups, except that it was not possible to differentiate between chronic schizophrenics and patients with organic disorders. However, this latter comparison was confounded by the inclusion of psychiatric patients, such as leucotomised individuals, within the organic cohort. The authors found that slowness differentiated most strongly between the various groups. The acute schizophrenics were slower than normals on all the speed tests, manic–depressives slower still and chronic schizophrenics the slowest. All the Babcock speed tests correlated with degree of illness and prognosis.

Findings of impaired performance of schizophrenic patients on the digit symbol subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955) have been reported by a number of authors (Ogilvie, 1954, cited in Eysenck, 1968; Kessell, 1955, cited in Eysenck, 1968; Campbell, 1957, cited in Eysenck, 1968; Broadhurst, 1957, cited in Eysenck, 1968; Eysenck *et al*, 1957; Shapiro & Nelson, 1955; Payne & Hewlett, 1960) suggesting that psychomotor speed is impaired in schizophrenia. Using a substitution test, Hausmann (1933) and Senf *et al* (1955) also demonstrated slowness among psychotic patients compared with controls. The latter investigators used the test in two ways, with and without a time limit, and found that the differences in test scores between the two groups were apparent only when the time limit was imposed. This result is similar to that found by Eysenck *et al* (1957) using the Nufferno test.

Hemsley (1982) considers that the generalised slowness of schizophrenics over a wide range of tasks is now well established. Although this slowness has generally been attributed to a slow rate of information processing (Yates, 1966; Asarnow & MacCrimmon, 1981), in a careful review of reaction time studies Hemsley (1982) concluded that the defect lay in response selection and execution, with the additional possibility of a slowness in search initiation.

Other authors have suggested that the slowness to respond in schizophrenia is primarily a motivational deficit, with evidence from reaction time studies suggesting that biological motivation (electric shock) has a greater effect than social motivation on speed of reaction (Rosenbaum *et al*, 1957) and learning (Cohen, 1956) in schizophrenic subjects. But although the use of electric shock improved the performance of some schizophrenic subjects to normal levels, it did not eradicate the slowness in all subjects.

Harris & Metcalfe (1956) studied flattening of affect in 40 schizophrenics, dividing them into three groups according to severity of this symptom. All

patients were given a battery of cognitive tests including tests of speed and level of functioning, but only the tests involving mental speed differentiated significantly between the groups: the more severe the flattening of affect the slower the speed of cognitive functioning.

In our own recent work (Nelson *et al*, 1990), 63 chronic in-patients with DSM-III-R schizophrenia were assessed for present and pre-morbid levels of intellectual functioning, and were given tests of motor and cognitive speed. Positive and negative symptoms were measured, to test the hypothesis that negative symptoms were associated with bradyphrenia. These chronic patients scored relatively more poorly on both the motor and cognitive speed tests than on tests of intelligence, with relatively poorer scores on the cognitive than on the motor speed test. There was a significant negative correlation between cognitive speed and negative symptoms, even after the effects of present and pre-morbid IQ were partialled out, so that the higher the score for negative symptoms, the slower was the speed of cognitive functioning. This was not accounted for by medication, nor by the presence of extrapyramidal symptoms.

This relationship between cognitive slowing and negative symptoms would be consistent with the notion of a 'frontal-subcortical' dementia in schizophrenia. This is in accord with the model proposed by Frith & Done (1988) who suggested that the negative symptoms of schizophrenia are due to a defect in the initiation of spontaneous action and that this depends on frontal-basal ganglia connections. It also suggests that in schizophrenia, slowed initiation is predominantly affected, a hypothesis which we are currently testing.

Of direct relevance to this cognitive slowing in schizophrenia is the evidence derived from electrophysiology, particularly the findings of a decreased amplitude (Duncan, 1988; Friedman, 1992 (review)) and delay in P300 latency in some schizophrenic patients (Pfefferbaum *et al*, 1984; Blackwood *et al*, 1987; St Clair *et al*, 1989; Ebmeier *et al*, 1990). P300, the long latency event-related potential, is generated either by the correct detection of an infrequent sensory stimulus or by the presentation of a novel and unexpected stimulus. P300 is independent of the input modality (auditory, somatosensory or visual) of the source (Snyder *et al*, 1980). It has been considered to arise from subcortical structures (see Friedman, 1992), is thought to be directly related to high-speed cognitive activity (Knight, 1988), and may provide a direct measure of cognitive slowing. Although studies have not found differences in P300 latency between various subtypes of schizophrenia (St Clair *et al*, 1989), Blackwood *et al* (1987) found a significant association between P300 latency increase and the presence of negative symptoms. This is in keeping with the hypothesis of a frontal-subcortical dementia and further work could be directed at investigating the association between P300, negative symptoms and bradyphrenia in patients with schizophrenia.

Procedural and declarative knowledge

Cohen & Squire (1980) made the distinction between two types of knowledge, a fact-based declarative knowledge which refers to 'knowing that' and a skill-based procedural knowledge which refers to 'knowing how'. Declarative knowledge has been viewed as a function of hippocampal-diencephalic structures (Squire, 1986). Procedural knowledge is probably dissociable according to the skills concerned (Butters *et al*, 1987), but the basal ganglia and associated areas have been considered as important in the acquisition and retention of motor skills (e.g. Mishkin & Petri, 1984). In view of the proposed different neuroanatomical substrates mediating these distinct types of learning and memory, it should not be unexpected that different patterns of memory and learning deficits have been reported in the cortical and subcortical dementias.

Eslinger & Damasio (1986) reported intact learning and retention of a motor skill (procedural knowledge) in patients with Alzheimer's disease who were quite unable to learn a list of ten grocery items or to recognise a set of eight faces (declarative knowledge). This result was in contrast to that reported by Martone *et al* (1984) who showed that patients with Huntington's disease were retarded in their ability to acquire a mirror reading skill (procedural knowledge) but showed normal recognition of the words used during the task (declarative knowledge). Heindel *et al* (1988) made a direct comparison between patients with Huntington's and Alzheimer's disease, who were matched for overall degree of dementia, on a motor skill acquisition task (the pursuit rotor) and a verbal memory task: whereas those with Huntington's disease were significantly poorer than the patients with Alzheimer's disease in the acquisition of the motor skill, they were significantly better on the verbal memory test. Similar results were found by Grafman *et al* (1990) in their study of procedural learning and recognition memory comparing Alzheimer's disease patients, PSP patients and normal controls.

It would appear that while subcortical dementia is characterised by impaired procedural learning, at least for motor skills, with relatively intact declarative

learning, cortical dementia is characterised by impaired declarative, with relatively intact procedural learning. The dissociability of these deficits strongly suggests that they are the result of different underlying processes.

Although schizophrenic subjects show learning in the pursuit rotor task, their initial and final levels of performance are generally so much lower than those of control subjects (Nachmani & Cohen, 1969) that it is difficult to compare learning abilities. In a study of 15 monozygotic twin pairs discordant for schizophrenia, Goldberg *et al* (1989) found no difference in performance on the pursuit rotor or variants of the Tower of Hanoi Test, which the investigators considered involved subcortical procedural learning. These latter investigators have further examined procedural learning in schizophrenia, employing Tower-of-Hanoi type tasks (Goldberg *et al*, 1990*b*; Goldberg & Weinberger, 1988). They consider that the three- and four-disc versions of this test involve different cognitive processes. This view is supported in a study comparing patients with the amnestic syndrome, Parkinson's and Huntington's diseases on the two tasks (Saint-Cyr *et al*, 1988). It is the more difficult four-disk task which Goldberg and colleagues (1990*b*) consider involves procedural learning and which implicates the basal ganglia. The three-disk version involves problem solving ability and planning, and they consider this to be dependent on the integrity of the frontal lobe. Contrary to the present hypothesis, their findings implicate the frontal lobe as dysfunctional in schizophrenia with greater preservation of basal ganglia function. The findings do not, however, imply that the basal ganglia are intact, as procedural learning is also impaired, although relatively less than would be predicted.

In keeping with the above suggestion of impairment on procedural tasks is the model proposed by Gray *et al* (1991). These authors discuss the relationship and neuronal connections between the pre-frontal cortex, striatum, and septohippocampal structures. They consider that in schizophrenia the specific impairment of this system is disruption of the projections from subiculum to nucleus accumbens which results in impairment of motor activity via the dopaminergic system, possibly mediated by glutamatergic pathways. They suggest that this adversely affects learned motor programmes in schizophrenia and explains the presence of abnormal movements, such as stereotypies, and predicts an association between movement disorder and cognitive impairment. This model therefore implies that procedural learning would be impaired in patients with schizophrenia.

Recall and recognition memory

Poor everyday memory is a feature of both cortical and subcortical dementia, but formal testing demonstrates different patterns of memory deficit. Patients with Parkinson's disease have greater difficulty in recall than recognition (Tweedy *et al*, 1982) and similar deficits are found in patients with Huntington's disease (Butters *et al*, 1976; Martone *et al*, 1984). In contrast, patients with Alzheimer's disease are poor in both recall and recognition tests (Eslinger & Damasio, 1986). The memory deficit in subcortical dementia has been related to an inability to initiate systematic retrieval of information, while in cortical dementia it has been related to an inability to store information (Butters *et al*, 1987).

Although this distinctive pattern of memory deficits is well established, it could be argued that the storage impairment seen in the cortical dementias is but a later stage of a single process of memory deterioration, the earlier stage being the retrieval impairment seen in the subcortical dementias. Whether or not this is so remains to be established, but one pertinent study is that of Fisher *et al* (1983) who compared mildly and moderately disabled patients with Huntington's disease and found that as memory deteriorated, recall was affected more than recognition, suggesting that in this condition the recall/recognition discrepancy is maintained as the dementia progresses.

Using a simultaneous and a delayed matching-to-sample task, Sahakian *et al* (1988) found that patients with Alzheimer's disease exhibited delay-dependent deficits, and medicated patients with Parkinson's disease showed delay-independent deficits. Both medicated and non-medicated patients with Parkinson's disease were significantly impaired in simultaneous matching, whereas those with Alzheimer's disease were significantly more impaired in a positional memory task.

The majority of studies using recognition tasks to assess memory have not found differences between schizophrenics and control groups while, in contrast, recall deficits are commonly reported in schizophrenia, even in patients who are relatively free of disturbance at the time of testing (Bauman & Murray, 1968; Koh *et al*, 1974; Traupman, 1975; Koh, 1978; Koh & Peterson, 1978; Cutting, 1985). Similarly, Goldberg & Weinberger (1988) found almost normal learning ability in their schizophrenic subjects on a selective reminding task. Recognition memory was unimpaired but recall was deficient. This pattern of recall and recognition memory is comparable to that found in patients with Huntington's and Parkinson's diseases. In the

Goldberg & Weinberger study, recall scores were found to correlate with scores on the Brief Psychiatric Rating Scale (BPRS) for blunted affect, motor retardation, disorientation, and emotional withdrawal, that is the Type II syndrome whose clinical features most closely resemble those of subcortical dementia. Goldberg & Weinberger (1988), however, have suggested that this pattern of deficit in schizophrenia supports the notion of dysfunction of the dorsolateral pre-frontal cortex, and indicates that medial temporal, diencephalic and orbito-frontal areas are intact, although more recent work by this group has also suggested abnormalities of the temporal lobe (Goldberg *et al*, 1992). A similar interpretation of frontal dysfunction was suggested by Clausen & Minas (1987), who also found disturbances of recall rather than recognition memory in their study of schizophrenic out-patients.

However, a subcortical pathological process might also explain the pattern described in schizophrenia, particularly as it matches that reported in other subcortical dementias. McKenna *et al* (1990) assessed memory and intellectual functioning in 60 patients with schizophrenia. They found that memory was impaired to a greater extent than general level of intellectual functioning and suggested that the pattern of memory impairment was more akin to that in the classic amnesic syndrome, which is traditionally associated with a diencephalic pathology, rather than that seen in cortical dementia.

Frontal activation studies

Gur *et al* (1987*a*) commented that more pronounced abnormalities in hemispheric activity in patients with schizophrenia were obtained during cognitive activation. Weinberger and his colleagues have reported a series of studies using the Wisconsin Card Sorting Test (WCST), as a cognitive task presumed to be specific to the dorsolateral pre-frontal cortex, and concluded that there is dysfunction of this area in schizophrenia (Weinberger *et al*, 1986, 1988*b*; Berman *et al*, 1986, 1988; Goldberg *et al*, 1987). Weinberger *et al* (1986) measured regional blood flow in both chronic schizophrenic patients and control subjects engaged in the task. They found frontal blood flow increased during the task in normal controls but not in the schizophrenic patients. This difference, which consistently differentiated patients from controls, was not considered to be attributable to medication, attentional deficits, amount of mental effort or severity of psychotic symptoms (Berman *et al*, 1986). The investigators postulated that, together with evidence from animal studies, their results were consistent with a lesion involving the dopamine innervation of the dorsolateral pre-frontal cortex and suggested that one "intriguing possibility" was that subcortical neuropathology may represent the primary abnormality. This suggestion of pre-frontal cortical hypoactivity and subcortical dopamine hyperactivity (see also Weinberger, 1987) would seem consistent with Gur *et al*'s findings of a steeper metabolic gradient between subcortex and cortex, compared with that of normals.

Weinberger *et al* (1986) pointed out that their method of determining regional cerebral blood flow (rCBF) does not provide information about function in subcortical regions, but PET studies using an activation task might be valuable in investigating such a cortical–subcortical relationship. One such study used an eye- tracking task as a frontal cortex activation task in chronic schizophrenics and found an association between hypofrontality and negative symptoms (Volkow *et al*, 1987).

Other work does not so clearly implicate subcortical structures in the genesis of frontal dysfunction. In their study of monozygotic twin pairs discordant for schizophrenia, Goldberg *et al* (1989) found that the affected twins tended to perform poorly on tests thought to be sensitive to frontal dysfunction, including the WCST. They also found that general attentional and information processing speed was impaired in the affected twin. The authors interpreted this and other neuropsychological data as suggesting that in schizophrenia there is frontal–temporal dysfunction, with relative sparing of posterior cortical and subcortical functions.

An inherent problem in the interpretation of all neuropsychological test results, and one which applies particularly to the more complex cognitive tests which are considered to be sensitive to frontal lobe dysfunction, is that performance on these tests may be adversely affected for a number of reasons. An example of this lack of specificity is the study reported by Goldberg *et al* (1990*a*) in which 11 patients with schizophrenia were matched with 11 with Huntington's disease on their performance of the WCST. Regional cerebral blood flow was determined while they performed the test and neuropsychological test data were examined. The patients with Huntington's disease performed worse on visual spatial tasks and recall memory than did schizophrenic patients, although IQ levels were equivalent. The schizophrenic patients had relatively low frontal and high parietal rCBF, while patients with Huntington's disease exhibited the reverse pattern. In view of the close anatomical connections between the subcortical structures and the frontal lobes one would expect cognitive functions to be interdependent, so that interpretation of neuro-

psychological results in terms of a fronto-subcortical system may be more valid than trying to distinguish between frontal and subcortical components. Support for this notion comes from work by Weinberger *et al* (1988*a*), in which there was abnormal rCBF in subcortical areas in patients with Huntington's disease during frontal activation tasks. The investigators considered that "the dementia represents a loss of neocortical (particularly prefrontal) function and that the role of subcortical pathology is in determining the pathophysiologic mechanism by which this function is lost".

Conclusions

Neuropsychological investigations of patients with known cortical lesions provide information about the function of particular areas, a process that is made possible by the relatively clearly demarcated structure of this area of the brain. When dealing with pathology in older and deeper structures, their widespread connectivity to most other brain areas results in a wide range of secondary symptoms due to disruptions to these connections. Thus, disrupted functioning in subcortical areas results in functional deficits in other brain regions with which there are intimate connections. A possible explanation for such deficits is deafferentation of cortical areas by pathology localised in the subcortex. A corollary of this hypothesis is that subcortical dementia will share many of the characteristics of the cortical dementias. In accord with this argument, only a few studies comparing subcortical and cortical dementia have shown clear dissociation of neuropsychological test data, with many other studies showing overlap (Brown & Marsden, 1988).

In schizophrenia a number of cortical as well as subcortical areas have been implicated as sites of pathology. The suggestion of a primary subcortical pathological process would help to explain the widespread disruption to brain function. We have adduced evidence relevant to the hypothesis that features of subcortical dementia, seen in conditions affecting the basal ganglia or thalamus, are also present in some patients with schizophrenia. Few investigations have systematically addressed this area of inquiry. Future studies might attempt to delineate the neuropsychological deficits present in schizophrenia, and then compare these with the deficits associated with recognised cortical and subcortical conditions (Pantelis *et al*, 1989; Nelson *et al*, 1990).

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