# Subcortical dementia[†]

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**Background**  Drawing a distinction between cortical and subcortical dementias seems both useful and justified. Recent research has, however, cast doubt on the clinical, neuropsychological, neuroimaging and neuroanatomical basis of the distinction.

**Aims**  To arrive at a reasoned conclusion about the relationship between the two types of dementia and the validity of distinguishing between them.

**Method**  The historical and recent clinical and scientific literature on subcortical dementia was reviewed.

**Results**  The traditional claim that subcortical dementia has distinct clinical manifestations, neuroimaging findings and a neuropathological profile is not altogether borne out by the literature. Some studies show that frontal executive dysfunction and the profile of memory deficits are not significantly different from those seen in Alzheimer's disease. Neuropathological findings also overlap.

**Conclusions**  The category of subcortical dementia may be clinically useful in highlighting the likelihood that an individual with dementia is more likely to suffer from bradyphrenia and motor difficulties. As neuroscience advances a preoccupation with the distinction may hinder the assessment and treatment of individual cases.

**Declaration of interest**  None.

[†]See editorial, pp. 97–98, this issue.

The concept of subcortical dementia developed out of clinical observations of dementia in the context of disease processes preferentially affecting the subcortical structures. The syndrome was claimed to be distinct in its clinical manifestations and its anatomicopathological correlates. The dichotomy between cortical and subcortical dementias has now come under attack from both the neuropsychological and neuroanatomical perspectives.

## BACKGROUND

Dementia is a degenerative disorder involving the compromise of multiple domains of cognition. This definition excludes acute confusion of any cause and also chronic focal brain syndromes, in particular the amnesic syndrome. The further classification of dementia, whether based on clinical presentation or on aetiology, is, however, fraught with difficulties. Despite this, the emerging view since the mid-1970s has been that dementia can be separated into cortical and subcortical types, a distinction that has found support from both the clinical (Pillon *et al*, 1993, for example) and aetiological perspectives (see Darvesh & Freedman, 1996, for a review). The differentiating features of subcortical dementia were said to be a profound slowing of cognition, memory disturbances, frontal executive dysfunction, and changes in personality and affect in the absence of aphasias, apraxias and agnosias (Cummings, 1986).

Other authors have highlighted the difficulties with the distinction by arguing that the neuropsychological profiles of cortical and subcortical cases are not sufficiently dissimilar (Brown & Marsden, 1988) or that cortical abnormalities often occur in so-called subcortical disease (Hughes *et al*, 1993). With improvements in investigative techniques, notably neuroimaging, the debate about this matter is likely to continue.

## The evolution of the concept

In 1872, at a time when dementia was a unitary concept, Huntington published 'On Chorea', describing the cognitive impairments in the disease that bears his name. In 1874 Meynert, whose interests were both clinical and neuroanatomical, published *Psychiatry: A Clinical Treatise on Diseases of the Forebrain Based upon its Structure, Function and its Nutrition*. In this book he sought to relate brain structure to function, and postulated that certain psychiatric symptoms resulted from an imbalance of blood flow between the subcortical and cortical structures. Meynert may have been mistaken in making his emphasis on blood flow, but if he had talked in neural terms instead, he would surely have pre-empted current thinking about the aetiology of subcortical dementia. In 1894 Binswanger introduced a vascular perspective and characterised *encephalitis subcorticalis chronica progressiva*, subsequently renamed subcortical arteriosclerotic encephalopathy by Olszewski in 1962.

In 1912 Wilson related subcortical disease to a clinical picture distinct from that seen in cortical dementia when he described cognitive impairments in the absence of apraxia and agnosia in cases of 'progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver', commonly known nowadays as Wilson's disease. Subsequently a number of other predominantly subcortical disease processes have been characterised and found to be associated with a pattern of cognitive impairment that supports the idea of distinction between cortical and subcortical dementias. Parkinson's disease was not formally incorporated into the notion of subcortical dementia until 1978, following work by Albert, although debate about its aetiology and its relationship with cognitive impairment started as far back as 1932 when Von Stockert introduced the term *subcorticale demenz* to characterise the cognitive impairment evident in a case of encephalitis lethargica. Concerning more obscure causes, in 1938 Smyth and Stern had described cognitive impairment in the presence of thalamic disease. More recently, in 1974 Segarra and co-workers supported the contention that subcortical dementia can occur in the presence of isolated thalamic disease, and in 1984 Katz also speculated that the dementia associated with

multi-system atrophy may be of thalamic origin.

Although McHugh apparently used the term 'subcortical dementia' to characterise the deficits seen in Huntington's disease in an unpublished communication in 1973, it was Albert and colleagues in 1974 who formally articulated the concept: in a discussion of the cognitive impairments associated with progressive supranuclear palsy, Albert *et al* (1974) specified the clinical features of the syndrome for the first time. Subsequently, a similar clinical picture was described in association with basal ganglionic calcification in hyperparathyroidism by Bachman & Albert (1984) and in human immunodeficiency virus dementia by Navia *et al* (1986). There are a number of other neurological disorders, including normal pressure hydrocephalus, the 'pugilistic encephalopathy' of repeated head injury, multiple sclerosis and the spinocerebellar degenerations, that can be postulated as subcortical dementias but are not mentioned again here. From the psychiatric perspective, there are similarities between the clinical features of subcortical dementia and those of depressive pseudodementia (Caine, 1981) and type II schizophrenia (Pantelis *et al*, 1992).

## CLINICAL AND NEUROPSYCHOLOGICAL MANIFESTATIONS

In Alzheimer's disease senile plaques and neurofibrillary tangles populate the cortex and there is generalised cortical atrophy, especially of the frontal and temporal lobes, with neuronal degeneration affecting particularly the outer three layers. The typical clinical findings include dyscalculia, dysphasias, dyspraxias and agnosias, and are said to be indicative of cortical dysfunction. However, features reflecting subcortical pathology, such as mild extrapyramidal signs, are common.

In the subcortical dementias, on the other hand, the lesions occur predominantly in the basal ganglia, the brainstem nuclei and the cerebellum (see Darvesh & Freedman, 1996, for a comprehensive review of the neuroanatomy and neuropathology), and the clinical picture is correspondingly different. In addition to the clinical features of the underlying disease process (whether it be Parkinson's, Huntington's or other disease) psychiatric disturbance, bradyphrenia, frontal executive dysfunction and impairment in memory characteristic of subcortical dementia may be present.

The psychiatric manifestations of subcortical disease come primarily in the form of personality changes and affective disorder. Apathy and irritability are particularly common (Aarsland *et al*, 1999), and depression is said to be significantly more common in subcortical disorders such as Parkinson's disease than it is in Alzheimer's disease. Aarsland *et al* (1999) found that 38% of a series of patients with Parkinson's disease had depression, and Cummings (1995) gave a figure of 30% for Huntington's disease that is broadly in keeping with the figure of 41% reported by Dewhurst *et al* (1969) for their series of Huntington's cases. Psychotic illness and mania are also overrepresented, particularly in Huntington's disease: psychotic illness was present in over 50% and mania in 21% of the Dewhurst series, and in the Parkinson's disease series 27% had hallucinations (Aarsland *et al*, 1999).

In terms of cognition, some evidence suggests that cortical dementia evolves differently from subcortical dementia. Stern *et al* (1998) evaluated cognitive changes over 1–3 years prior to the time dementia was diagnosed in 40 matched pairs of patients with Alzheimer's disease and Parkinson's disease. The study showed that the decline in naming on the Boston Naming Test (Kaplan *et al*, 1983) and in performance on the Selective Reminding Test (Buschke & Fuld, 1974) was more rapid in Parkinson's disease than in Alzheimer's disease, which Stern and colleagues felt was in keeping with different underlying pathological processes.

In terms of the actual pattern of deficits, slow thinking (bradyphrenia) has been demonstrated in both Parkinson's disease and Huntington's disease and is independent of attendant motor slowness. Frontal/executive function, as evidenced by difficulties with verbal fluency, set shifting, categorisation and planning, is also disturbed in all the major subcortical diseases (Elias & Treland, 1999). It is also impaired in early Alzheimer's dementia (Kopelman, 1991). There is evidence to suggest that patients with early Alzheimer's disease are disproportionately impaired in category fluency as compared with letter fluency, a fact that comfortably fits with more severe semantic memory problems in the former.

In subcortical dementia (e.g. in Parkinson's disease and Huntington's dementia), there is a learning impairment which can be partially corrected by providing richer (more salient) cues to encourage learning and promote recognition (Pillon *et al*, 1993). In contrast, it was claimed that cortical dementias (such as Alzheimer's dementia) are characterised by accelerated forgetting (e.g. Cummings, 1986). However, this distinction does not hold good on detailed neuropsychological analysis of the patterns of learning and forgetting in, for example, Huntington's disease and Alzheimer's dementia (Kopelman, 1985), and Kuzis *et al* (1999) could not demonstrate a different profile of memory deficits between patients with Alzheimer's dementia and those with dementia consequent upon Parkinson's disease. In remote memory, there are variable patterns of impairment. In Alzheimer's dementia a gentle 'temporal gradient' (an extensive remote memory loss with some degree or relative sparing of early memories) is found in many studies (Kopelman, 1989), although there have been claims that this is specific for autobiographical memories as opposed to memories of famous events (Dorrego *et al*, 1999), whereas in Huntington's disease there is a 'flat', uniform loss of remote memories across all earlier periods. In Parkinson's disease, the severity of remote memory impairment is related to the clinical severity of dementia; however, these patients additionally seem to have difficulty in dating past events, even when they do not suffer from formal dementia.

There have been many studies of procedural (perceptuomotor) learning in Parkinson's disease and Huntington's dementia. Saint-Cyr *et al* (1988) found that in both conditions patients were impaired at the Tower of Hanoi task, whereas amnesic patients performed normally (on the basis of the latter's intact procedural memory); on verbal memory tasks, in contrast, the amnesic patients were severely impaired, whereas those with Parkinson's disease performed normally and those with Huntington's disease showed a variable pattern. More recently, Reber & Squire (1999) have demonstrated that skill learning is not a single entity: patients with Parkinson's are impaired at 'habit' learning, implicating the neostriatum, but show intact learning of artificial grammars and dot pattern prototypes, which were postulated to reflect brain regions outside both the neostriatum and the medial temporal lobes.

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## SUBCORTICAL CONTRIBUTION TO PSYCHIATRIC DISORDER?

For the purposes of investigating cognitive impairments in depression, Caine (1981) defined 'pseudodementia' as follows:

(a) it is an intellectual impairment in a patient with a primary psychiatric disorder;

(b) the features of the neuropsychological disorder resemble, at least in part, the presentation of a neuropathologically induced cognitive deficit;

(c) the intellectual disorder is reversible;

(d) the patient has no apparent primary neuropathological process leading to the genesis of the disturbance.

The disorder in question is usually hysteria or depression but, because of the additional complexities of understanding the mechanism of the former and how it relates to the purposeful behaviour of malingering, attention is here confined to depressive pseudodementia.

Depression is common in subcortical disorders and it is perhaps not surprising therefore that the pattern of cognitive impairment that one sees in the context of depression can be 'subcortical'. As Lishman (1987: p. 410) eloquently puts it:

> The patient becomes slow to grasp essentials, thinking is laboured, and behaviour becomes generally slipshod and inefficient. Events fail to register either through lack of ability to attend and concentrate or on account of the patient's inner preoccupations. In consequence he may show faulty orientation, impairment of recent memory, and a markedly defective knowledge of current events. The impression of dementia is sometimes strengthened by the patient's decrepit appearance due to self-neglect or loss of weight.

To clarify the nature of the transient cognitive impairments associated with psychiatric disorder, Caine performed neuropsychological testing on a series of patients with pseudodementia and depression. The results indicated a sparing of 'cortically mediated intellectual functions' (Caine, 1981: p. 1363), including language functions and motor praxis, but difficulties with inattention, slow mental processing and a verbal elaboration 'demonstrating a subcortical pattern of intellectual deficit' (Caine, 1981: p. 1364). In keeping with this line of argument, Rogers et al (1987) subsequently drew attention to the similarities between the cognitive slowness of Parkinson's disease and that seen in depression,

thereby raising the interesting question of whether or not depression and the subcortical dementias share a common or closely related aetiology. There is support for this hypothesis from both the neuropathological and the functional imaging perspectives. In patients with Parkinson's disease who had both depression and dementia, Ring et al (1994), for example, found hypometabolism in the medial prefrontal cortex using positron emission tomography (PET), suggesting that frontal/subcortical changes may contribute to (or reflect) depressed mood in this disorder.

In type II schizophrenia, Pantelis et al (1992) addressed the question of whether the features that are similar to those seen in subcortical dementia (such as apathy and lack of motivation) should be taken as evidence of a subcortical aetiology. In support of this, there is some neuropsychological and neuropathological evidence. In terms of neuropsychology, Nelson et al (1990), for example, showed a significant negative correlation between cognitive speed and negative symptoms in patients with schizophrenia. The neuropathological evidence is less convincing, in spite of the fact that a number of studies have revealed subcortical structural abnormalities in schizophrenia. Recent work suggests that the loss of tissue is more general and that it may preferentially affect the cortex. The tentative conclusion is therefore that, while subcortical structures are likely to be affected in schizophrenia and may be responsible for some of the clinical features of the disorder, other regions of the brain are also affected.

## THE LEGITIMACY OF THE DISTINCTION

It is well-recognised that cortical abnormalities are frequently found in 'subcortical' diseases and vice versa. Hughes et al (1993) looked at 100 cases of histologically confirmed Parkinson's disease and found that in 17 there was coexistent neuropathological evidence of Alzheimer-type change. In fact, dementia had occurred in 44% of these patients and of these 29% had confirmed Alzheimer pathological change. Cortical change has also been documented in Huntington's disease and progressive supranuclear palsy. In Alzheimer's disease, Whitehouse et al (1981) demonstrated loss of cholinergic neurons in the 'subcortical'

nucleus basalis of Meynert, a finding corroborated by many others.

Neuroimaging findings in some studies add further weight to the idea that the dichotomy is not strict. Starkstein et al (1997), for example, compared patients with Alzheimer's and Parkinson's disease with dementia with patients with Parkinson's disease without dementia, using single-photon emission computed tomography (SPECT). They found that the two groups with dementia did not differ significantly from each other, but showed significantly more severe hypoperfusion in the superior frontal, superior temporal and parietal areas than did those without dementia. As a consequence, any classification of the dementias must be sensitive to the fact that they seem to lie along a continuum involving a greater or lesser degree of cortical and subcortical pathology.

Even if one accepts the notion of a continuum, this still leaves a number of unresolved issues. It is difficult to sustain the idea that cortical dementia alone is characterised by some combination of aphasia, apraxia and agnosia, since apraxia is known to occur in disorders affecting the basal ganglia. In addition, a number of published care reports indicate that thalamic lesions sometimes produce dementia indistinguishable from Alzheimer's disease, and that frontal dysfunction – said to be one of the characteristic features of subcortical dementia – is common in early Alzheimer's disease (Kopelman, 1991).

In conclusion, there is no specific neuropsychological pattern in subcortical dementia. However, the subcortical disorders may still be more similar to one another than they are to Alzheimer's dementia. In so far as this is the case, they are characterised by cognitive slowness, concomitant motor abnormalities, and a relatively low frequency of aphasias and apraxias. When the latter occur, they reflect damage to subcortical–cortical projections. However, modern neuropsychology focuses its attention on specific patterns of cognitive impairment in relation to underlying neurochemistry or neuropathology: to this extent, concepts such as 'subcortical dementia' are likely to blur, rather than to illuminate, our understanding.

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## CLINICAL IMPLICATIONS

■ Psychiatric illness, including psychosis, is relatively common in patients with subcortical disease and is a major cause of morbidity.

■ Clinical, neuropsychological and neuropathological findings do not allow the strict separation of the dementias into subcortical and cortical subgroups.

■ Less emphasis should be placed on the issue of whether or not clinical and neuropsychological findings fit typical cortical or subcortical pictures and assessments should be directed towards identifying the precise cause of a dementia and appraising functional deficits that have implications for management.

## LIMITATIONS

■ This paper is a brief review with a limited number of references and so by necessity a considerable amount of interesting neuropsychological material has had to be excluded.

■ The clinical differentiation between subcortical and cortical dementias using standardised instruments is not discussed.

■ Neuroimaging and neurochemical work are increasingly important in understanding the pathological basis of neuropsychological deficits and a more comprehensive discussion of these matters would have been useful.

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