

## Subcortical Dementia: A Neurobehavioral Approach

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The subcortical dementias are a heterogeneous group of disorders in which the predominant pathological lesions occur in subcortical structures such as basal ganglia, brainstem nuclei, and the cerebellum. When the cerebral cortex is involved, the lesions are most often in the frontal lobes. These pathologic lesions are associated with cognitive changes that include bradyphrenia, personality change (apathy, depression, irritability), memory impairment, and impaired manipulation of acquired knowledge (calculation, abstraction). Aphasia, apraxia, and agnosia are commonly seen in the cortical dementias, but are absent in the subcortical dementias. Progress in research on the anatomy and connectivity of cortical–subcortical structures has led to refinement in our understanding of the cortical dementias. Despite the connectivity between the cortical and subcortical structures, patterns of cognitive impairment in subcortical dementias remain distinct. © 1996 Academic Press, Inc.

### INTRODUCTION

The subcortical dementias are a heterogeneous group of disorders in which cognitive changes include bradyphrenia, personality change (apathy, depression, irritability), memory impairment, and impaired manipulation of acquired knowledge. Aphasia, apraxia, and agnosia are commonly seen in the

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cortical dementias, but are absent in the subcortical dementias. The pathological lesions in subcortical dementias occur in the basal ganglia, the brainstem nuclei, and the cerebellum. When the cerebral cortex is involved the lesions are most often in the frontal lobes. The prototypic example of cortical dementia is Alzheimer's disease, whereas classical examples of subcortical dementias include Parkinson's disease (PD), Huntington's disease (HD), Progressive Supranuclear Palsy (PSP), and Multiple System Atrophy (MSA).

The concept of subcortical dementia has led to considerable debate centered around the validity of the cortical-subcortical dichotomy in relation to cognitive dysfunction (Cummings, 1986; Brown, & Marsden, 1988; Whitehouse, 1986). Nevertheless, there is a growing body of evidence in favor of distinct patterns of neurological, neuropsychological, and neuropathologic profiles that support the concept of subcortical dementia (Cohen, & Freedman, 1995; Cummings, 1986; Cummings, & Benson, 1988; Cummings, 1990; Cummings, 1993; Huber et al., 1986a; Foster, 1986; Dunne, 1993; Huber, & Paulson, 1985; Freedman, & Oscar-Berman, 1986a; Freedman, & Albert, 1985; Weiner, & Lang, 1995). Moreover, it has become increasingly clear that different patterns of neurobehavioral disturbance result depending on the site of the lesion along the cortico-subcortical axis.

We shall summarize the history underlying the concept of subcortical dementia. This will be followed by a discussion of the neuroanatomy, the neurochemical anatomy, and the connectivity of relevant subcortical structures. Within this framework we shall review the neurological, neuropsychological, and neuropathologic aspects of prototypic subcortical dementias. Where appropriate, comparison will be made with the prototypic cortical dementia, Alzheimer's disease. We shall conclude with a summary of the debate surrounding the cortical-subcortical dementia dichotomy, as well as an overall perspective on this issue.

## HISTORICAL PERSPECTIVE

James Parkinson (1817), in his "An Essay on the Shaking Palsy," recognized depression as part of the disorder that bears his name. He quoted Dr. Maty's description of a patient, Count de Lordat, as follows; "A more melancholy object I never beheld. The patient, naturally a handsome, middle-sized, sanguine man, of a cheerful disposition, and an active mind, appeared much emaciated, stooping, and dejected.—his senses, and the powers of his mind, unimpaired; he was attentive to, and sensible of everything which was said in conversation, and shewed himself very desirous of joining in it; but was continually checked by the impendiment in his speech, and the difficulty which his hearers were put. Happily for him he was able to read, and as capable as ever of writing, as he shewed me, by putting into my hands an account of his situation, drawn by himself: and I am informed that he spent his time to the very last, in writing upon some of the most abstrusive sub-

jects.” In 1861, Charcot and Vulpian observed cognitive impairment in patients with Parkinson’s disease (Boller, 1980). Huntington (1872) subsequently described cognitive impairment in Huntington’s disease. It was not until 1912, however, that Wilson (1912) became the first to observe a clear distinction between dementia involving subcortical structures and other forms of cognitive impairment. He described cognitive impairment in Progressive Lenticular Degeneration (Wilson’s disease) and noted “narrowing of the mental horizons” in this disorder. He also indicated that it never included apraxia or agnosia. He likened this pattern of dementia to that seen in Huntington’s disease. During the encephalitis pandemic, Naville (1922) reported a psychiatric syndrome in which patients had “reduction in voluntary attention, spontaneous interest, initiative, capacity for work and effort and slight subjective diminution of memory.” The pathology of Encephalitis Lethargica was further described by Stern in 1928, and the disorder was described more fully by von Economo in 1929 (Mandell, & Albert, 1990). Subsequently, von Stockert (1932) coined the term “Subcortical Demenz” (subcortical dementia) to describe the cognitive impairment in his post-encephalitic patient. The patient had “memory disorder, slowness, a personality change, and disturbance of affect.” The anatomic correlate for this disturbance, he felt, was involvement of the substantia nigra. In 1929, Van Bogaert and Bertrand brought to attention cognitive impairment associated with Olivopontocerebellar Atrophy (OPCA). This was characterized by disinterest, slowing of intellectual activity, confusion, and incoherent agitation. Smyth and Stern (1938) and Stern (1939) described cognitive impairment in patients with thalamic dysfunction. These patients had “inattention, disorientation, confusion, emotional disturbance, lack of memory, perseveration, change in personality such as inertia and lack of initiative.” In 1954, Williams and Pennybacker, in their extensive analysis of patients with intracranial tumors, observed memory impairment when structures surrounding the third ventricle were involved.

It was not until the mid 1970s, however, that the concept of subcortical dementia was crystallized into a distinct clinical entity. In 1974, Albert et al. analyzed five patients with Progressive Supranuclear Palsy and reviewed 42 cases from the literature. Albert and his colleagues reintroduced the concept of subcortical dementia on the basis of a distinctive neuropsychological profile that emerged from their analysis. They described memory loss, impaired ability to manipulate acquired knowledge, personality changes with apathy or inertia with episodic irritability, general slowness of thought processes, and the absence of aphasia, apraxia, and agnosia. In 1975, McHugh and Folstein reported cognitive and behavioral changes in patients with Huntington’s disease. These patients had difficulties in problem solving, insight, judgment, abstraction, attention, motivation, and concentration. They did not have aphasia, agnosia, apraxia, and alexia, the deficits found in Alzheimer’s disease.

The reintroduction of subcortical dementia as a clinical entity generated a considerable amount of interest (Cummings, 1986, 1990). There have been some thoughtful uncertainties expressed about this disorder as a distinct entity (Whitehouse 1985). However, there has been a large body of data to support a distinction between the subcortical and cortical dementias (Weiner, & Lang, 1995).

## ANATOMY AND CONNECTIVITY OF SUBCORTICAL STRUCTURES

Substantial insight has recently been gained into the neuroanatomical, neurochemical, and functional organization of subcortical structures (Gerfen, 1984, 1992; Alexander et al., 1986, 1990; Albin et al., 1989; Graybiel, 1990; Angulo, & McEwen, 1994). The notion of the basal ganglia "funneling" information from several cortical areas to restricted cortical regions via the thalamus has undergone significant refinement. Several parallel but segregated basal ganglia-thalamocortical circuits have been identified (Alexander et al., 1986, 1990). Intricate details about the connectivity and chemoarchitecture of subcortical structures such as the basal ganglia and the thalamus have led to a better understanding of the neural substrates for information processing (Parent, & Hazrati, 1993; Alexander, & Crutcher, 1990). These advancements have been helpful for understanding some of the behavioral and cognitive disturbances that occur with subcortical dysfunction.

Tract tracing studies and physiological evidence suggest the existence of at least five parallel but segregated basal ganglia-thalamocortical circuits (Alexander et al., 1986, 1990). Two of these circuits, the "motor" and the "oculomotor" circuits, have been studied extensively. Their anatomical arrangement and functional significance is better understood. Consequently, these circuits have been given names reflecting their function. The anatomical arrangement of the other three circuits, the "dorsolateral," the "lateral orbitofrontal," and the "anterior cingulate" or "limbic" circuits is less well understood. It is only recently that the function of these circuits has started to be defined. Therefore, the latter three circuits have been given anatomical names rather than functional labels. In general, the cerebral cortex sends excitatory projections to the striatum (caudate, putamen, and ventral striatum) (Cordingley, & Weight, 1986; Gerfen, 1984; Malneka, & Kocsis, 1988; McGeorge, & Faull, 1989). These projections terminate on medium spiny neurons which constitute over 90% of the striatal neuronal population (Gerfen, 1992). These neurons utilize gamma-amino-butyric acid (GABA) as their inhibitory neurotransmitter. Other neurotransmitters/neuromodulators in the striatum include substance P, enkephalins, dynorphins, neurokinin A and B, somatostatin, neurotensin, and neuropeptide Y (Angulo & McEwen, 1994; Graybiel, 1990).

The striatum also contains interneurons that utilize acetylcholine as the neurotransmitter (Graybiel, 1990). The inhibitory striatal projection neurons

follow two parallel but segregated pathways (Albin et al., 1989), the “direct” and the “indirect” pathways. In the direct pathway, the GABAergic striatal neurons containing substance P project to globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) (Graybiel, & Ragdale, 1983). These two nuclei also contain GABAergic inhibitory neurons that project topographically to the thalamus. The thalamus in turn projects topographically to the cerebral cortex. This pathway therefore has a disinhibitory effect on the thalamic neurons and hence an excitatory effect on the cortical neurons (Albin et al., 1989). In the indirect pathway, the GABAergic striatal neurons containing enkephalin project to globus pallidus pars externa (GPe). These neurons also utilize the inhibitory neurotransmitter GABA and project to the subthalamic nucleus (STN). This nucleus contains excitatory neurons and presumably utilizes glutamate as the neurotransmitter (Alexander et al., 1990). These neurons in turn project to GPi and SNr GABAergic inhibitory neurons. The net effect in this pathway is inhibition of thalamic neurons and hence a net inhibitory effect on the cerebral cortex (Albin et al., 1989). The details about the operation of these pathways remain to be clarified. It is speculated that they either have a “smoothing” effect on the final action of the cortical neurons or alternately there may be a reinforcing effect on the action of the selected cortical neurons and a suppressing action on the opposing set of cortical neurons (Alexander, & Crutcher, 1990). The basal ganglia–thalamocortical circuits and the subchannels within them utilize the same basic pattern to influence the cortical neurons (Alexander et al., 1986, 1990). Furthermore, each of these circuits have “open” and “closed” aspects to their arrangement. The open aspect is that the striatum receives input from multiple cortical and subcortical regions. For example, it has strong reciprocal connections with substantia nigra pars compacta (SNc), projections from dorsal raphe nuclei, and locus coeruleus. Furthermore, there are projections from subcortical structures to other circuit-related structures. For example, the dopaminergic ventral tegmental neurons project to the medial septal area, medial frontal cortex, and anterior cingulate cortex (Moore, 1982). The closed aspect of the circuits is that the information projecting to each of these circuits emanates from functionally related cortical regions and projects to restricted cortical regions.

The basal ganglia–thalamocortical circuits have been reviewed (Alexander et al., 1986, 1990) and are summarized below.

### *The Motor Circuit*

In the motor circuit, the principal striatal target is the putamen. It receives somatotopic projections from the primary motor cortex, arcuate premotor area, supplementary motor area, primary somatosensory cortex, and somatosensory association cortex. The putamen in turn sends topographic projections to the ventrolateral two-thirds of the GPi and GPe as well as caudolat-

eral SNr. In the direct pathway within this circuit, GPi and SNr send topographic projections to thalamic nuclei. These thalamic nuclei include nucleus ventralis lateralis pars oralis (VLo), nucleus ventralis anterior pars parvocellularis (lateral VApc), nucleus ventralis anterior pars magnocellularis (lateral VAmc), and centromedium nucleus (CM). The thalamocortical projections then complete the circuit. From VLo and lateral VAmc there are projections to the supplementary motor area, from lateral VApc to premotor cortex, and from CM to the motor cortex. Although there appears to be convergence of information from the cortex through the basal ganglia and the thalamus, functional and topographic segregation is maintained. Furthermore, within this circuit in the direct and indirect pathways, there are sub-channels that process information about different aspects of movements.

### *The Oculomotor Circuit*

In the oculomotor circuit, the excitatory cortical projections emanate from interconnected frontal eye fields, supplementary eye fields, dorsolateral prefrontal cortex, and posterior parietal cortex. They project to the body of the caudate nucleus as well as the superior colliculus. From the body of the caudate there is projection to the caudal and dorsomedial GPi and ventrolateral SNr. The latter nuclei project to VAmc and nucleus dorsalis pars multiformis (MDmc), and VApc. The collaterals from GPi and SNr project to the superior colliculus. The thalamic nuclei complete the circuit by projecting to frontal eye fields and supplementary eye fields.

### *The Dorsolateral Prefrontal Circuit*

In the dorsolateral prefrontal circuit, the dorsolateral prefrontal region corresponding to Brodmann's areas 9 and 10 projects to the dorsolateral head of the caudate nucleus extending to the tail of the caudate. This region also receives projections from posterior parietal cortex and arcuate premotor area. These cortico-striate projections interdigitate rather than overlap in the caudate nucleus and maintain segregation within the striatum. In a topographic fashion the striatum projects to the GPi and SNr. These nuclei in turn project to VApc and MDpc thalamic nuclei, respectively. The circuit is completed by these thalamic projections to the dorsolateral prefrontal cortex.

### *The Lateral Orbitofrontal Circuit*

In the lateral orbitofrontal circuit, the head of the caudate nucleus receives projections from Brodmann's area 10, as well as from the auditory association area in the superior temporal gyrus and the visual association cortex in the inferior temporal gyrus. From the caudate nucleus there are topographic projections to GPi and SNr, which in turn project to VAmc and MDmc tha-

lamic nuclei. These thalamic nuclei project to the lateral orbitofrontal cortex thus completing the circuit.

### *The Limbic Circuit*

In the limbic or "anterior cingulate" circuit the cortical projections are to the ventral striatum (nucleus accumbens and olfactory tubercle). This portion of the striatum is also called the limbic striatum and receives projections from hippocampus, amygdala, entorhinal and perirhinal cortices (Brodmann's areas 28 and 35, respectively), temporal pole, inferior temporal gyrus, posterior part of medial orbitofrontal area, and anterior cingulate region (Brodmann's area 24). From the ventral striatum there are projections to the ventral pallidum. From here there are projections to MDmc thalamic nucleus which in turn projects to anterior cingulate area and medial orbitofrontal cortex. It is postulated that the ventral pallidum may also have the equivalent of the internal and external segments giving rise to parallel direct and indirect pathways based on reciprocal connections between STN and the ventral pallidum. There are also extensive projections from ventral pallidum to hypothalamus, lateral habenula, and ventromedial tegmental area.

## NEUROPATHOLOGIC PERSPECTIVES

The predominant pathologic changes in the subcortical dementias occur in the basal ganglia, the brainstem nuclei, and the cerebellum. When the cerebral cortex is involved, the lesions are usually in the frontal lobes. In PD, for example, there is predominant degeneration of dopaminergic neurons in the SNc which also contain intracytoplasmic inclusions known as Lewy bodies. This then reduces dopaminergic input to the putamen and anterodorsal sector of the head of the caudate in the striatum. There is also cell loss in the ventral tegmental area which is the course of dopaminergic projections to the mesolimbic mesocortical regions. Apart from this, cell loss has been observed in locus coeruleus and nucleus basalis of Meynert. The neurotransmitter systems that have been observed to be reduced other than dopaminergic include noradrenergic, acetylcholinergic, somatostatinergic, and serotonergic (Mohr et al., 1995; Mayberg, & Solomon, 1995). In HD there is severe involvement of the caudate nucleus. Within this nucleus there appears to be early selective loss of the GABAergic neurons that also contain enkephalin and which project to the GPe. Later, however, there is progressive involvement of all the striatal projection neurons (Albin et al., 1989).

In PSP there are more widespread areas of involvement which include the pallidum, subthalamic nucleus, striatum, nucleus basalis of Meynert, brainstem tegmentum, the colliculi, periaqueductal grey, red nucleus, substantia nigra, basis pontis, dorsal and median raphe nuclei, inferior olives, dentate nucleus of the cerebellum, oculomotor complex, and trochlear nucleus, as well as the prefrontal and precentral cortices. Some of these structures con-

tain numerous neurofibrillary tangles and neuropil threads while others show neuronal loss and astrogliosis (Hauw, et al., 1994).

## NEUROBEHAVIORAL PERSPECTIVES

The subcortical structures influence the function of the frontal systems by their participation in the open and the closed loops of the basal ganglia–thalamocortical circuits. The predominant pathological changes in subcortical dementias occur in the basal ganglia, brainstem nuclei and the cerebellum, as well as the frontal cortex.

Although the different types of subcortical dementia have different areas of predominant subcortical pathology, they share a common pattern of neurobehavioral change due to disruption in the frontal–subcortical systems. The clinical presentation includes abnormalities in general appearance, mood, personality, speed of information processing, memory, and manipulation of acquired knowledge.

### *General Appearance*

The general appearance of patients with subcortical dementia is often significantly different from those with cortical dementia due to the presence of prominent extrapyramidal motor deficits. For example, Parkinson's disease is marked by tremor, shuffling gait, hypomimia, and bradykinesia. There is also often hypophonia. In Huntington's disease there is chorea. In Progressive Supranuclear Palsy, facial spasticity, the "surprise look," and nuchal dystonia may be an obvious change in the physical appearance. In Multiple System Atrophy, depending on the subtype, there may be ataxia and parkinsonian features. The alteration in the physical appearance in these patients is due primarily, if not exclusively, to dysfunction in the subcortical structures and hence impairment in functioning of the motor-basal ganglia–thalamocortical circuit.

### *Mood and Personality*

Mood and personality changes have been recognized in patients with subcortical dementia. In PD, the estimate of the frequency of depression is between 37 to 90% (Mindham, 1970; Celesia & Wanamaker, 1972). The variability in the frequency has been attributed to methodologic differences. Mayeux et al. (1981), in their analysis of 55 consecutive patients with Parkinson's disease, showed that 47% of their patients were significantly depressed. This study suggested "that depression in Parkinson patients may be accompanied by mild intellectual impairment and inattention which is independent of the severity of the illness." It has been postulated that the substrate for dementia and depression may share certain features. Neuropathological studies have shown that there is disproportionate degeneration of dopaminergic

neurons in the ventral tegmental area in patients with depression and dementia (Torack, & Morris, 1988). This area has projections to the orbitofrontal and other prefrontal cortices (Glowinski et al., 1984; Simon et al., 1979; Nauta & Domesick, 1984), that is, the open portion of the basal ganglia–thalamocortical circuits described above. Although the dorsal raphe nuclei project widely to the cerebrum (Azmitia, & Gannon, 1986), the major cortical afferents to the dorsal raphe nuclei originate from the orbitofrontal cortex (Nauta, 1971). Furthermore, functional imaging studies using PET have shown hypometabolism in the inferior frontal lobes in depressed patients with PD (Mayberg et al., 1990). Taken together, the dysfunction of the open portion of the basal ganglia–thalamocortical circuits may lead to the dysfunction of the closed and the open portions of the limbic circuits. From a neurochemical perspective within this anatomic framework, a decrease in dopaminergic, serotonergic, and noradrenergic tone in these systems may, in part, lead to depression and some aspects of the cognitive disturbance in PD (Mayberg, & Solomon, 1995).

Similarly, patients with HD have depression with an estimated frequency in the order of 30% (Cummings, 1995; Morris, 1991). The predominant neuropathologic alteration in this disorder is the loss of GABAergic projection neurons in the caudate nucleus, which has an impact on the normal functioning of various basal ganglia–thalamocortical circuits. This type of dysfunction has been corroborated by the observation that there is hypometabolism in the orbitofrontal and other prefrontal cortices of patients with HD and depression (Mayberg et al., 1992). Apart from depression, these patients may also exhibit hypomania, mania, or psychosis. The estimated frequency of psychosis is between 6 and 25% (Morris, 1991; Folstein, 1989). The substrate for psychosis has been postulated to be the medial as well as the ventral striatum (Cummings, 1995). Functional imaging studies using PET have shown hypometabolism in the anterior hemispheric structures (Kuwert et al., 1989). An imbalance with elevated dopaminergic tone is felt to be one of the transmitter system abnormalities contributing to psychosis (Cummings, 1995). These patients also exhibit changes in personality with apathy, irritability, lability, impulsivity, and aggressive behavior. Functional imaging studies have shown a correlation between metabolic changes in the caudate nucleus and the abnormalities of personality (Mazziotta, 1990). In general, the anatomic substrate for early change in personality is felt to be the orbitofrontal and the limbic circuits (Cummings, 1993).

### *Memory*

Memory deficits comprise an integral component of the deficits in the subcortical dementias. There appears to be a specific pattern of memory disturbance in PD. Immediate memory, that is, the ability to retain information in the absence of distraction, appears to be spared. However, recent memory,

that is, the recall of information after a short delay, is impaired (Huber et al., 1986b). Although recall is impaired, these patients benefit from encoding enrichment and recognition cuing. Thus it is postulated that there is a retrieval deficit in these patients (Tweedy et al., 1982). Remote memory is also impaired. The remote memory deficit appears to be equal across all decades, with no temporal gradient when tested using the Famous Faces Test (Freedman et al., 1984). However, there appears to be a temporal gradient in remote memory for public and personal events when tested using the Famous Scenes Test and Modified Croget's Personal Memory Test (Sagar et al., 1988). Many investigators have shown that patients with PD have a memory disturbance reflected by impairment in performance on tests sensitive to visual memory, learning of superspan word lists, logical memory and paired associated learning, tactile memory, and recall of remote personal and socio-political events (Cummings, 1986; Warburton, 1967; Reitan & Boll, 1971; Pirozzolo et al., 1982; Freedman et al., 1984; Globus et al., 1985). Apart from the recent and remote memory disturbance, these patients have impairment on procedural learning tasks as tested by a simplified version of Tower of Hanoi (Saint-Cyr et al., 1988). Similarly, in HD there is no impairment of immediate memory (Aminoff et al., 1975; Caine et al., 1977). Recent memory is impaired (Caine et al., 1977, 1978; Moss et al., 1986). Recall is, however, aided by cuing and implies the deficit is in retrieval (Weingartner et al., 1979; Butters et al., 1978). Although these patients also have impairment in remote memory without a temporal gradient (Albert et al., 1981a,b; Beatty et al., 1988), they are aided by recognition with multiple choice (Caine et al., 1978).

In PSP, memory disturbance has also been documented (Albert et al., 1974). Although these patients are forgetful, an alternate explanation is that they have an impaired timing mechanism of recall rather than a true impairment of memory (Albert et al., 1974). Subsequently, however, it has been shown that these patients also have true impairment in memory (Litvan et al., 1989). Tests sensitive to assessing aspects of verbal memory including learning, information scanning, consolidation, and retrieval have shown abnormalities in the rate of forgetting, increased sensitivity to interference, and problems using strategies for long-term scanning mechanisms. Although these patients were aided by recognition, as in PD and HD, they also demonstrated sufficient impairment to suggest dysfunction in the storage of information (Litvan et al., 1989).

### *Language*

In general, the subcortical dementias are not associated with significant abnormalities in language. There are, however, abnormalities in speech. For example, patients with PD have dysarthria, reduced phrase length, and impairment in prosody (Cummings et al., 1988). Similarly, patients with HD

may also have dysarthria (Butters et al., 1978; Caine et al., 1978). Furthermore, these patients have reduced phrase length and have an increased number of "mumbled" words, as well as short and simple sentences (Gordon et al., 1987; Podoll et al., 1988). Patients with HD also have abnormalities of prosody. A study of comprehension of prosody in HD showed abnormalities in both affective and propositional prosody (Speedie et al., 1990).

Although patients with PD show some abnormalities in comprehension, the impairment is mild (Cummings et al., 1988). Furthermore, it has been proposed that this abnormality in PD may be due to general cognitive decline rather than a true language disturbance (Podoll et al., 1988). Patients with PD and dementia show mild deficits in naming in some studies (Globus et al., 1985; Freedman et al., 1984), but not in others (Bayles, & Tomoeda, 1983; Huber et al., 1985; Pirozzolo et al., 1982; El-Awar et al., 1987; Pillon et al., 1986). Mild naming deficits have also been observed in patients with HD (Smith et al., 1988).

Writing is impaired in both PD and HD. In both of these disorders, this impairment is primarily due to the motor disturbance (Cummings, & Benson, 1988; Podoll, 1988), although errors of letter omission have been observed in later stages of HD (Podoll, 1988).

### *Visuospatial Functions*

In PD, the existence and the nature of visuospatial function deficits is controversial (Brown, & Marsden, 1986). There is, however, significant evidence that visuospatial function is impaired in PD (Levin et al., 1991; Growdon et al., 1990; Mohr et al., 1990; Stern et al., 1984; Cummings, & Huber, 1992). In a study comparing patients with AD and PD on visuospatial function tasks, both groups performed poorly relative to control subjects although patients with PD performed better (Mohr et al., 1990). It has been postulated that impairment in dorsolateral frontal-striatal connections accounts for these abnormalities. Patients with PD also performed poorly on facial recognition, mental object assembly, manual visuoconstruction, angular judgment, and identifying embedded objects and geometric figures (Mohr et al., 1995).

In HD, there is impairment on the Block Design and Object Assembly subtests of the WAIS (Morris, 1995). Striking abnormalities in these patients are found on tests that require mental rotation to maintain personal orientation. Impairment in localization of a stimulus after a sideways shift of the patient has been observed (Potegal, 1971). Caudate dysfunction has been postulated as the anatomic substrate for this impairment. Furthermore, these patients show significant abnormalities on the Standardized Road Map Test of direction (Fedio et al., 1979; Brouwers et al., 1984). The ability to draw to command and to copy is impaired in both PD and HD. There is some doubt as to whether this impairment is solely due to motor impairment (Brown, & Marsden, 1988).

### *Frontal System Tasks*

Due to predominant dysfunction of the frontal systems in the subcortical dementias, the common predominant theme has been impairment of manipulation of acquired knowledge and other frontal systems tasks. For example, in PD there is impairment in tasks of verbal fluency, abstraction, planning, categorization, and shifting set, as well as in tasks requiring divided attention (Cummings, 1986; Matison et al., 1982; Lees, & Smith, 1983; Talland, & Schwab, 1964; Reitan, & Boll, 1971; Globus et al., 1985; Taylor et al., 1986; Bowen et al., 1975; Flowers, & Robertson, 1985; Flowers, 1982; Cools et al., 1984; Robbins et al., 1994; Owen et al., 1992).

On the Wisconsin Card Sorting Test (WCST), patients with PD show abnormalities in set formation and maintenance of set response. Some investigators have observed perseverative errors in patients with PD (Levin et al., 1989), while others have not observed this defect (Bowen et al., 1976; Taylor et al., 1986; Flowers, & Robertson, 1985). By utilizing experimental paradigms adopted from non-human animal models, Freedman and Oscar-Berman (1986b) have found impairment on delayed response in patients with PD and dementia. Deficits on delayed response are most sensitive to lesions in the dorsolateral frontal cortex in non-human primates (Goldman et al., 1971). Furthermore, perseverative errors on the WCST are most sensitive to lesion in dorsolateral prefrontal cortex in humans (Milner, 1964). Taken together, these impairments in dorsolateral prefrontal function suggest the involvement of the dorsolateral prefrontal circuit due to impaired mesencephalic dopaminergic projections to the striatum and the prefrontal cortex. Similarly, in HD there is poor verbal fluency, impaired abstraction, perseveration, and poor planning (Boll et al., 1974; Butters et al., 1978; Fisher et al., 1983; Wexler, 1979; Josiassen, 1982, 1983; Fedio, 1979; Caine et al., 1978). On the WCST, these patients have difficulty with shifting conceptual set and they make perseverative errors (Josiassen et al., 1983). Thus, these abnormalities also reflect dysfunction in the frontal systems. Since the predominant pathology in this disorder is degeneration of striatal neurons, these abnormalities recapitulate dysfunction of basal ganglia-thalamo-fronto-cortical circuits.

In PSP there is also a profile suggestive of frontal system dysfunction (Lees, 1990) characterized by poor abstraction, impaired calculation, and inability to shift set (Rafal, & Grimm, 1981; Maher et al., 1985). These patients also show impairments on verbal fluency, perseveration on the WCST (Dubois et al., 1988), motor impersistence, and utilization behavior (Pillon et al., 1986; Maher et al., 1985; Pillon, 1991; Dubois et al., 1988). Functional PET Imaging has shown frontal hypometabolism in these patients (D'Atana et al., 1985).

Patients with MSA also display impairments on tasks sensitive to frontal system dysfunction (Robbins et al., 1994). In OPCA (Spinocerebellar Atro-

phy type I) there is cognitive impairment with poor performance on a variety of tests sensitive to frontal lobe dysfunction. These include the WCST (Kish et al., 1994, 1988). Furthermore, patients show impairment on delayed alternation, a test adopted from animal models and which is sensitive to both dorsolateral and orbitofrontal dysfunction (El-Awar et al., 1991).

In OPCA, the frontal cognitive deficits have been attributed to lesions affecting subcortical projections to the prefrontal cortex, although it is hypothesized that cerebellofrontal dysfunction may also play a part in these impairments. Similarly, in striatonigral degeneration with or without Shy-Drager syndrome, patients show impaired performance suggestive of frontal system dysfunction on tasks of letter fluency, attentional set shifting, planning on the Tower of London, and spatial working memory (Sullivan et al., 1991; Robbins et al., 1992).

### *Perspectives on Cortical–Subcortical Dichotomy*

Since the reintroduction of the concept of subcortical dementia, there have been numerous studies comparing the cortical and subcortical dementias, as well as studies examining different forms of subcortical dementias. While the debate about the existence of subcortical dementia will undoubtedly continue, it is becoming increasingly evident that patients with subcortical brain lesions display distinct, identifiable patterns of cognitive impairment. Conceptually, the mechanisms underlying cognitive impairment in these patients are felt to be due to abnormalities in the “instrumental” functions (Cummings, 1986). These mechanisms include timing, arousal, attention, motivation, and mood. Dysfunction in these mechanisms is felt to result in slowing of information processing, memory loss, impairment in manipulation of acquired knowledge, apathy, inertia, and mood disorder. In the cortical dementias, the dysfunction is felt to be in “fundamental” functions which include language, memory, perception, praxis and calculations. Deficits in the fundamental functions lead to impairments such as aphasia, agnosia, apraxia, memory loss, and acalculia.

The anatomic substrates underlying the “instrumental” functions are predominantly the subcortical structures, and those underlying fundamental functions involve mainly the cortical structures. Given the strong anatomic connections between the subcortical and the cortical structures, particularly the frontal lobes, it is not surprising that there are overlapping cognitive impairments in the cortical and subcortical dementias. For example, both cortical and subcortical dementias are associated with abnormalities in frontal system tasks such as abstraction, verbal fluency, and set shifting. The overlap in these impairments increases as the dementias progress.

From a mechanistic point of view it appears that those dementias beginning with predominant subcortical degeneration and those that begin with predominant cortical degeneration represent a continuum. It has been argued

that separation of cortical and subcortical dementias into distinct entities is artificial (Whitehouse, 1986). From a strictly anatomic point of view this is true. From a neurobehavioral perspective, however, it is clear that distinct patterns of cognitive impairments emerge in the cortical and subcortical dementias. Moreover, from a neuropathologic point of view, there are also differences in the profile of neuronal systems affected. For example, in PD there is loss of mesencephalic dopaminergic neurons (Jellinger, 1990), and in HD there is loss of striatal GABAergic/enkephalinergic neurons (Albin et al., 1989). In AD, on the other hand, there are more widespread chemoarchitectural abnormalities which include, in part, the basal forebrain cholinergic neuronal system (Selkoe, 1991).

Thus, clinically and chemoarchitecturally the cortical and subcortical dementias appear to be distinct. Separation of dementia into these two broad categories has several advantages. Given selective vulnerability of populations of neurons, it provides a basis for studying the role of various "systems" or "circuits" in cognitive function. Furthermore, it also provides a fertile ground for studying the role of various neurotransmitters/neuromodulators in cognitive dysfunctions which in turn may have significant implications in management of these abnormalities. Dopaminergic system in PD provides a model to illustrate this point.

While anatomic terminology for clinical entities may raise concern, it is becoming evident that the term "subcortical dementia" is becoming consolidated in the neuroscience lexicon.

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