Frontal-Subcortical Circuits and Human Behavior

Jeffrey L. Cummings, MD

• *Objective.*—This synthetic review was performed to demonstrate the utility of frontal-subcortical circuits in the explanation of a wide range of human behavioral disorders.

Data Sources.—Reports of patients with degenerative disorders or focal lesions involving frontal lobe or linked subcortical structures were chosen from the English literature. Individual case reports and group investigations from peer-reviewed journals were evaluated.

Study Selection.—Studies were included if they described patient behavior in detail or reported pertinent neuropsychological findings and had compelling evidence of a disorder affecting frontal-subcortical circuits.

Data Extraction.—Information was used if the report from which it was taken met study selection criteria.

Data Synthesis.—Five parallel segregated circuits link the frontal lobe and subcortical structures. Clinical syndromes observed with frontal lobe injury are recapitulated with lesions of subcortical member structures of the circuits. Each prefrontal circuit has a signature behavioral syndrome: executive function deficits occur with lesions of the dorsolateral prefrontal circuit, disinhibition with lesions of the orbitofrontal circuit, and apathy with injury to the anterior cingulate circuit. Depression, mania, and obsessive-compulsive disorder may also be mediated by frontal-subcortical circuits. Movement disorders identify involvement of the basal ganglia component of frontal-subcortical circuits.

Conclusions.—Frontal-subcortical circuits mediate many aspects of human behavior.

(*Arch Neurol.* 1993;50:873-880)

The frontal lobes play a critical role in human behavior, and some of the most dramatic neurobehavioral syndromes are associated with frontal lobe dysfunction. Regional specialization within the frontal lobe is recognized, with injury of prefrontal convexity, orbitofrontal, and medial frontal cortex producing distinctive syndromes.[1] Similar behavioral changes, however, have been observed in patients with lesions in other brain regions,[2-4] challenging the anatomic specificity of "frontal lobe" syndromes. Recently, a series of parallel frontal-subcortical circuits have been described that link regions of the frontal lobes to subcortical structures.[5-7] The circuits provide a unifying framework for understanding the similarity of behavioral changes associated with diverse anatomic lesions. A wide range of behavioral alterations, including disorders of executive function, personality changes, mood disturbances, and obsessive-compulsive disorder (OCD), can be linked to dysfunction of frontal-subcortical circuits. In the synthesis presented herein, the anatomy of the circuits is reviewed; studies of patients with degenerative neurologic diseases or informative focal lesions involving circuit structures are then used to demonstrate the value of frontal-subcortical circuits as an interpretive model for understanding human behavioral disorders.

FRONTAL-SUBCORTICAL CIRCUITS

Five circuits are currently recognized: a motor circuit originating in the supplementary motor area, an oculomotor circuit with origins in the frontal eye fields, and three circuits originating in prefrontal cortex (dorsolateral prefrontal cortex, lateral orbital cortex, and anterior cingulate cortex).[5-7] The prototypic structure of all circuits is an origin in the frontal lobes, projection to striatal structures (caudate, putamen, and ventral striatum), connections from striatum to globus pallidus and substantia nigra, projections from these two structures to specific thalamic nuclei, and a final link back to the frontal lobe (Fig 1). Within each of the circuits there are two pathways: (1) a direct pathway linking the striatum and the globus pallidus interna/substantia nigra complex and (2) an indirect pathway projecting from striatum to globus pallidus externa, then to subthalamic nucleus, and back to the globus pallidus interna/substantia nigra.[7] Both direct and indirect circuits project to the thalamus. All circuits share common structures—frontal lobe, striatum, globus pallidus, substantia nigra, and thalamus—and are contiguous but remain anatomically segregated throughout. Projections are progressively focused onto a smaller number of neurons as they pass from cortical to subcortical structures, but circuit segregation is maintained. There are open and closed aspects to the circuits; structures receive projections from noncircuit cortical areas, thalamus, or amygdaloid nuclei and project to regions outside the circuits. Structures projecting to or receiving projections from specific circuits are anatomically and functionally related.[8,9] The circuits focus input on restricted cortical targets; several cortical regions project to the striatum, where the output is

Accepted for publication January 7, 1993.

From the Departments of Neurology and Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, Calif, and the Behavioral Neuroscience Section, West Los Angeles Veterans Affairs Medical Center.

Reprint requests to Neurobehavior Unit, Bldg 256B (691B/116AF), West Los Angeles VAMC, 11301 Wilshire Blvd, Los Angeles, CA 90073 (Dr Cummings).

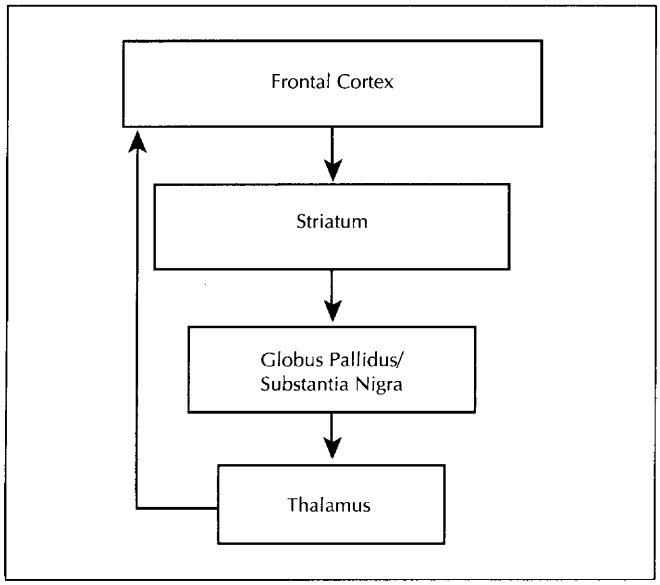

Fig 1.—*General organization of the frontal-subcortical circuits.*

funneled through sequential circuit structures to limited frontal lobe areas.

The *motor circuit* originates from neurons in the supplementary motor area, premotor cortex, motor cortex, and somatosensory cortex.[6,7] These areas project principally to the putamen in a somatotopic distribution. The putamen in turn projects to ventrolateral globus pallidus interna, globus pallidus externa, and caudolateral substantia nigra. The globus pallidus connects to ventral lateral, ventral anterior, and centromedianum nuclei of the thalamus, whose major efferents are to the supplementary motor area, premotor cortex, and motor cortex, completing the circuit. Thalamic nuclei have reciprocal connections with the putamen and cerebral cortex. Throughout the circuit, the discrete somatotopic organization of movement-related neurons is maintained. Information processing in the circuits is not strictly sequential; neurophysiologic investigations of movement demonstrate preparatory premovement activity, serial processing of movements initiated in the cortex, and concurrent parallel processing in the structures of the circuit.[5]

The *oculomotor circuit* originates in the frontal eye fields (Brodmann's area 8) as well as prefrontal and posterior parietal cortex and connects sequentially the central body of the caudate nucleus, dorsomedial globus pallidus and ventrolateral substantia nigra, ventral anterior and medial dorsal thalamic nuclei, and frontal eye fields.[6,7]

The *dorsolateral prefrontal circuit* originates in the convexity of the frontal lobe (Brodmann's areas 9 and 10) and projects primarily to the dorsolateral head of the caudate nucleus (Fig 2).[6,7] This caudate region connects to the dorsomedial globus pallidus interna and rostral substantia nigra through the direct pathway and through the globus pallidus externa to subthalamic nucleus, then to globus pallidus interna and substantia nigra through the indirect pathway. Pallidal and nigral neurons of the circuit project to the ventral anterior and medial dorsal thalamic nuclei that in turn connect with the dorsolateral prefrontal region.

The *lateral orbitofrontal circuit* begins in the inferolateral prefrontal cortex (Brodmann's area 10) and projects to ventromedial caudate nucleus (Fig 2).[6,7] This caudate region projects via the direct pathway to the dorsomedial pallidum and the rostromedial substantia nigra, medial to the area receiving projections from the dorsolateral caudate. The indirect pathway includes the globus pallidus externa and subthalamic nucleus receiving connections from the caudate and projecting to globus pallidus interna/substantia nigra. Pallidum and nigra connect to medial portions of the ventral anterior and medial dorsal thalamic nuclei that project back to the orbitofrontal cortex.

The *anterior cingulate circuit* begins in the cortex of the anterior cingulate gyrus (Brodmann's area 24) and projects to the ventral striatum (also known as the limbic striatum), including nucleus accumbens, olfactory tubercle, and the ventromedial portions of the caudate and putamen (Fig 2).[6,7,9] Neurons from related limbic structures, including hippocampus, amygdala, and entorhinal and perirhinal cortices, also project to the ventral striatum. Ventral striatum has efferent connections with ventral and rostrolateral globus pallidus and rostrodorsal substantia nigra. The ventral pallidum is not clearly divided into internal and external segments giving rise to direct and indirect pathways, but reciprocal connections of the ventral striatum with the subthalamic nucleus have been identified, and the existence of direct and indirect pathways is likely.[7] Pallidal and nigral efferents project to paramedian portions of the medial dorsal nucleus of the thalamus as well as to the ventral tegmental area, habenula, hypothalamus, and amygdala. Medial dorsal thalamic neurons complete the circuit by projecting to the anterior cingulate cortex.

Several transmitters and modulators are involved in the frontal-subcortical circuits; these include glutamine, γ-aminobutyric acid, glutamate, dopamine, acetylcholine, substance P, and enkephalin.[5,7,9,10] The cortical-striatal projections use excitatory glutamatergic neurons; γ-aminobutyric acid is the inhibitory transmitter of neurons originating in the striatum and projecting to the globus pallidus. The direct pathway also contains substance P, while the indirect pathway uses enkephalin. Output from the globus pallidus and substantia nigra reticulata to the subthalamic nucleus and thalamus is γ-aminobutyric acid–ergic. Glutamate is the transmitter of projections from the subthalamic nucleus to globus pallidus interna and externa. Intrinsic excitatory cholinergic neurons are present within the striatum. Projections from substantia nigra compacta to striatal structures use dopamine. The ascending dopamine system originating in the ventral tegmental area projects to several circuit-related structures, including the septal area, amygdala, medial frontal cortex, and anterior cingulate cortex.[11]

FRONTAL-SUBCORTICAL CIRCUIT SYNDROMES

Frontal Lobe Syndromes

Three distinct frontal lobe neurobehavioral syndromes are recognized, and each corresponds to a region of origin of one of the three prefrontal-subcortical circuits. The *dorsolateral prefrontal syndrome* is characterized primarily by "executive function" deficits and motor programming abnormalities. Patients with restricted cortical lesions in this area are unable to generate hypotheses and flexibly maintain or shift sets as required by changing task demands on such tests as the Wisconsin Card Sort Test.[12] They also exhibit reduced verbal and design fluency, poor organizational strategies for learning tasks, and poor constructional strategies for copying complex designs.[13,14] Motor programming disturbances are evident in alternating and reciprocal motor tasks and sequential motor tests.[1]

The *orbitofrontal syndrome* features marked changes in personality. In a study of 79 survivors of rupture of anterior communicating artery aneurysms with orbitofrontal injury, Logue and colleagues[15] found personality alterations in 75 percent. Thirty-three percent of patients were more outspoken, 32% worried less, 27% were more irritable, 19% had an elevated mood, and 8% were more tactless. Forty-six percent had alterations in interest, initiative, or conscientiousness. Similar syndromes have been described in patients with orbitofrontal tumors[16] and inferior frontal lobe infarction.[17] Irritability, lability, and a fatuous euphoria may be present. Lhermitte and colleagues[18] described two additional behavioral syndromes in patients with large bilateral anterior orbitofrontal lobe lesions—imitation and utilization. These behaviors reflect an enslavement to environmental cues with automatic imitation of the gestures and actions of others or enforced utilization of objects in the environment. Unlike individuals with dorsolateral prefrontal lesions, patients with orbitofrontal dysfunction have been found to perform card-sorting tasks normally.[19]

The *anterior cingulate syndrome* has been studied less extensively. The most dramatic examples of anterior cingulate injury are cases of akinetic mutism associated with bilateral lesions. The patients are profoundly apathetic. They typically have their eyes open, do not speak spontaneously, and answer questions in monosyllables if at all. They move little, are incontinent, and eat and drink only if fed. They display no emotion even when in pain and are indifferent to their dire circumstances.[20-22] Unilateral lesions produce transient akinetic mutism.[23] The major neuropsychological deficit demonstrated in patients with medial frontal lobe lesions is failure of response inhibition on go–no go tests.[24,25]

Striatal Syndromes

The dorsolateral prefrontal cortex projects to the dorsolateral caudate nucleus, the orbitofrontal cortex projects to the ventromedial region of the caudate, and the anterior cingulate gyrus projects to the ventral striatum and nucleus accumbens. There have been relatively few reports of the behavioral consequences of focal striatal lesions, but Mendez and coworkers[2] observed contrasting behavioral consequences of dorsal and ventral caudate lesions. Patients with dorsal lesions were more confused and disinterested, whereas patients with ventral lesions were disinhibited, euphoric, and inappropriate. These two syndromes recapitulate the corresponding dorsal and ventral frontal lobe syndromes. All patients had deficits on tests of memory, attention, and executive function, including the Wisconsin Card Sort Test.

Huntington's disease is the best-known disorder affecting primarily the caudate nuclei. The degeneration begins in the medial caudate region and progresses to affect more lateral areas.[26] Behavioral and neuropsychological abnormalities are marked in Huntington's disease. Among 186 patients with Huntington's disease described by Folstein,[27] 37% had a mood disorder, 30% had irritability and explosive disorder, and 6% were diagnosed as having antisocial personality disorder. Apathy was also common. Obsessive-compulsive disorder has also been linked to Huntington's disease,[28] and all patients with Huntington's disease evidence cognitive abnormalities. Patients with Huntington's disease manifest deficits on the Wisconsin Card Sort Test,[29] decreased verbal fluency, and poor recall of recently learned information similar to the abnormalities noted in patients with dorsolateral prefrontal dysfunction.[30] Behavioral abnormalities in Huntington's disease correlate with the severity of metabolic changes in the caudate and are present when cortical metabolism is normal.[31] Thus, in Huntington's disease, cognitive and behavioral alterations corresponding to dysfunction of all three behaviorally relevant frontal-caudate circuit projections are evident. The early appearance of personality alterations in Huntington's disease corresponds to the involvement of the medial caudate regions receiving projections from the orbitofrontal and anterior cingulate circuits mediating limbic system function.[26] The cognitive deficits of Huntington's disease reflect involvement of the head of the caudate nucleus receiving lateral prefrontal-striatal projections.

Observations of patients with neuroacanthocytosis, a rare degenerative disorder affecting primarily the caudate

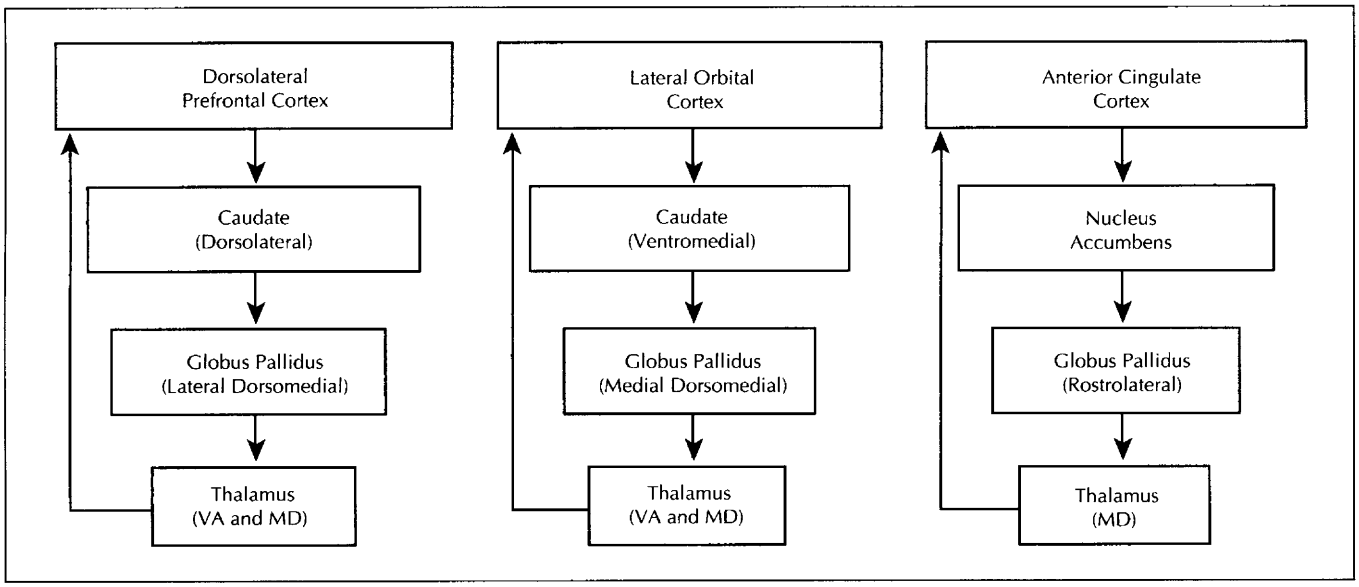

Fig 2.—*Organization of the three frontal-subcortical circuits in which lesions produce alterations of cognition and emotion. VA indicates ventral anterior; MD, medial dorsal. The indirect circuits and connections of the substantia nigra and the subthalamic nucleus are not shown.*

Table 1.—Neuropsychiatric Alterations Associated With Abnormalities of Specific Frontal-Subcortical Circuit Structures*

Structure	Mood	Personality	OCD
Prefrontal dorsolateral cortex	Depression	UD	No
Orbitofrontal cortex	Mania	Disinhibition, irritability	Yes
Anterior cingulate cortex	No	Apathy	Yes
Caudate	Depression (L, B), mania (R, B)	Disinhibition, irritability	Yes
Nucleus accumbens	No	Apathy	No
Globus pallidus	UD	Apathy, irritability	Yes
Thalamus	Mania (R)	Apathy, irritability	No

*OCD indicates obsessive-compulsive disorder; UD, undetermined; and B, bilateral.

nuclei, also support a relationship between caudate dysfunction and behavioral and intellectual alterations resembling those observed in patients with frontal lobe lesions. The patients have intellectual deficits and personality alterations with irritability and disinhibited behavior.[32]

Behavioral changes resulting from lesions of the ventromedial striatum–nucleus accumbens area have not been fully documented, and potential similarities between behaviors associated with anterior cingulate lesions and injury to the nucleus accumbens require further investigation. A few pertinent observations have been reported. Phillips et al[33] noted apathy, withdrawal, and loss of initiative similar to the symptoms of akinetic mutism in a patient with rupture of a posteriorly located anterior communicating artery aneurysm. Neuropsychological assessment revealed that the patient performed normally on tests of intelligence, constructions, verbal fluency, and set shifting (including the Wisconsin Card Sort Test). His memory was defective, and confabulation was evident. At autopsy, the patient had bilateral lesions confined to the region of the rostroventral globus pallidus, nucleus accumbens, septal gray matter, and nucleus of the diagonal band of Broca. Akinetic mutism has also been described with craniopharyngiomas, obstructive hydrocephalus, and tumors in the region of the third ventricle[34-36]—conditions involving ventral striatum, ventral globus pallidus, and medial thalamus.

Together these observations support the hypothesis that the behavioral syndromes observed with frontal lobe lesions are recapitulated with striatal dysfunction and that there are recognizable circuit-specific behaviors. Dorsal caudate lesions produce executive function deficits (ie, impaired performance on the Wisconsin Card Sort Test), ventral caudate lesions are associated with disinhibition and inappropriate behavior, and nucleus accumbens lesions produce apathy and lack of initiative.

Globus Pallidus Syndromes

The striatal structures of the frontal-subcortical circuits project to subregions of the globus pallidus and substantia nigra. Focal insults of the globus pallidus are rare but have been reported after carbon monoxide poisoning and manganese intoxication and occasionally in the course of vascular disease. Strub[4] described a patient with bilateral globus pallidus hemorrhages and noted the marked similarity of the behavior of the patient to that of patients with frontal lobe dysfunction. The patient manifested a marked change in personality with prominent apathy, withdrawal, and loss of interest. Neuropsychological testing revealed normal intelligence, poor memory, and severely impaired performance on the Wisconsin Card Sort Test.

Laplane et al[37] described three patients with bilateral globus pallidus lesions after anoxic insult or carbon monoxide intoxication. After recovery from the acute phase of the disorder, all patients exhibited "psychic akinesia" with reduced spontaneous activity, impaired initiative, and diminished ability to conceive new thoughts. Neuropsychological assessment revealed normal language, reasoning, and intact mental control with impaired memory.

Manganese toxicity has a disproportionate effect on the globus pallidus, and behavioral abnormalities commonly accompany manganese-induced parkinsonism. Irritability was present in all 13 of the patients studied by Mena et al[38]: seven had compulsions and six were depressed. Of the 15 patients described by Schuler et al,[39] seven were apathetic, six were irritable, and three were withdrawn. (The total does not add up because some patients had more than one symptom.)

Three discrete syndromes equivalent to the frontal lobe symptom complexes cannot be identified in patients described with globus pallidus lesions. Nevertheless, mixtures of apathy and irritability similar to the symptoms of frontal lobe dysfunction and neuropsychological deficits affecting memory and executive function resembling those of patients with frontal lobe lesions are present in patients with lesions confined to this structure. Given the progressive spatial restriction of the parallel circuits at this anatomic level, focal lesions may involve several circuits simultaneously, resulting in mixed behavioral syndromes.

Thalamic Syndromes

Frontal-subcortical circuit projections continue from the globus pallidus and substantia nigra to the nuclei of the thalamus. The dorsolateral prefrontal and lateral orbito-

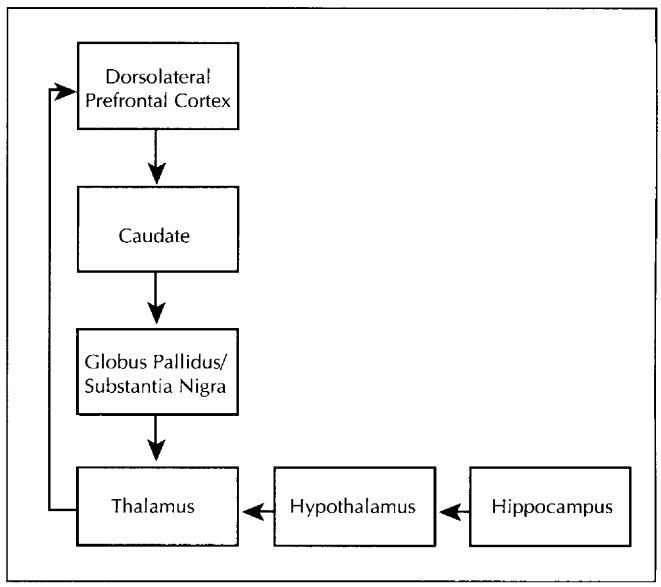

Fig 3.—*Intersection of the dorsolateral prefrontal-subcortical circuit and the hippocampal-medial limbic circuit in the thalamus.*

Table 2.—Behavioral Abnormalities Associated With Basal Ganglia Disorders*					
Disease	Personality Change	Mania	Depression	OCD	Subcortical Dementia
Parkinson's disease	Yes	No	Yes	No	Yes
Progressive supranuclear palsy	UD	No	Yes	UD	Yes
Huntington's disease	Yes	Yes	Yes	Yes	Yes
Wilson's disease	Yes	Yes	Yes	No	Yes
Neuroacanthocytosis	Yes	Yes	Yes	Yes	Yes
Fahr's disease	UD	Yes	Yes	No	Yes
Gilles de la Tourette's syndrome	No	No	Yes	Yes	No

*OCD indicates obsessive-compulsive disorder; UD, undetermined.

frontal circuits project primarily to regions of the ventral anterior and medial dorsal nuclei; the anterior cingulate circuit incorporates primarily subregions of the medial dorsal nuclei.[6] Lesions of the medial dorsal nuclei produce neuropsychological deficits and behavioral disturbances. Gentilini et al[40] studied eight patients with bilateral paramedian thalamic infarctions and noted that several were dysphoric and irritable, one alternated between fretfulness and silly cheerfulness, and one was disinhibited and inappropriate. Six of the seven testable patients had marked memory deficits. Eslinger et al[41] also described a patient with bilateral medial thalamic infarction. They observed disinhibition, apathetic irritability, utilization behavior, and distractibility. Neurobehavioral examination revealed decreased mental control, normal language, poor memory, and reduced verbal fluency. The similarity of the patient's clinical syndrome to that observed with frontal lobe dysfunction was noted. Stuss and colleagues[42] studied three patients with paramedian thalamic infarction: one with bilateral symmetric lesions, one with bilateral asymmetric lesions (more severe on the right), and one with unilateral left-sided infarction. Memory impairment was present in all three; it was most severe in the patient with bilateral symmetric lesions, involved primarily nonverbal information in the patient with predominantly right-sided damage, and affected verbal memory more severely in the patient with left-sided injury. The patient with bilateral lesions and the individual with a large left-sided lesion performed poorly on the Wisconsin Card Sort Test. The patient with bilateral lesions had marked persistent apathy, whereas the patients with more limited lesions exhibited transient passivity with at least partial recovery of motivation. Sandson et al[3] described a patient with an infarction involving primarily the left medial dorsal thalamic nucleus. The patient was apathetic and exhibited neuropsychological abnormalities on tests of recent memory and of executive function, including serial motor behavior, set shifting, and word list generation. The disorder was observed to have many similarities to frontal lobe syndromes.

Thalamic degenerative diseases produce behaviors similar to those observed with thalamic infarction. Severe memory abnormalities and impaired insight are characteristic, and both apathetic and disinhibited behaviors have been described.[43,44]

These observations in vascular and degenerative disorders affecting the thalamus reveal that typical "frontal lobe"–type behaviors can be observed with lesions of the thalamus. As noted with lesions of the globus pallidus, discrete syndromes corresponding to the the three frontal syndromes have not been established at the thalamic level, and disorders with mixed features are the rule.

Circuit-Specific Behaviors

Three frontal lobe symptom complexes are recognizable: a dorsolateral prefrontal syndrome with neuropsychological deficits, including decreased verbal and design fluency, abnormal motor programming, impaired set shifting, reduced learning and memory retrieval, and poor problem solving; an orbitofrontal syndrome with prominent disinhibition and irritability; and a medial frontal-anterior cingulate syndrome with apathy and diminished initiative. Similar behavioral syndromes have been observed with disorders of subcortical structures of the three frontal-subcortical circuits. These observations support the existence of circuit-specific behavioral syndromes with executive function deficits marking dysfunction of the dorsolateral prefrontal circuit, irritability and disinhibition implicating involvement of the orbitofrontal circuit, and apathy indicating disturbances of the anterior cingulate circuit.

COMMENT

Frontal-subcortical circuits have implications for understanding several neuropsychiatric disorders, the syndrome of subcortical dementia, and the occurrence of behavioral disturbances and neuropsychological deficits in patients with movement disorders.

Neuropsychiatric Disorders and Frontal-Subcortical Circuits

In addition to personality alterations (eg, apathy and disinhibition), mood changes and obsessive-compulsive behaviors are also associated with focal brain lesions affecting frontal-subcortical circuits. Depression occurs with lesions of the dorsolateral prefrontal cortex and caudate nucleus, particularly when the left hemisphere is affected.[45-47] Positron emission tomographic studies in Huntington's disease and Parkinson's disease reveal diminished metabolism in the orbitofrontal cortex in depressed compared with nondepressed patients,[48,49] and positron emission tomography in patients with idiopathic unipolar depression shows diminished glucose metabolism in the prefrontal cortex and the caudate nuclei.[50] These investigations suggest that dysfunction of the dorsolateral or orbitofrontal circuits may serve as a common anatomic substrate for idiopathic and acquired mood disorders.

Secondary mania has a contrasting set of anatomic cor-

relates, but the lesions also involve primarily nuclei and connections of frontal-subcortical circuits. Mania has been observed with lesions of the medial orbitofrontal cortex, diseases of the caudate nuclei, such as Huntington' disease, and injury to the right thalamus.[28,51-53] Thus, orbitofrontal cortex, caudate nuclei, and thalamic nuclei, all members of the orbitofrontal circuit, participate in the mediation of manic behavior.

Both idiopathic and acquired OCD have been related to dysfunction of frontal-subcortical circuits. Obsessive-compulsive behavior has been observed in patients with caudate dysfunction in Huntington's disease and after Sydenham's chorea[28,54] and with globus pallidus lesions in postencephalitic parkinsonism, progressive supranuclear palsy, and manganese-induced parkinsonism and after anoxic injury.[28,38,55,56] Obsessive-compulsive disorder occurs in many patients with Gilles de la Tourette's syndrome,[57] a disorder associated with hyperdopaminergic activity of the putamen and caudate.[58] Idiopathic OCD has been associated with increased glucose metabolism in the orbitofrontal region and caudate nuclei[59] and with increased blood flow in the medial frontal area.[60] These studies indicate that frontal-subcortical circuit structures are involved in the mediation of both idiopathic and acquired OCD.

Participation of specific neurotransmitters in frontal-subcortical circuits may allow an integration of behavioral neuroanatomy and behavioral pharmacology. For example, dopamine projections originating in the midbrain project to the nucleus accumbens and the medial frontal cortex.[61] These structures are members of the anterior cingulate circuit. Apathy is the behavioral syndrome associated with dysfunction of this circuit, and dopaminergic agents have been successfully used to treat akinetic mutism, the extreme version of the apathetic state.[62] Antidepressants, antimanic agents, and serotoninergic agents used in the treatment of OCD may exert their effects on circuit function.

Table 1 summarizes the neuropsychiatric syndromes associated with lesions involving the structures of the frontal-subcortical circuits.

Frontal-Subcortical Circuits and the Syndrome of Subcortical Dementia

The cardinal features of subcortical dementia are memory deficits, executive function abnormalities, slowed information processing, and mood and personality changes.[63,64] Similarities between the characteristics of subcortical dementia and those of frontal lobe dysfunction were noted in the first contemporary descriptions of subcortical dementia.[63] Neuropsychological deficits occurring with dorsolateral prefrontal lesions and with damage in other structures of the dorsal-prefrontal circuit are compatible with definitions of subcortical dementia. The anatomic basis of the subcortical dementia syndrome can be expanded to include the restricted regions of the dorsolateral prefrontal cortex that project to the head of the caudate as well as the basal ganglionic and thalamic structures constituting the dorsolateral prefrontal-subcortical circuit.[64] This system mediates executive function and motor programming.

An important exception to the similarity between frontal lobe deficits and neuropsychological abnormalities observed with subcortical disorders is the occurrence of an amnestic disorder with lesions of the thalamus. Memory deficits associated with lesions of the dorsolateral prefrontal cortex and caudate nucleus are characterized by poor recall with relative preservation of recognition abilities,[65] whereas thalamic lesions produce amnesia with impairment of both recall and recognition.[42] The thalamus is poised at the interface of the medial temporal-limbic circuit (incorporating the hippocampus, fornix, hypothalamus, and thalamus) and the frontal-subcortical circuits (Fig 3). The medial temporal-thalamic circuit mediates memory storage, and lesions produce an amnestic syndrome; the frontal-subcortical circuits mediate memory activation and search functions, and lesions produce deficits of information retrieval with relatively preserved recognition. Thalamic lesions combine the amnesia of medial limbic dysfunction with features typical of subcortical dementia and frontal-subcortical circuit dysfunction.[41-43]

Movement Disorders and Frontal-Subcortical Circuits

Basal ganglia dysfunction has traditionally been associated with disturbances of movement. In addition to motor dysfunction, however, patients with basal ganglia diseases have alterations in intellectual function, personality, and mood. Subcortical dementia is present in Huntington's disease, neuroacanthocytosis, Parkinson's disease, progressive supranuclear palsy, Wilson's disease, and other subcortical disorders.[63,64] Executive function deficits in these disorders reflect involvement of the dorsolateral prefrontal circuit as it projects through the basal ganglia. Depression is present in most of these diseases, and mania has been reported in patients with Huntington's disease, Fahr's disease, and neuroacanthocytosis.[27,32,48,49,66-68] Mood disorders are associated with dysfunction of the prefrontal cortex (dorsolateral and orbitofrontal) and the caudate nuclei. Personality changes—apathy, irritability, and disinhibition—are prominent in Huntington's disease and have also been described in neuroacanthocytosis, Wilson's disease, and Parkinson's disease.[27,32,68,69] Basal ganglionic dysfunction with disturbances of the anterior cingulate and orbitofrontal circuits are implicated as the anatomic substrate of these behavioral alterations. Obsessive-compulsive disorder has been associated with Huntington's disease, Sydenham's chorea, Gilles de la Tourette's syndrome, postencephalitic parkinsonism, manganese-induced parkinsonism, and progressive supranuclear palsy.[28,38,54-57] Involvement of the orbitofrontal or anterior cingulate circuits as they project through the basal ganglia correlate with the occurrence of OCD. Table 2 summarizes the relationship of neuropsychiatric syndromes to basal ganglia disorders.

The nature and severity of behavioral changes observed in basal ganglia diseases reflect the extent of involvement of the behaviorally relevant structures in frontal-subcortical circuits. The putamen is involved primarily in the motor circuit, whereas the caudate nucleus is a critical structure of the prefrontal circuits, mediating executive and emotional function; diseases affecting primarily the putamen, such as Parkinson's disease and Wilson's disease, exhibit less marked intellectual and emotional alterations than diseases affecting primarily the caudate, such as Huntington's disease and neuroacanthocytosis. In Parkinson's disease, dementia is present when there is involvement of the medial substantia nigra projecting to caudate nucleus and medial frontal cortex and not when

changes are confined to the lateral nigral neurons projecting to the putamen.[70]

The high frequency of neuropsychological alterations, the notable occurrence of personality and mood disturbances, and the similarity between behaviors of patients with basal ganglia diseases and patients with frontal lobe injury are attributable to dysfunction of multiple frontal-subcortical circuits in basal ganglia disorders. In this framework, movement disorders are markers of dysfunction of caudate nucleus, putamen, globus pallidus, and subthalamic nucleus within the frontal-subcortical circuitry.

CONCLUSIONS

This synthesis of information allows several axioms governing the relationship of behavioral disturbances to frontal-subcortical circuit function to be posited. First, frontal-subcortical circuits are implicated in mediating behavioral alterations when (1) lesions in several circuit-related structures produce a similar behavioral disorder, (2) the behavioral syndrome is not commonly seen with lesions in other brain regions, and (3) simultaneous lesions in several circuit structures produce analogous rather than additive effects. Second, behavioral changes associated with subcortical lesions resemble those occurring with frontal lobe dysfunction because these anatomic structures are linked in discrete, parallel frontal-subcortical circuits. Third, there are identifiable circuit-specific behavioral markers for the prefrontal-subcortical circuits. They are (1) executive dysfunction and motor programming deficits for the dorsolateral prefrontal circuit, (2) irritability and disinhibition for the orbitofrontal circuit, and (3) apathy for the anterior cingulate circuit. Fourth, syndromes with mixed behavioral manifestations indicating involvement of several circuits are frequent with subcortical lesions and degenerative processes. Fifth, the precise anatomic correlates of mood disturbances and OCD require further study, but dorsolateral prefrontal or orbitofrontal-subcortical circuits are candidates for the mediation of depression, and orbitofrontal or anterior cingulate circuits are currently implicated in the mediation of OCD. Sixth, classic movement disorders (parkinsonism, chorea) are markers for involvement of the frontal-subcortical circuits at the level of the basal ganglia. Seventh, dysfunction of a circuit structure may produce symptoms by altering its effects on distant structures within the circuit. Disinhibition of the subthalamic nucleus by caudate dysfunction produces chorea,[71] and disinhibition of thalamocortical connections may be the common physiologic abnormality in both idiopathic OCD and OCD associated with caudate and globus pallidus lesions.[28] Eighth, circuit structures may have connections with noncircuit anatomic regions and may participate in non–circuit-related behavioral syndromes. For example, amnesia is associated with thalamic lesions, and delusions occur with caudate dysfunction but these conditions are not seen with other frontal-subcortical circuit lesions. These axioms can be verified or disconfirmed by experiment and observations; they can guide a research agenda exploring the putative relationship between behavioral disorders and frontal-subcortical circuits.

Advances in defining the anatomic relationships between the frontal lobe and subcortical structures provide a framework for linking behavioral alterations with frontal-subcortical circuit dysfunction. The model is applicable to neuropsychiatric as well as neurobehavioral disorders and offers insights into the pathophysiology of a variety of human behavioral syndromes.

This project was supported by the Department of Veterans Affairs, a National Institute on Aging Alzheimer's Disease Core Center grant, and a grant from the Marv and Mildred Conney Family.

References

1. Cummings JL. *Clinical Neuropsychiatry*. New York, NY: Grune & Stratton Inc; 1985.
2. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. *Neurology*. 1989;39:349-354.
3. Sandson TA, Daffner KR, Carvalho PA, et al. Frontal lobe dysfunction following infarction of the left-sided medial thalamus. *Arch Neurol*. 1991; 48:1300-1303.
4. Strub RL. Frontal lobe syndrome in a patient with bilateral globus pallidus lesions. *Arch Neurol*. 1989;46:1024-1027.
5. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci*. 1990;13: 266-271.
6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci*. 1986;9:357-381.
7. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog Brain Res*. 1990;85:119-146.
8. Groenewegen HJ, Berendse HW, Wolters JG, et al. The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. *Prog Brain Res*. 1990;85:95-116.
9. Parent A. Extrinsic connections of the basal ganglia. *Trends Neurosci*. 1990;13:254-258.
10. Gabriel AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci*. 1990;13:244-254.
11. Moore RY. Catecholamine neuron systems in brain. *Ann Neurol*. 1982;12:321-327.
12. Milner B. Effects of different brain lesions on card sorting. *Arch Neurol*. 1963;9:90-100.
13. Benton AL. Differential behavioral effects in frontal lobe disease. *Neuropsychologia*. 1968;6:53-60.
14. Jones-Gotman M, Milner B. Design fluency: the invention of nonsense drawings after focal cortical lesions. *Neuropsychologia*. 1977;15:653-674.
15. Logue V, Durward M, Pratt RTC, et al. The quality of survival after an anterior cerebral aneurysm. *Br J Psychiatry*. 1968;114:137-160.
16. Hunter R, Blackwood W, Bull J. Three cases of frontal meningiomas presenting psychiatrically. *BMJ*. 1968;3:9-16.
17. Bogousslavsky J, Regli F. Anterior cerebral artery territory infarction in the Lausanne Stroke Registry. *Arch Neurol*. 1990;47:144-150.
18. Lhermitte F, Pillon B, Serdaru M. Human autonomy and the frontal lobes, part I: imitation and utilization behavior: a neuropsychological study of 75 patients. *Ann Neurol*. 1986;19:326-334.
19. Laiacona M, De Santis A, Barbarotto R, et al. Neuropsychological follow-up of patients operated for aneurysms of anterior communicating artery. *Cortex*. 1989;25:261-273.
20. Barris RW, Schuman HR. Bilateral anterior cingulate gyrus lesions. *Neurology*. 1953;3:44-52.
21. Fesenmeier JT, Kuzniecky R, Garcia JH. Akinetic mutism caused by bilateral anterior cerebral tuberculous obliterative arteritis. *Neurology*. 1990;30:1005-1006.
22. Nielsen JM, Jacobs LL. Bilateral lesions of the anterior cingulate gyri. *Bull Los Angeles Neurol Soc*. 1951;16:231-234.
23. Damasio H, Damasio AR. *Lesion Analysis in Neuropsychology*. New York, NY: Oxford University Press; 1989.
24. Drewe EA. Go–no go learning after frontal lobe lesions in humans. *Cortex*. 1975;11:8-16.
25. Leimkuhler ME, Mesulam M-M. Reversible go–no go deficits in a case of frontal lobe tumor. *Ann Neurol*. 1985;18:617-619.
26. Vonsattel J-P, Myers RH, Stevens TJ, et al. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol*. 1985;44:559-577.
27. Folstein SE. *Huntington's Disease: A Disorder of Families*. Baltimore, Md: Johns Hopkins University Press; 1989.
28. Cummings JL, Cunningham K. Obsessive-compulsive disorder in Huntington's disease. *Biol Psychiatry*. 1992;31:263-270.
29. Weinberger DR, Berman KF, Ladorola M, et al. Prefrontal cortical blood flow and cognitive function in Huntington's disease. *J Neurol Neurosurg Psychiatry*. 1988;51:94-104.
30. Butters N, Sax D, Montgomery K, et al. Comparison of the neuropsychological deficits associated with early and advanced Huntington's disease. *Arch Neurol*. 1978;35:585-589.
31. Mazziotta JC. PET and Huntington's disease. In: Martin WRW, ed.

Functional Imaging in Movement Disorders. New Boca Raton, Fla: CRC Press; 1990:177-192.
32. Wyszynski B, Merriam A, Medalia A, et al. Choreoacanthocytosis: report of a case with psychiatric features. *Neuropsychiatry Neuropsychol Behav Neurol.* 1989;2:137-144.
33. Phillips S, Sangalang V, Stern G. Basal forebrain infarction: a clinicopathologic correlation. *Arch Neurol.* 1987;44:1134-1138.
34. Klee A. Akinetic mutism: review of the literature and report of a case. *J Nerv Ment Dis.* 1961;133:536-553.
35. Lavy S. Akinetic mutism in a case of craniopharyngioma. *Psychiatr Neurol.* 1959;138:369-374.
36. Messert B, Henke TK, Langheim W. Syndrome of akinetic mutism associated with obstructive hydrocephalus. *Neurology.* 1966;16:635-649.
37. Laplane D, Baulac M, Widlocher D, et al. Pure psychic akinesia with bilateral lesions of basal ganglia. *J Neurol Neurosurg Psychiatry.* 1984;47:377-385.
38. Mena I, Marin O, Fuenzalida S, et al. Chronic manganese poisoning. *Neurology.* 1967;17:128-136.
39. Schuler P, Oyanguren H, Maturana V, et al. Manganese poisoning. *Ind Med Surg.* 1957;26:167-173.
40. Gentilini M, De Renzi E, Crisi G. Bilateral paramedian thalamic artery infarcts: report of eight cases. *J Neurol Neurosurg Psychiatry.* 1987;50:900-909.
41. Eslinger PJ, Warner GC, Grattan LM, et al. 'Frontal lobe' utilization behavior associated with paramedian thalamic infarction. *Neurology.* 1991;41:450-452.
42. Stuss DT, Guberman A, Nelson R, et al. The neuropsychology of paramedian thalamic infarction. *Brain Cogn.* 1988;8:348-378.
43. Deymeer F, Smith TW, DeGirolami U, et al. Thalamic dementia and motor neuron disease. *Neurology.* 1989;39:58-61.
44. Moossy J, Martinez J, Hamin I, et al. Thalamic and subcortical gliosis with dementia. *Arch Neurol.* 1987;44:510-513.
45. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients: importance of location of lesion. *Brain.* 1984;107:81-93.
46. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of post-stroke mood disorders. *Brain.* 1987;110:1045-1059.
47. Starkstein SE, Robinson RG, Berthier ML, et al. Differential mood changes following basal ganglia vs thalamic lesions. *Arch Neurol.* 1988;45:725-730.
48. Mayberg HS, Starkstein SE, Peyser CE, et al. Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease. *Neurology.* 1992;42:1791-1797.
49. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann Neurol.* 1990;28:57-64.
50. Baxter LR, Phelps ME, Mazziotta JC, et al. Cerebral metabolic rates for glucose in mood disorders. *Arch Gen Psychiatry.* 1985;42:441-447.
51. Bogousslavsky J, Ferrazzini M, Regli F, et al. Manic delirium and frontal lobe syndrome with paramedian infarction of the right thalamus. *J Neurol Neurosurg Psychiatry.* 1988;51:116-119.
52. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. *Am J Psychiatry.* 1984;141:1084-1087.
53. Starkstein SE, Boston JD, Robinson RG. Mechanisms of mania after brain injury: 12 case reports and review of the literature. *J Nerv Ment Dis.* 1988;176:87-100.
54. Swedo SE, Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry.* 1989;146:246-249.
55. Laplane D, Levasseur M, Pillon B, et al. Obsessive-compulsive and other behavioral changes with bilateral basal ganglia lesions. *Brain.* 1989;112:699-725.
56. Schilder P. The organic background of obsessions and compulsions. *Am J Psychiatry.* 1938;94:1397-1416.
57. Frankel M, Cummings JL, Robertson MM, et al. Obsessions and compulsions in Gilles de la Tourette's syndrome. *Neurology.* 1986;36:378-382.
58. Singer HS, Hahn I-H, Moran TH. Abnormal dopamine uptakes sites in postmortem striatum from patients with Tourette's syndrome. *Ann Neurol.* 1991;30:558-562.
59. Baxter LR, Phelps ME, Mazziotta JC, et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1987;44:211-218.
60. Machlin SR, Harris GJ, Pearlson GD, et al. Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study. *Am J Psychiatry.* 1991;148:1240-1242.
61. Nieuwenhuys R. *The Chemoarchitecture of the Brain.* New York, NY: Springer-Verlag NY Inc; 1985.
62. Ross ED, Stewart RM. Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. *Neurology.* 1981;31:1435-1439.
63. Albert ML, Feldman RG, Willis AL. The 'subcortical dementia' of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry.* 1974;37:121-130.
64. Cummings JL. Introduction. In: Cummings JL, ed. *Subcortical Dementia.* New York, NY: Oxford University Press; 1990:3-16.
65. Butters N, Wolfe J, Granholm E, et al. An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. *Cortex.* 1986;22:11-32.
66. Cummings JL. Depression and Parkinson's disease: a review. *Am J Psychiatry.* 1992;149:443-454.
67. Trautner RJ, Cummings JL, Read SL, et al. Idiopathic basal ganglia calcification and organic mood disorder. *Am J Psychiatry.* 1988;145:350-353.
68. Akil M, Schwartz JA, Yuzbasiyan-Gurkan V, et al. The psychiatric presentations of Wilson's disease. *J Neuropsychiatry Clin Neurosci.* 1991;3:377-382.
69. Starkstein SE, Mayberg HS, Preziosi TJ, et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1992;4:134-139.
70. Rinne JO, Rummukainen J, Paljarvi L, et al. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Ann Neurol.* 1989;26:47-50.
71. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 1990;13:281-285.