CHAPTER 18

Frontal-Subcortical Dementias

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INTRODUCTION

Whereas Alzheimer's disease (AD), the most common form of dementing illness, is typically characterized by initial deterioration within limbic and reticular structures (hippocampal/entorhinal regions and basal forebrain cholinergic systems) with later involvement of the neocortex (particularly in temporal and parietal cortices), a second and diverse group of dementias do not initially present with a primary amnestic syndrome or initial pathology in regions affected in AD. Instead, these conditions are characterized by variable but primary changes in personality, working memory, attentional and executive function, and affective regulation and behavioral organization. These conditions constitute a large and heterogeneous group of conditions termed frontal-subcortical dementias (Bonelli & Cummings, 2008; Stewart, 2006; Bak, Crawford, Berrios, & Hodges, 2010). Unlike most typical presentations of AD, this group of dementias is typically characterized by primary deterioration in the prefrontal cortices, in various regions of the basal ganglia, within the white matter tracts connecting these regions, or in other associated subcortical systems in a functional partnership with prefrontal systems. As a result, these dementias can have very diverse etiologies, with clinical phenotypes mapping onto any number of etiologic substrates, making correlation of clinical syndrome and underlying etiology often difficult and challenging (Manes et al., 2010; Chow et al., 2008). Any disease process that affects the frontal lobes and/or their connections to subcortical structures, including basal ganglia, cerebellum, thalamus, or reticular activating systems, can generate a frontal system dementia phenotype. Additional complexities emerge from a host of low-grade encephalopathic conditions (see Chapter 19) that produce a subsyndromal presentation of confusional states that can closely mimic several behavioral and cognitive phenotypes of these frontal-subcortical dementias, with varying degrees of apathy versus behavioral and affective disinhibition along with cognitive disorganization, but shy of a full-blown delirium. These wide-ranging mild encephalopathic conditions can also mimic the neurocognitive phenotype of these frontal-subcortical dementias. Because of this enormous diversity of etiologies, the differential diagnosis of any condition presenting with the cognitive and behavioral phenotype of a frontal-subcortical dementia is particularly challenging to the clinician, even if one is confident that the etiology is neurodegenerative (Duff et al., 2010) and not due to a low-grade reversible encephalopathy. Thus, this group of frontal-subcortical dementias has highly diverse neuropathologies associated with a group of common clinical syndromes; diverse treatment implications, depending on neuropsychological phenotype and behavioral issues; as well as underlying etiology.

TABLE 18.1 Abbreviated List of Common Causes of Frontal-Subcortical Dementia

AIDS dementia complex
Chronic alcoholism (with or without thiamine deficiency)
Anoxic encephalopathy
Carbon monoxide poisoning
Closed head injuries
Cerebrovascular disease (both cortical as well as subcortical)
Creutzfeldt–Jakob disease and other prion diseases
Frontotemporal lobar degeneration (four distinct diseases at a histological level)
Huntington disease
Lyme disease
Multiple sclerosis
Neurosyphilis
Normal pressure hydrocephalus
Parkinson disease (both brainstem and diffuse Lewy body disease)
Progressive supranuclear palsy
Multiple system atrophy (striatonigral degeneration)
Corticobasal Degeneration
Tumors
Wilson's disease
Other moderate to severe metabolic diseases
Any advanced dementing process (AD included)
Milder versions of virtually any medical condition that would cause delirium if more severe
Schizophrenia/schizoaffective disorders
Severe chronic substance abuse of almost any psychoactive drug

NEUROPATHOLOGY AND PATHOPHYSIOLOGY

The neuropathology and pathophysiology of this group of conditions depends on the underlying etiology. This often cannot be definitively established premortem, particularly in the case of neurodegenerative disorders (see the following), where postmortem brain biopsy and histopathology are required for definitive identification of underlying etiology. The likely primary causes (at a bare minimum) for this type of dementia are included in Table 18.1.

Space limitations preclude detailed discussions of each of these neuropathologies, and we will instead provide highly abbreviated summaries of each major etiology and its relevant neuropathology.

In AIDS, where there is a significant neurotoxic effect from the virus, this is typically combined with damage associated with the subject's own immune system and inflammatory responses, and these joint influences produce subsequent degeneration of white matter and gray matter (Navia & Rostasy, 2005). Histopathologically, AIDS dementia complex is typically associated with infiltration of monocytes and macrophages (classes of immune cell) into the CNS, as well as with gliosis, pallor of myelin sheaths, and with abnormalities of dendritic processes and both synaptic and neuronal loss (Abdulle et al., 2007; Anthony & Bell, 2008). In some cases, the degree of clinical dementia correlates poorly with these classic markers, suggesting that synaptic loss may be due to elevated cytokines, or perhaps other poorly understood neurotoxic effects of the virus, particularly its protein coat (Xing et al., 2009).

Alcoholism with severe thiamine deficiency—typically associated with binge drinking and severe nutritional compromise—initially results in acute Wernicke encephalopathy, a confusional state often presenting with sluggish eye movements (ophthalmoplegia) and ataxia, and greatly affecting medial thalamic nuclei, mammillary bodies, periaqueductal and periventricular brainstem nuclei, cranial nerves, and superior cerebellar vermis (Pitel et al., 2010). If the thiamine deficiency state is not rectified relatively rapidly, a Korsakoff dementia ensues (Shimamura, Jernigan, & Squire, 1988). Classic structural findings have emphasized atrophy of mamillary bodies and of the heteromodal (older) diencephalon, particularly medial dorsal, pulvinar, and anterior thalamus (Mair, Warrington, & Weiskrantz, 1979), but these are very difficult regions to image clinically because of their small size, and atrophy is typically

confirmed only on postmortem examination. More recent studies have considered specific effects on cerebellar regions and associated effects on neurocognitive functions (Wijnia & Goossensen, 2010). Chronic alcoholism without thiamine deficiency tends to produce generalized atrophic change in the cerebellum and cerebellar vermis in particular, with loss of Purkinje cells (Zahr, Pitel, Chanraud, & Sullivan, 2010) and typically milder amnestic difficulties, whereas degeneration of medial/heteromodal thalamic systems in severe thiamine deficiency can create severe amnestic syndromes, often confounding any easy discrimination from AD.

Anoxic encephalopathy causes widespread and severe oxidative stress in mitochondria upon reperfusion with oxygenated blood and appears functionally identical to global ischemic injury (leading to the term hypoxic-ischemic insult). This can be generated by any number of common conditions, including common cardiac arrest, asphyxiation, and carbon monoxide poisoning. However, the brain's vulnerability to this severe oxidative stress in mitochondria appears to be regionally uneven, such that certain brain regions appear to take a greater hit, including particularly the globus pallidus, the hippocampus, and perhaps the substantia nigra (Lou, Jing, Selim, Caplan, & Ding, 2009). Additionally, contributions may be mediated by glutamatergic excitotoxicity and microglial activation/inflammatory signaling. The presence of amnestic features, particularly in elder victims of ischemic hypoxic injury, obviously complicates discrimination from AD, suggesting that a careful history is essential to discern a sudden onset of behavioral and amnestic difficulties after a presumed primary ischemic-hypoxic event.

Closed head injury (CHI) is a complex and heterogeneous syndrome, characterized by enormous regional variability of effect, an equally enormous spectrum of severity, and protean effects on behavior, cognition, and emotion/affective regulation (Silver, Hales, & Yudofsky, 2010). However, because of the frequent presence of diffuse axonal injury, inflammatory processes, and excitotoxicity in mild as well as moderate head trauma, a single moderate to severe CHI (as well as serial milder CHIs) can result in a frontal-subcortical dementia syndrome. Longer-term changes associated with serial CHIs can result in chronic traumatic encephalopathy (CTE), which is associated with cerebral atrophy, cavum septi pellucidi with fenestrations, atrophy of mamillary bodies, widespread tau immunoreactive inclusions (intraneuronal and glial tangles and neuropil neurites), and, in some cases, a TDP-43 proteinopathy (see the following discussion of the frontotemporal dementias, McKee et al., 2010; Gavett, Stern, & McKee, 2011). This disorder has prominent features of affective dysregulation, with poor memory and executive functioning and a wide variety of behavioral and affective regulatory disturbances (irritability, impulsiveness, apathy, depression, and suicidality). CTE can also show parkinsonism and, occasionally, motor neuron disease and should be considered in the differential diagnosis of anyone with possibly recurrent head trauma.

Cerebrovascular disease can similarly have very protean and diverse neurocognitive manifestations, depending on whether the primary pathology is microvascular (typically affecting white matter), or in a larger vessel, and also depending, of course, on the locations most affected by vascular disease and white matter loss. White matter ischemic change, commonly found on structural imaging studies, is classically seen on MRI as white matter hyperintensities (WMH). WMH tend to develop in ''watershed'' areas supporting the traditional assumption that they represent a marker of small vessel vascular disease, possibly from damage due to chronic hypoperfusion. Recent work suggests they may have fundamental connections to AD and not simply to classic vascular disease risk factors (hypertension, diabetes, dyslipidemia, smoking, sedentary lifestyle, etc.), given evidence that amyloid angiopathy is a primary, but not exclusive, factor in microangiopathy and white matter loss (Brickman et al., 2009).

Creutzfeldt–Jakob disease (CJD) is a prion disease where the infectious agent is a pathologically folded protein. It is thought to be the most common of the so-called transmissible spongiform encephalopathies, characterized by rapid progression and an invariably fatal outcome almost always within 1 year, and occasionally within a matter of a few months (Appleby & Lyketsos, 2011). All prion diseases are caused by central accumulation of a misfolded isoform of the human prion protein (PrP), a constituent of neuronal membranes, with

five known major types: kuru, CJD, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnia (FI), and variant CJD (vCJD). These subtypes have some differences in their classic clinical phenotypes and somewhat different brain histopathologies that allow their postmortem discrimination. First symptoms can include a wide variety of behavioral difficulties (including disinhibition or apathy), along with myoclonus, ataxia, declining ambulation, and vulnerability to seizures. One can acquire CJD through a mutation of the prion protein (5%–10% of cases), or through eating or otherwise absorbing prions, including from exposure to contaminated human growth hormone products (typically derived from human pituitaries), blood transfusions, other blood products such as immunoglobulins, corneal grafts, or other organ donation (Spero & Lazibat, 2010). CJD or one of the other prion diseases should be considered whenever someone has a rapidly progressive dementia, particularly with myoclonus, and diagnosis of CJD can be made more probable in the context of characteristic triphasic waves on EEG, spinal taps with characteristic proteins (14-3-3 protein), and high signal intensity in putamen and caudate on T2 MRI images. Histopathologically, the brain of patients with CJD shows neuronal loss, reactive astrocytic proliferation and classic spongiform appearance in the gray matter with round vacuoles (holes) in multiple cortical layers, and occasionally cerebellar involvement as well.

Frontotemporal dementias (now referred to as frontotemporal lobar degeneration [FLTD]), characterized structurally by increased atrophic change in frontotemporal regions, constitute a group of four discrete illnesses at a histopathological level, including a tauopathy (demonstrating neurofibrillary tangling, but without amyloid deposition), a disease demonstrating Pick's bodies, and a disease showing ubiquitin inclusions and deposition of TAR DNA-binding protein 43 (TDP-43), and a version lacking distinctive histopathology (Geser, Martinez-Lage, Kwong, Lee, & Trojanowski, 2009). TDP-43 protein appears to also play a role in amyotrophic lateral sclerosis as well as in a significant percentage of FTD. Although initially assumed to be specific to ALS and FTLD, TDP-43 pathology has now been found in other diseases involving tau pathology, including Guam Parkinson dementia complex and, most intriguingly, AD. TDP-43 pathology has recently been detected in one-quarter to one-half of AD cases, particularly in those with more severe Alzheimer's histopathology, as well as in those with hippocampal sclerosis (Wilson, Dugger, Dickson, & Wang, 2011). The comorbidity of this histopathology with more advanced AD is still mysterious and unexplained. TAR DNA-binding protein 43 is thought to be involved in transcriptional repression, gene splicing, and RNA metabolism during cellular stress responses (Wilson et al., 2011). Mutations of tau protein are associated with tauopathy/tangling histopathologies, whereas mutations of progranulin, a growth factor involved in the regulation of apoptosis and inflammation, can show ubiquitin positive inclusions (Baker et al., 2006). Clinical phenotypes for each of these four histopathologies are diverse and can include a primary progressive aphasia, a semantic dementia, classic frontal behavioral variants with primary disinhibition or apathy, and a motor neuron (ALS) phenotype, or patients can present with admixtures of these clinical phenotypes. This makes the large family of frontotemporal lobar degenerative disorders perhaps the most heterogeneous and confusing family of neurodegenerative dementing disorders, and still very poorly understood, particularly relative to both AD.

Huntington's disease (HD) is characterized by progressive atrophy of caudate and putamen and failure of basal ganglia inhibitory operations due to primary loss of indirect pathway functions (Yang & Chan, 2011). It is an autosomal dominant disorder with complete penetrance and is associated with poly-glutamine (nCAG) repeats, with the number of CAG repeats influencing age of onset, and encoding poly-glutamine residues at the terminal end of huntingtin (HTT) protein on chromosome 4. Since the discovery of the mutated *HTT* gene in 1993, how aggregated and mutant HTT protein contributes to neurodegeneration remains mysterious, and no disease-modifying therapy is available. Choreiform and other involuntary movement is regarded as the classical marker in adult onset HD, with tremor and myoclonus (and even parkinsonism—an opposite problem to chorea) seen in more juvenile (early-onset) variants (Thompson et al., 2010). Problems are also seen with eye movement (defective pursuit and tracking), gait abnormalities, and, as the disease progresses, speech motor abnormalities. Behavioral disinhibition and psychosis are not uncommon as the disease advances, consistent with failure of the inhibitory indirect pathway, but depression and apathy are also seen.

Tardive dyskinesia is probably the illness most commonly misdiagnosed as HD (Bhidayasiri & Boonyawairoj, 2011).

NEUROPSYCHOLOGICAL AND BEHAVIORAL SEQUELAE

Characteristics of the Neuropsychological Presentation

In order to understand the often protean neuropsychological and behavioral effects of these various dementing conditions, it is essential to understand the functions of cortico-striatal-pallidal-thalamic-cortical circuitry, as these relatively segregated circuitries help link characteristic neuropsychological and behavioral deficits to the relevant frontostriatal systems (Chase, 2010). In general, these dementias are characterized by various forms of executive dysfunction and associated disorganization and behavioral change. These dementias also can present with slowed declarative learning and poor recall, complicating their discrimination from AD. However, recollection is usually significantly improved in recognition paradigms, implying that retrieval of newly presented information can be disrupted, but not necessarily the encoding or retention (storage) of that data (Swartz, Stuss, Gao, & Black, 2008). Generalized mental slowing, or bradyphrenia, is common (Kehagia, Barker, & Robbins, 2010). There are difficulties in mentally manipulating acquired knowledge (working memory), and with a wide variety of executive deficits. Performance deficits on all tasks of spontaneous word generation or fluency are common (Davis et al., 2010). Disturbances in visuospatial functioning have also been reported (Fukui et al., 2009).

The psychological and behavioral presentation is often characterized by apathy, or, in contrast, lability and disinhibition. Occasionally, patients can display fluctuating admixtures of apathy and abulia alternating with lability, impulsiveness, and poor affective regulation (Chaudhuri, Ondo, Chaudhuri, & Reddy, 2010). These affective and mood changes may or may not be accompanied by depression (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006). Indeed, a primary apathy state can partially mimic and be misdiagnosed as an apathetic or retarded depression, a difficult clinical distinction to draw. Nevertheless, there is frequently a loss of interest in the environment and a lack of initiative in this group of frontal-subcortical dementias. Irritable mood is also often apparent. Patients are frequently unaware of these affective changes, suggesting failure of self-monitoring and insight. In fact, they may even deny any deficits or difficulties of any kind, underscoring the importance of collateral sources of history and background in relation to these patients (Prigatano, Maier, & Burns, 2010). The onset of these conditions is often marked by relatively insidious changes in the direction of apathy or loss of emotional control (Ceravolo, Frosini, Rossi, & Bonuccelli, 2010).

This group of frontal-subcortical dementias often lacks the striking instrumental deficits of anterograde amnesia and other posterior cortical deficits that are characteristic of AD past its earliest stages. Instead, it is the deterioration in anterior brain systems and/or their associated subcortical partners that generates the picture of changes in personality and executive functions. The frontal-subcortical system is composed of distinct subsystems subsumed by various specific cortico-striatal-pallidal-thalamic-cortical tracts, such that there really is no single ''frontal lobe syndrome.'' Instead, most frontal-subcortical dementias are characterized by disturbances in multiple frontostriatal systems, resulting in behavioral presentations that are often varied or mixed (Bonelli & Cummings, 2008). Although some patients with frontal-subcortical dementias demonstrate movement disorder because motor circuits can be affected, a movement disorder is not a precondition for subcortical dementia because in numerous instances, motor circuitry is initially spared in the beginning stages of the disease process (Huey et al., 2009; Kertesz & McMonagle, 2010).

THE *DSM* AND FRONTAL-SUBCORTICAL DEMENTIAS: A Biased Description of Dementia?

The *Diagnostic and Statistical Manual of Mental Disorders*, also known as the *DSM*, is a behaviorally defined diagnostic classification system that is not anatomically organized (American

Psychiatric Association [APA], 2007). The disorders listed within the *DSM* are not categorized according to principles of known brain–behavior relationships. Instead, diagnosis is syndromal, and made on the basis of observing and/or reporting a cluster of behavioral symptoms or mental status changes. Curiously, the *DSM* does not even list a specific category of frontal-subcortical dementia. However, it does categorize ''Dementia Due to Other General Medical Conditions,'' which can include dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson disease, dementia due to Huntington disease, dementia due to Pick's disease, and dementia due to CJD. There is also a general category that includes medical conditions such as ''normal pressure hydrocephalus, hypothyroidism, brain tumor, vitamin B12 deficiency, and intracranial radiation.'' Notably, the current working draft of the *DSM-5* criteria has eliminated the frontal dementia concept along with the entire dementia concept (Sachdev, Andrews, Hobbs, Sunderland, & Anderson, 2009). Regardless, from our perspective, this approach to dementia classification has several major problems.

Clearly, a first concern is that the listing of possible etiologies is very incomplete and leaves out numerous disorders appearing even in our admittedly truncated list, such as the frontotemporal lobar degeneration family, corticobasal degeneration, progressive supranuclear palsy, and numerous other conditions. Additionally, *DSM-IV-TR* criteria for all forms of dementia are heavily canted in the direction of an AD phenotype, emphasizing memory impairment and posterior cortical deficits such as aphasia, apraxia, or agnosia (as well as possible executive deficits that are often seen in both frontal-subcortical dementias as well as in AD). Thus, *DSM-IV-TR* criteria intrinsically short the critical personality, behavioral, and affective alterations (described earlier) central to the frontal-subcortical syndrome description. Therefore, if a patient presents with personality and affective changes and associated executive changes indicative of a possible early-stage frontal-subcortical dementia process, particularly when these disturbances are relatively mild, but does not demonstrate amnestic difficulties, a literal-minded application of the *DSM-IV-TR* criteria for dementia would encourage diagnostic error (in this case, a false-negative result).

This set of issues is particularly seen in the *DSM-IV-TR* listing for vascular dementia, which is basically identical to the criteria for dementia due to AD (excepting motor difficulties or radiologic evidence of vascular disease), whereas many patients with moderate to severe white matter ischemic change (what used to be called Binswanger's disease) or with multiple cortical infarcts develop a mild dementia that looks quite different from AD. An additional complication is that many patients diagnosed with vascular dementia probably have mixed vascular AD processes (Craft, 2009; Li et al., 2010a; see Chapter 17).

Major neurocognitive disorder (including what was formerly known as dementia) is a disorder with greater cognitive deficits in at least one (typically two or more) of the following domains: (1) complex attention, (2) executive ability (planning, decision making, working memory, responding to feedback/error correction, overriding habits, mental flexibility), (3) learning and memory (immediate memory, recent memory [including free recall, cued recall, and recognition memory]) (4) language (expressive language [including naming, fluency, grammar, and syntax] and receptive language), (5) visuoconstructional-perceptual ability (construction and visual perception), and (6) social cognition (recognition of emotions, theory of mind, behavioral regulation). For the entire rationale and criteria, please see the neurocognitive disorders proposal for *DSM-5* at the *DSM-5* website (www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=421.). Readers will find that evidence for significant decline in one or more of the previous domains is required and should be determined by reports by the patient or a knowledgeable informant or observation by the clinician and demonstrated on objective assessment of the relevant domain (typically greater than 2.0 SD below the mean [or below the 2.5th percentile] of an appropriate reference population [i.e., age, gender, education, premorbid intellect, and culturally adjusted]). The cognitive deficits must be sufficient to interfere with functional independence and not be wholly attributable to delirium or other CNS or Axis I disorder. Important changes from the *DSM-IV-TR* criteria include change in nomenclature (MNCD or dementia), not necessarily requiring memory to be one of the impaired domains, and allowing cognitive deficit limited to one domain. In the

introductory text, we offer a table that offers more details about the assessment of each domain in the form of specific symptoms of decline that can be elicited or observed, and assessment procedures that can be used to document the cognitive impairment and quantify its severity.

THE FUNCTIONAL NEUROANATOMY OF FRONTAL-SUBCORTICAL DEMENTIAS

A basic understanding of anterior brain circuitry is essential for conceptualizing frontal-subcortical dementia symptom presentations. The frontal lobes can be divided into several separate regions, which include the prefrontal cortex, the supplementary and premotor cortices, the frontal eye fields, and the primary motor cortex. The prefrontal cortex is further subdivided into three regions. These major subdivisions include dorsolateral prefrontal cortex, lateral and medial subdivisions of the orbitofrontal cortex, and anterior cingulate/medial frontal cortex (Blumenfeld, 2002). Dependent upon specific functional neuroanatomic considerations, these regions can be divided into further subdivisions. However, the divisions listed here are sufficient to establish a framework for the clinical practitioner with a practical diagnostic focus. Each of these frontal regions send white matter projections to the basal ganglia, a collection of bilaterally represented gray matter nuclei located deep within the white matter of the cerebral hemispheres. These nuclei lie at the core of the cerebral hemispheres and are central to the basal forebrain (Alexander, DeLong, & Strick, 1986).

The term basal ganglia most commonly refers to four structures (Middleton, 2003). These structures comprise the striatum (caudate and putamen), the globus pallidus (internal and external subdivisions), the substantia nigra, and the subthalamic nucleus. These structures in turn feature a number of important subdivisions, such as the nucleus accumbens and olfactory tubercle. A number of texts address these areas in detail; interested readers should consult these for more information (Middleton, 2003; Utter & Basso, 2008; Koziol & Budding, 2009). The frontal cortices and other cortical regions are connected to the basal ganglia in a highly specific manner: The cortex projects to the striatum, the striatum projects to the globus pallidus, which projects to the thalamus, and then back to the cortex to the same region where the circuit originated. This simplified circuitry is depicted in Figure 18.1.

Each basal ganglia circuit features two essential connectional profiles: the direct and indirect pathways. These connectional systems essentially enable the basal ganglia to function as a gating system or variable ''brake'' upon the cerebral cortex (Anderson, Fincham, Qin, & Stocco, 2008). When the cerebral cortex—which always has an excitatory, activational influence on either pathway—activates a direct pathway, the striatum releases the tonic inhibitory control that the globus pallidus exerts on the thalamus. Thus disinhibited, the thalamus

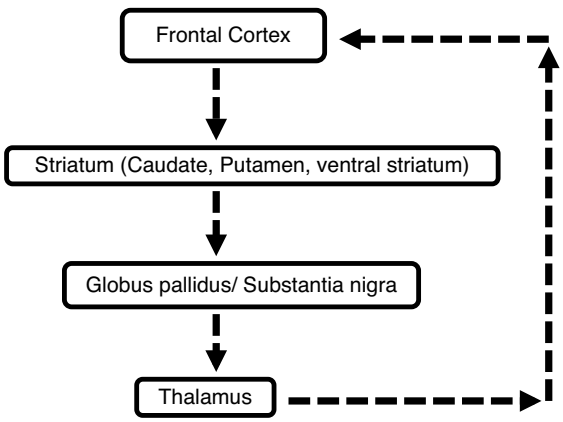

FIGURE 18.1 Fronto-subcortical connections. The diagram outlines the primary components of the fronto-subcortical circuitry.

activates cortex, resulting in perceptual activation in sensory circuits and motor activation in motor circuits. When the cortex activates the indirect pathway, the inhibitory influence the globus pallidus exerts upon the thalamus is increased. This inhibits the thalamus so it can no longer exert an excitatory influence on the cortex. Perceptions are thus inhibited in sensory circuits, and behavioral release is inhibited in motor circuits. In essence, this circuitry allows the basal ganglia to tell which regions of the highly compartmentalized cortex when they should and should not become active. This process allows attention (perception) and action (motor behavior) to be focused in a particular direction while precluding attention and action from being focused in other directions (Hikosaka & Isoda, 2010; Houk et al., 2007).

Seven differentiated, prototypical circuits have been identified that connect the frontal lobes and the remainder of the cortex to the basal ganglia and thalamus. Each circuit is named according to its point of origin and follows the same projection pattern while remaining segregated from the other circuits (Alexander et al., 1986; Bonelli & Cummings, 2007). These circuits include: (1) the dorsolateral prefrontal circuit, (2) the orbitofrontal circuit, (3) the medial/anterior cingulate circuit, (4) the skeletal-motor circuit, and (5) the oculomotor circuit. Subsequent to Alexander's classic work, posterior sensory circuits, including the temporal and parietal circuits, have been revealed that follow the same connectional pattern (Middleton & Strick, 2001). These posterior circuits are mentioned so that the reader understands that the basal ganglia play a role in all attentional (perceptual) and behavioral (motor) selections.

Each of these segregated and discrete circuits have separate functions. The skeletal-motor circuit mediates movement, the oculomotor circuit originates in the frontal eye fields and controls visual search eye movements, the dorsolateral prefrontal circuit mediates the activation of cognitive activity, the orbitofrontal circuit plays an important role in mediating adaptive social behavior and in empathy and the internalization of social rules and contingencies, and the medial/anterior cingulate circuit governs motivation (Levy & Krebs, 2006). The temporal and parietal circuits are involved in perception and certain types of categorization and information-integration learning (Ashby & O'Brien, 2007; Seger, 2008). We will focus upon the anterior circuits, specifically, the dorsolateral, orbitofrontal, and anterior cingulate/medial tracts to assist in understanding the role of this projection system in the most common frontal-subcortical dementias.

Parkinson disease is in part characterized by difficulties initiating and stopping movements, and by perseveration that makes switching from one movement to another difficult. This occurs because of deterioration within the substantia nigra pars compacta, which deprives the striatum of dopamine essential for activating the direct pathway (Bamford & Cepeda, 2009). As a result, the striatum cannot inhibit the control the globus pallidus has over the thalamus, and motor behavior cannot easily be released. HD is characterized by release of fragments of purposeful movements. In the early, initial stages of this disease, the striatum is primarily affected, resulting in alterations in certain neuropeptides within the indirect pathway (Thompson et al., 2010). This results in an inability to activate the globus pallidus, so that thalamic activity can no longer be suppressed, which is manifest by the release of fragments of purposeful, unwanted movements. These two classic basal ganglia diseases thus reflect opposite problems with frontostriatal function, and initially primarily involve motor circuitry, but past earlier stages, show a deepening involvement of other frontostriatal circuits beyond primary motor loops.

Because all cortical-striatal circuits run in parallel and are governed by the same organizational principles and functional mechanisms, the inability to translate intention to action that manifests in motor problems in these patients would be predicted to manifest in a variety of other pathologies when other circuits are involved (Ligot et al., 2010). These two disease processes are always characterized by cognitive and personality changes because deterioration in these pathologies involves degeneration in other frontal-subcortical circuits as well. This is why both of these classic movement disorders are characterized by features of frontal-subcortical dementia. The next sections will focus upon the functions of the dorsolateral, orbital, and anterior cingulate/medial circuits in order to assist in applying these (oversimplified) principles of movement to cognitive and affective functions. The functions of these circuits have previously been described in detail by Koziol and Budding (2009) and can be reviewed in further detail in that publication. The following section includes the detailed

projection patterns of these individual tracts so that the reader can appreciate the segregated nature of these connections, while applying the basic principles of movement disorders to analogues or deficits in cognitive, affective and motivational, and social/behavioral function. This discussion will be concluded with a case presentation that illustrates the application of these principles to clinical practice.

THE DORSOLATERAL PREFRONTAL CIRCUIT

The dorsolateral prefrontal (DLPF) circuit originates on the lateral surface/convexity of the prefrontal lobes. Neurons in this region project to the dorsolateral head of the caudate nucleus. Fibers from this region of the caudate project to the lateral aspect of the mediodorsal Gpi and to the rostrolateral SNpr as part of the direct pathway. The indirect route projects from the caudate to the dorsal Gpe, which projects to the lateral STN. Output of the DLPF circuit from the basal ganglia projects to the ventral anterior and to the mediodorsal thalamus. The circuit is closed by the mediodorsal thalamus projecting back to the region of origin of the circuit (Lichter & Cummings, 2001). This thalamic projection defines the prefrontal lobe (Fuster, 1997). The DLPF circuit is responsible for executive cognitive activity. Executive function can be described as the capacity to generate adaptive behavior autonomously, in the absence of external direction, support, or guidance. The capacities necessary to accomplish the behavior include the ability to focus attention, inhibit inappropriate responses, provide the working memory required for the frontal lobe's planning and organizational functions, and to program behaviors in order to solve problems that do not have an immediate, stimulus-based solution. When affect is disturbed in patients with damage to this circuit, the most common presentations are apathy and depression. Most neuropsychological and cognitive tests access or go through this specific circuit (Ardila, 2008; Malloy & Richardson, 2001; Stewart, 2006).

ORBITOFRONTAL CIRCUITRY

The orbitofrontal circuit (OFC) has two divisions—the lateral and medial divisions—that can be considered two circuitries based upon their projection patterns. The medial OFC originates in ventromedial prefrontal cortex and projects to the medial nucleus accumbens, ventral regions of the pallidum, and back to medial-dorsal thalamus and medial OFC. This region of the OFC has reciprocal connections with the limbic system and insula (Frank & Claus, 2006). Medial OFC circuitry is believed to integrate and modulate visceral drives and the internal milieu (Lichter & Cummings, 2001). This circuitry is not directly assessed through neuropsychological and/or psychological testing. Aspects of this circuitry would be evaluated informally, through history and observation, in regard to alimentary, gustatory, and olfactory behaviors (Ibarretxe Bilbao et al., 2010; Li et al., 2010b). These functions could play roles in areas of adaptation more traditionally understood as related to personality functioning. Changes in eating patterns or in the sense of smell can betray involvement of medial circuitry. Personality changes include anergy and anhedonia (Mega & Cummings, 2001).

The lateral OFC also originates in the ventromedial prefrontal cortex, sending projections to the ventromedial striatum/caudate. This region projects to the most medial region of the mediodorsal Gpi and to rostromedial SNpr. The ventral anterior and mediodorsal nuclei are the thalamic targets that project back to OFC (Lichter & Cummings, 2001). Lateral OFC circuit involvement results in the ''Phineas Gage'' syndrome. The primary deficits are related to personality changes including disinhibition, impulsivity, irritability, and emotional lability. In terms of social behavior, tactlessness and undue familiarity are often described (Ardila, 2008; Chow & Cummings, 2007; Mega & Cummings, 2001). This circuitry is important for the temporal ordering of behavior in determining the proper time and place for expressing behaviors (Fuster, 1997). As a result, damage to this circuit often results in socially inappropriate behavior. This circuit plays an important role in sustaining motivated behaviors in the absence of external cues or contingencies. It assists in allowing the individual to maintain

behavior without immediate, tangible reinforcement, or environmental influence. It is involved in inhibiting responding to external distractions and other interfering influences. Therefore, attention is disturbed as manifest by impairment in inhibitory/exclusionary functions (Fuster, 1997).

Deficits involving this region often result in social disinhibition and socially inappropriate behaviors because instincts are disinhibited. Patients with OFC involvement are often ''stimulus bound.'' This has been termed the environmental dependency syndrome or utilization behavior (Lhermitte, Pillon, & Serdaru, 1986; Lhermitte, 1986). Involvement within this circuit is often broadly characterized by dysregulation of affect, judgment, and social behavior. The affective tone is frequently characterized by euphoria or mania (Cummings & Miller, 2007).

Few neuropsychological test measures of orbitofrontal functions in humans exist (Malloy & Richardson, 2001). Inferences about the integrity of this circuitry are thus frequently drawn from observation or report. Therefore, the methodologies for evaluating involvement of this region are vulnerable to all the biases that can affect self-report and observational report instruments. Patients with focal OFC pathology can perform adequately on many neuropsychological tests because discrete lesions in this region do not necessarily affect cognitive function (Ardila, 2008). However, competing programs and go/no-go tasks can be useful for identifying the disinhibition frequently characteristic of people with OFC pathology.

THE ANTERIOR CINGULATE/MEDIAL FRONTAL CIRCUITS

The medial frontal circuit originates in the anterior cingulate, which projects primarily to the nucleus accumbens and related regions of the ventral striatum, including the olfactory tubercle (which is technically part of the basal ganglia according to detailed classification systems and has functions largely identical to the nucleus accumbens). These regions can be considered the limbic striatum (Heimer, Van Hoesen, Trimble, & Zahm, 2008). This circuit returns near its point of origin through the rostrolateral globus pallidus and the dorsomedial nucleus of the thalamus to the anterior cingulate area. Dysfunction in this circuit is characterized primarily by apathy and motivational deficits. Patients appear indifferent and to lack interest. Observed deficits are not primarily cognitive as they are in the dorsolateral syndrome. Rather, MFC circuit involvement results in what is known as a-motivational syndrome. In its most extreme form, this is characterized by akinetic mutism, classically associated with bilateral cingulate lesions (Mega & Cummings, 2001). Severe forms of akinetic mutism can be seen in subcortical injury, specifically to systems closely affiliated with the cingulate including particularly bilateral ventral basal ganglia insults, lesions of the ventral tegmental area, or full lesions of midbrain periaqueductal gray (Watt, Pincus, & Panksepp, 2004). Patients with this condition are literally mute and show minimal to no response to those stimuli that were previously sources of reward and reinforcement. In less extreme forms, spontaneous speech is diminished, verbalizations are brief, and there is little drive and motivation. Apathetic depressions obviously involve lesser disruption of this same paralimbic-subcortical network (Kirsch-Darrow et al., 2006).

Because of these aspects of the presentation, cognitively capable patients with reasonably intact cognitive profiles can often escape detection through traditional neuropsychological tests, while the presenting difficulties might be attributed to psychological or emotional variables. This helps to foster the misleading notion that cognitive and emotional functions are separate, and that problems with motivation and drive are not brain-related. In brain–behavior relationship reality, these types of executive deficits result from interactions between brain circuitries, although neuropsychological test psychometric scores are not particularly useful for identifying and characterizing these possible interactions. In this regard, deficits in executive functioning can and do occur for reasons other than cognitive pathology (Ardila, 2008; Chow & Cummings, 2007). As is the case with OFC pathology, go/no-go task performance is often pathognomonic of involvement, although due to performance overlap, these types of competing programs tasks lack highly specific localization capability. There are

currently no commercially available neuropsychological procedures that are specific to identifying apathy and/or motivation.

FRONTAL SYSTEM SYNDROMES

These circuitries help demonstrate that there is no one frontal lobe syndrome. Instead, there are multiple frontal system syndromes. Each broad type of frontal lobe syndrome is characterized by the specific behavior patterns described previously. Particularly at the level of the cortical convexity, lesions can be very discrete and can result in distinct cognitive and behavioral presentations. A lesion anywhere within the looped architecture of any specific circuit will generate a similar if not identical symptom picture. However, it is not unusual for more than one circuit to be involved in a patient's clinical presentation, and this is manifest by a mixture of behaviors and symptoms that would characterize malfunctions of several circuits (Chow & Cummings, 2007; Malloy & Richardson, 2001).

Although more than one circuit is often involved in a patient's presentation, the functioning of every circuit cannot be approached through using the same assessment methodologies. For example, if dorsolateral pathology in particular is not involved, it can be very difficult and sometimes impossible to identify deficits using classic neuropsychological tests. When this occurs, a neuropsychologist might conclude that the patient's executive functioning is perfectly normal. This conclusion is not necessarily justified. Instead, it may very well be that the testing procedures did not access regions demonstrating pathology. This fact contributes significantly to the problems with ecological validity frequently noted in relation to neuropsychological evaluation (Sbordone, 2001; Odhuba, van den Broek, & Johns, 2005; Silver, 2000; Sbordone, 2010). Simply put, as they exist today, neuropsychological tests do not measure every possible brain-related function, particularly in more affective and personality domains. In addition, an important principle of this distributed circuitry is that lesions in areas to which these circuits project can have a strikingly similar (if not identical) presentation (Mega & Cummings, 2001). The psychometric properties of neuropsychological tests are simply not sensitive to making these differential localization discriminations. For example, lesions of the dorsolateral prefrontal cortex, a lesion within the dorsolateral head of the caudate, or a lesion in the medial dorsal region of the internal section of the globus pallidus can all generate a very similar symptom picture (Cummings & Miller, 2007; Grau-Olivares, Arboix, Bartres-Faz, & Junque, 2007a; Grau-Olivares et al., 2007b; Bombois et al., 2007; Lee & Chui, 2007; Su, Chen, Kwan, Lin, & Guo, 2007).

These frontal-basal ganglionic circuits are organized around different channels or modules of function. Despite the fact that these circuits originate in widespread regions of the frontal cortices and project deep inside the basal forebrain to a spatially restricted region, the integrity and segregation of each of these circuits is maintained. However, because of the spatial extent of the convexity, lesions in very circumscribed cortical regions can result in very specific frontal lobe syndromes, with fairly well-delineated cognitive, affective, and behavioral manifestations. As lesions descend deeper into anterior brain regions toward the basal forebrain, however, the spatial constriction of the area greatly increases the likelihood that one lesion would impact on more than one circuit. At this deeper level, behavioral manifestations become more mixed, with one lesion generating the effects and features of multiple circuitries (Su et al., 2007; Lee & Chui, 2007; Bombois et al., 2007). In fact, descending deep into the brain, it becomes difficult to imagine a single lesion impacting only upon a single circuit (Middleton, 2003). The involvement of multiple circuits with mixed cognitive, affective, and motivational features becomes the rule rather than the exception because the spatial geography or territory becomes increasingly constricted and shared. Therefore, in considering frontal system syndromes, it is critical to remember that neuropsychological tests do not measure all relevant cognitive, affective, motivational, and behavioral functions; that the involvement of multiple frontal system circuitries is common; and that the various and differing multiple etiologies of frontal-subcortical pathologies are not neuropsychologically friendly with respect to differential diagnostic interpretations. As a result, it is best to consider,

interpret, and report neuropsychological test results in cognitive and behavioral terms (Alvarez & Emory, 2006). The following case example illustrates many of these issues.

FRONTAL SYSTEMS DEMENTIA: A CASE EXAMPLE

This is a case of a 70-year-old right-handed male with a doctorate degree who was functioning in an independent health care practice. At the time of evaluation, his family reported a 1.5-year history of insidiously deteriorating function. Personality and emotional changes included a high degree of anxiety, easily provoked crying, frustration and irritability, and an unusual indifference to things that would formerly engage him. In addition, he began to develop a blank facial expression. Cognitive changes included memory lapses, forgetfulness, and failures in information retrieval. He became easily distractible. At times, he exhibited obsessive-like fixations on aspects of tasks to the exclusion of grasping the broader picture, leading to increasing interpersonal difficulty. He became concrete in his thinking, failing to see the whole picture within the appropriate context. He exhibited difficulties with time estimation and management. He became impulsive with episodes of behavioral dyscontrol (e.g., hitting the dog or the cat). He increasingly needed to be reminded about things, even eating. In fact, he needed to have food put in front of him or he would not initiate eating independently. While previously a reasonably neat person, his desk and office became visibly disorganized. The patient himself complained of indistinct-onset memory problems that he felt were gradually becoming worse. He was not highly concerned about this symptom, but was bothered that his work efficiency had decreased. He did not notice changes in his mood. He denied experiencing emotional changes. He denied experiencing problems with his attention or concentration. He denied problems with speech or language, and these types of instrumental cognitive changes were not observed during interview conversation or discourse.

He was cooperative in relation to the evaluation. He was friendly, eager to engage, and not observably anxious. His mood was euthymic. When experiencing difficulties in completing certain cognitive tasks, he showed no concern about this, and either denied or benignly rationalized them. His disinhibition was readily evident. While completing several testing tasks, he would insist on calling his family, which he did on his cell phone, right in the middle of the task administration. As the evaluation session progressed, he became irritable and agitated about the time the session was taking, but he was able to continue working to avoid a return appointment. When answering questions, either about personal history information or formal test questions, he had a tendency to associate to something that interested him instead of strictly adhering to what was asked, and he was unaware that his replies were off target. He was also unable to return to the central theme of what was originally asked. His test results are presented in Table 18.2

Perhaps the most obvious differential diagnosis here would be between a frontotemporal lobe dementia versus depression. However, although there is behavioral evidence of affective change in terms of irritability, lack of initiation, and apathy, there are really no substantive observations of depression, at least not in terms of meeting the behaviorally defined diagnostic criteria for that condition as listed within the *DSM-IV-TR*. However, there is behavioral evidence of dorsolateral, orbitofrontal, and anterior cingulate/medial circuitry involvement. For example, there are indications of executive function changes not only in terms of cognitive activity, but in terms of the appropriate inhibition and motivation that are necessary for placing circumstances within proper context for proper social and professional judgment as well. Forgetfulness, retrieval problems, distractibility, and diminished insight implicate involvement of the dorsolateral system (working memory deficits are often perceived by patients or evidenced by observing family members as forgetfulness and distractibility). Disinhibition is readily evident in terms of impulsive behavior, episodic dyscontrol, and even irritability. Attention is poorly controlled at least in terms of an inability to maintain a focused stream of response in responding to questions. Anxiety, irritability, crying spells, and appetitive disturbance all imply involvement of lateral and medial orbitofrontal tracts. Apathy, lack of concern over the relevance of behaviors, and lack of purposeful behavioral initiation all implicate involvement of anterior cingulate/medial pathways that project into

TABLE 18.2 Case Example: Neuropsychological Data/Test Performance

Gordon Diagnostic System

	raw	z
Vigilance task		
correct =	26	−5.1
commis =	8	−3.0
latency =	290	+1.2
Distractibility task		
correct =	7	−2.6
commis =	9	−2.3
latency =	440	−0.1

Digit Vigilance Test

iTotal Time = 362. T = 63

Total Errors = 48. T = 24

Wisconsin Card Sorting Test

	raw	T
Categories	6	
Responses	101	
Errors	22	54
Percent Persev Err	12	53
Fail Maintain Set	1	
Trials to 1st cat	10	

MOANS Age and Ed Corrected Scaled Scores

	Raw	SS
Control'd Oral Word Assoc	36	7.1
Boston Naming Test	60	14.7
Token Test	44	10.2
Stroop Word	77	4.4
Stroop Color	46	3.9
Stroop Color/Word	31	8.5
Trails A	33	9.9
Trails B	73	9.2
Judgement of Line Orient	24	10.1

Mattis Dementia Rating Scale-2

	raw score	AMSS	AEMSS
Attention =	37	13	
Initiation/Perseveration =	37	13	
Constructions =	36	10	
Conceptualization =	39	13	
Memory =	25	13	
Total Score =	143	14	13

Word Association (3 stimuli, 1 min each)

Letters = 36 (MAE COWA %tile = 99)

Categories = 46

Animals only = 22. T = 40

Frontal Systems Behavioral Scale

Ratings were done by daughter ''Before'' illness 2 years ago and ''At Present Time.''

Higher T scores are more troublesome relative to normal controlpopulation.

Ratings done by daughter

	Before illness T score	Current T score
Apathy	53	79
Disinhibition	62	89
Executive	70	107
Total	65	101

(continued)

TABLE 18.2 Case Example: Neuropsychological Data/Test Performance *(Continued)*

WAIS-III	WMS-III
Index Scores	Primary Index Scores
Processing Speed = 106	Auditory Immed = 97 Visual Immed = 88 Immed Mem = 91 Auditory Delay = 99 Visual Delayed = 94 Aud Recog Del = 100 General Mem = 96
Performances subtest scaled scores DSy = 12 SmS = 10	
Dsym percentible levels: Incident learn pairing > 50 Incident free recall = 2-5 Copy > 50	Subtest scaled scores Log Mem I = 12 Faces I = 7 Verb PA I = 7 Fam Pic I = 9 LNS =
Ravens Colored Matrices Correct = 29. Percentile = 90	Spa Span =
	Log Mem II = 12
Facial Recognition (short form, extrapolated) Correct = 47. Percentile = 71	Faces II = 11 Verb PA II = 8 Fam Pic II = 7 Aud Rec Del = 10
	Inf & Orien = (72 %tile level) LM Thermatic I = 15 LM Thermatic II = 15 Ment Contr = 11

Rey Auditory Verbal Learning Test(recall of 15 word list)

Trail:	I	II	III	IV	V	Int	VI	trial VI Recog	30° Rcl	30° Recog
	5	6	7	8	8	3	6	14	6	14
ss*:	10					9	8		9	11

*MOANS age & education adjusted; Learning Over Trials ss = 8.

the basal forebrain, limbic basal ganglia, and deep mesodiencephalon. Therefore, history review provides many important clues for a possible diagnosis of frontal-subcortical dementia. Psychometric test findings need to be interpreted using these behavioral observations and their neuroanatomic implications as anchor points.

The patient's test results were revealing, with several subtle interpretive issues. On the Raven's matrices, he performed at the 90th percentile ranking, with the implication that global concept formation remained intact. He did score at a level consistent with expectation in

view of his educational history, although to be sure, the ''colored'' version of this task is decidedly easier than the standard matrices. Nevertheless, one would not predict significant global cognitive deficits in a case of early onset dementia, and this conclusion would be supported by his performance on the Mattis Dementia Rating Scale-II. Similarly, there were no indications of instrumental cognitive deficits such as aphasic speech, agnosia or other perceptual disturbance, or apraxia, with the possible exception of mild dyscalculia because he made errors with simple mental subtraction, implying a loss of calculation efficiency and accuracy. Performances on measures of ''processing speed'' were also generally within normal limits. However, it was suspicious that on the incidental recall paradigm of the Digit Symbol subtest, his score fell between the 2nd–5th percentile ranking, implying either inattention and/or deficits in the initial encoding of information.

Although speech was fluent and without paraphasias in spontaneous conversation or in naming upon object confrontation, his abilities to associate and retrieve words to categories (animal naming fluency) and letters (FAS) were both below the level of expectation for a person of his intellectual and educational backgrounds, and this finding frequently occurs in patients with involvement of anterior brain regions.

Multiple aspects of the attentional matrix were affected. Fluctuations in performances on immediate recall tasks clearly implied he was not able to consistently encode the same range of information as his peers, with scores ranging from above average to a standard deviation below the mean. Therefore, this information that was missed would obviously not be available to executive working memory to assist in guiding behavior. His performance on two tasks of sustained monitoring was poor, characterized by numerous errors of omission (inattention) as well as significant errors of commission (disinhibition). An attentional shifting task required him to switch the focus of attention from one idea to another; his performance was well within normal limits on this task (Wisconsin Card Sorting Test), which is presumably heavily dependent upon the input of dorsolateral cognitive circuitry.

This patient's most notable deficits were observed in relation to a word list learning task. He acquired new information slowly, and he learned less information than his peers. He exhibited the shallow learning slope often characteristic of ''frontal system'' patient populations. Although voluntary (unstructured) retrieval was poorer than expected, significant improvement was observed upon recognition, again indicative of a frontal system pattern. In this regard, although information retrieval for newly learned information was sometimes incomplete, there was no clear or convincing evidence that he ever forgot what he learned during the assessment, again implying involvement of anterior brain regions. Rating scale data was provided by his daughter, who had contact with him on a daily basis. On the Frontal Lobe Personality Scale, significant deterioration in behavioral functioning was reported within dimensions of apathy, disinhibition, and executive functioning, characteristic of patients with involvement of frontal-subcortical circuitry.

Overall, the patient exhibited abnormal changes in behavioral (executive) and emotional functioning, accompanied by deficits within certain attentional functions. All of these deficits were considered mild to moderate in severity. Strictly cognitive changes were considerably milder. His disinhibition clearly implied ventral orbital and medial prefrontal involvement. Although the neuropsychologist who completed the evaluation recognized that these findings were not highly specific as to etiology, frontotemporal dementia (FTD) was strongly suspected. This certainly represented a reasonable diagnostic conclusion, but later histopathology did not confirm this, and suggested a significantly rarer prion disorder. For example, as summarized by Salmon and Bondi (2009), FTD patients have greater deficits in executive functions than in other cognitive abilities, whereas AD patients have executive disturbances that are proportional to their instrumental cognitive deficits in language and visuospatial abilities. On the other hand, FTD patients have been characterized as exhibiting significantly worse performance on word generation subtests sensitive to frontal lobe dysfunction (as on letter and category fluency tasks) but as functioning much better on tests sensitive to medial temporal lobe memory system impairment and parietal association cortices that support instrumental cognitive abilities (Salmon & Bondi, 2009).

Subsequent MRI of the brain revealed a pronounced degree of periventricular ischemic white matter changes of a confluent nature bilaterally, much more than might be expected

for his age. The confluent character of these changes was consistent with involvement of multiple prefrontal-subcortical circuits. In other words, this patient's primary pathology on imaging was not cortical. Instead, abnormalities were observed within the white matter tracts connecting the frontal lobes with the direct and indirect pathways of the striatum. The patient's condition took a progressively downward course; he was bedridden within a few months, lost all ability to speak, developed aspects of decerebrate posture/rigidity, and died approximately 5 months after this neuropsychological evaluation. Autopsy confirmed a diagnosis of the sporadic form of CJD, not any one of the frontotemporal lobar degeneration diseases discussed earlier. This illustrates that the actual postmortem histopathology, clearly the gold standard for diagnosis for the underlying neurological illness, is often very difficult to estimate based even on the most careful and detailed assessment of clinical phenotype, and that any given clinical phenotype maps to several histopathologies, even though a given histopathology may prefer or gravitate toward a limited range of clinical phenotypic manifestations.

To summarize, these test results are significant for several reasons. This case exemplifies the diagnostic issues that need to be considered in frontal-subcortical dementias, particularly at the subcortical level. Important considerations include the fact that disturbances in frontal-basal ganglia circuitry can generate a similar cognitive and behavioral presentation regardless of the level at which cortico-striatal-pallidal-thalamo-cortial circuitry is affected. Neuropsychological tests do not assess all relevant cognitive, affective, and motivational influences on behavior, so that test profiles need to be interpreted within the context of both neuroanatomical and behavioral frameworks. This approach requires information from multiple sources. Test results need to be interpreted and reported in cognitive and behavioral descriptive terminology instead of strictly in terms of neuroanatomical reference points (Alvarez & Emory, 2006). Finally, neuropsychological test results cannot be interpreted by using the points of reference established through behaviorally defined, *DSM*-type diagnostic systems. Our current state of knowledge dictates that neuropsychological test data are to be employed as one source of information, integrated with data from other points of reference, in order to assist in guiding diagnostic conclusions. This will remain the case until the field of neuropsychology can further develop methodologies for assessing segregated frontal-subcortical circuitries that contribute to the expression of cognitive, affective, motivational, and social functioning.

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