**WHITE MATTER DEMENTIA**

Cognitive dysfunction is the most common brain-behavior syndrome related to white matter disorders, and, in many cases, the dysfunction is severe enough to be called “white matter dementia.” The prevalence of cognitive dysfunction and dementia from white matter disorders as a whole is uncertain; the epidemiologic data are just not available. But much clinical experience supports the sense that cognitive dysfunction is prevalent among these white matter disorders. Moreover, research suggests that syndromes of widespread white matter dysfunction far outnumber syndromes of isolated, regional white matter dysfunction. A case in point is MS, in which cognitive dysfunction or dementia may afflict as many as two thirds of patients, whereas more specific problems such as language impairment, known as aphasia, occurs in less than one percent of patients. Similarly, although neuropsychiatric syndromes such as depression are common in patients with white matter disorders, they may result from many causes, so the cause-effect relationship is less clear. All this suggests that cognitive impairment will prove to be a leading source of clinical distress and disability in cases of damage to cerebral white matter.

Not surprisingly, in early stages of any white matter disorder milder cognitive dysfunction is more common than dementia, but dementia often follows. In MS, for example, estimates are that 10 to 20 percent of patients will develop dementia. Despite this, it is important to realize that in clinical practice the recognition of early cognitive dysfunction in the white matter disorders is far from simple. Many patients show subtle cognitive symptoms and signs, frequently co-mingled with other neurologic or medical features of their disease, challenging the clinician to interpret the relationship of white matter manifestations to cognitive status.

Moreover, the range of clinical features that herald the onset of cerebral white matter involvement is impressively broad: inattention, executive dysfunction, confusion, memory loss, personality change, depression, somnolence, lassitude, and fatigue. This nonspecific clinical profile often suggests a primary psychiatric disorder, and many patients with white matter dementia do display early psychiatric dysfunction before measurable cognitive impairment. Here, we see the relevance of white matter disorders to the growing field of neuropsychiatry, but we still have no commonly accepted term to describe white matter disorders presenting as early cognitive impairment. One suggestion is to use the term “dysmentia,” meaning disordered (Greek dys) mind (Latin mens). Properly defined

and standardized, dysmentia could describe early cognitive impairment in white matter disorders, just as mild cognitive impairment describes early cognitive loss preceding the development of the gray matter disease recognized as Alzheimer's. How do cognitive dysfunction and dementia actually present themselves to the physician? What profile of deficits and strengths can we use in diagnosis, counseling, rehabilitation, and research on new therapeutic strategies? A profile seems to be developing that includes a sustained attention deficit, executive dysfunction, memory retrieval deficit, visuospatial impairment, and psychiatric dysfunction with normal language, motor function, and procedural memory. Although still preliminary, this specific combination differs from that seen with cortical dementia such as Alzheimer's disease and from subcortical gray matter dementias such as Huntington's disease. Again, we see cerebral white matter's possible unique role in the organization of cognition and emotion.

Sustained attention deficits, executive dysfunction, and memory retrieval deficits are most typical of patients with white matter disorders; all relate to a general slowing of cognition, often called impaired speed of information processing. In terms of brain anatomy, sustained attention (concentration, vigilance), executive thinking, and memory retrieval are all closely associated with the operation of the frontal lobes, and most white matter disorders show a preference for the frontal white matter. Even when white matter lesions are situated in more posterior cerebral locations, frontal lobe functions are still affected, probably because of the dense connectivity between frontal and other regions. Visuospatial skills are also affected in white matter disorders.

In contrast, language is typically normal or only mildly affected in patients with white matter disorders because the language-related cortex is spared. Motor function also tends to be intact, in keeping with the relative sparing of deep gray matter structures. Likewise, procedural memory, or memory for skills such as bicycle riding, is retained.

What about white matter lesions linked with narrower brain-behavior disturbances, including classic syndromes such as aphasia and amnesia? Although these are rightly viewed as more common with cortical lesions, recent research also links them with white matter damage. For example, there are reports of isolated amnesia associated with stroke that affects a white matter region called the mamillothalamic tract. A language disturbance known as conduction aphasia is related to MS plaque in another part of the brain, the left arcuate fasciculus. Thus, although they are uncommon compared with syndromes caused by diffuse

white matter damage, the focal brain-behavior syndromes illustrate the importance of white matter tracts in all domains of higher function. Research here can enhance our understanding of the neural networks that underlie these higher brain functions.

**WHITE MATTER AND NEUROPSYCHIATRY**

Abnormalities of cerebral white matter are associated with a spectrum of emotional disturbances. This category of disorders is vaguer than the brain-behavior syndromes because the correlation of white matter disorders with psychiatric syndromes is much less clear; and psychiatric impairments are notorious for having multiple causes. Still, there is much new information on the role of white matter in emotional function, shedding light on both white matter disorders and psychiatric diseases.

These neuropsychiatric syndromes fall into two general groups: psychiatric features in patients who have known white-matter disorders, and the many psychiatric diseases in which white matter abnormalities are implicated. In patients with known white matter disorders, reports document the presence of depression, mania, psychosis, pathologic crying or laughing, and euphoria. We do not know, as yet, how closely these psychiatric syndromes correlate with measures of white matter dysfunction. Thus, the possibility remains that a given psychiatric syndrome is related only indirectly, or not at all, to the patient's specific white matter disorder.

When it comes to primary psychiatric diseases, often considered idiopathic (of uncertain cause) and as yet not linked with structural brain damage, there are recent intriguing reports from neuroimaging research on the structure of white matter. In patients with schizophrenia, for example, imaging studies have detected microscopic abnormalities in white matter structures, and widespread myelin and oligodendrocyte dysfunction are linked with altered cerebral connectivity.[5] Much evidence also supports an association between white matter changes and geriatric depression, although a firm correlation has yet to be established. MRI studies have found that white matter abnormalities are more common in patients with bipolar disorder than in the general population. In children with attention deficit/hyperactivity disorder, a diminished volume of right frontal white matter was found to correlate with impaired sustained attention. In contrast, an increase in the volume of hemispheric white matter in all lobes was observed in autism. Finally, diffusion tensor imaging studies of schizophrenic men found a correlation of inferior frontal lobe white matter abnormalities with impulsive aggression.

Obviously, we need far more detailed investigation of how white matter abnormalities may contribute to psychiatric disease, perhaps by disrupting neural networks devoted to emotional function.

## WANTED: A BEHAVIORAL NEUROLOGY OF WHITE MATTER

The study of higher functions in humans requires consideration of all the brain's neural tissues. Long neglected as a contributor to the organization of cognitive and emotional operations, white matter is the object of intense, intriguing, and increasingly fruitful efforts to improve our understanding. Studying people with white matter disorders to correlate their brain lesions with specific behavior changes promises a wealth of insights. Increasingly, this method will be complemented by sophisticated neuroimaging techniques that yield detailed visualization of white matter tracts as they participate in the cognitive and emotional operations of distributed neural networks.

In practical terms, an appreciation of the brain-behavioral importance of white matter disorders can greatly benefit patients, especially as early recognition and treatment often determine an outcome. In theoretical terms, further study of white matter and its disorders expands our knowledge of the brain as an extraordinarily complex structure in which the connectivity provided by white matter is central to cognition, emotion, and consciousness itself.

In the most general sense, the gray matter of the brain facilitates information processing, and the white matter facilitates information transfer; both are critical for efficient operation of the neural networks responsible for a specific mental domain. In the presence of damaged white matter, information processing occurs only in a slowed and inefficient manner, and, if the white matter is severely impaired, there may be no processing at all. Considerations like these argue strongly for the evolving field of the behavioral neurology of white matter, an organizing framework that can stimulate urgently needed study, with no less a goal than a more complete and powerful portrait of the organ of the mind.