Chapter 1

Brain–behavior relationships: a reconsideration

In 1906, the esteemed anatomist Santiago Ramón y Cajal shared the Nobel Prize in Medicine or Physiology with Camillo Golgi, another well-known anatomist of the time. In his acceptance speech for the award, Ramón y Cajal defended what has come to be known as the neuron doctrine – the idea that all neurons of the central nervous system (CNS) are linked but not physically connected – while in his address Golgi defended his reticular theory – the notion that all CNS neurons are fused as one within a diffuse network (Bock, 2013). This vigorous debate was eventually resolved by growing evidence at the time and much subsequent work that incontrovertibly confirmed the neuron doctrine, establishing a fundamental tenet of neuroscience (Kandel et al., 2013). The neuron doctrine has exerted enormous influence in structuring thinking about how the brain subserves behavior by focusing attention squarely on the roughly 100 billion nerve cells of the human brain. In the quest to discover more precision about the relationship between the brain and behavior, however, many more details of CNS neurons become important, including their location, microstructure, physiology, pharmacology, and, most recently, their position within widespread distributed neural networks mediating cognition and emotion. All of these aspects of neural structure and function are critical not only for understanding the brain and its operations, but also for the care of millions of people around the world with devastating neurologic disorders.

Behavioral neurology is commonly described as the study of higher cortical function, a characterization held so firmly by many neuroscientists that a "corticocentric" explanation for the varieties of human behavior is often adopted without question (Parvizi, 2009). Everyday experience indicates that the vast majority of physicians and scientists, and the general public, would doubtless endorse the assumption that a person's intelligence is primarily a function of the amount of gray matter in that individual's brain. Among all the gray matter regions of the brain, however, the cerebral cortex holds a special place in neuroscientific thinking, compelling an almost reflexive allegiance to this thin mantle of tightly arrayed neuronal cell bodies, dendrites, and synapses. As much as the cortex deserves its reputation as critical for the higher functions, however, a wealth of evidence also supports the notion that brain–behavior relationships extend beyond those that can be developed with respect to the cerebral cortex (Geschwind, 1965; Schmahmann et al., 2008; Parvizi, 2009; Filley, 2012). Whereas the importance of the cortical mantle in elaborating human behavior is firmly established, the contributions of neurons and their projections in noncortical regions – the subcortical gray matter and the white matter – cannot be neglected.

As more clinical and experimental data are gathered, it is increasingly evident that a more nuanced view of the neural underpinnings of behavior is needed, and the regions below the cerebral cortex are entirely appropriate areas of study. Experienced neurologists recognize the potential for damage to these regions to produce significant neurobehavioral dysfunction, but the long-standing preeminence of the cortical gray matter in the neuroscience of behavior has to some extent hampered investigation of the full range and subtlety of brain–behavior relationships. This limitation is nowhere more evident than in the study of dementia.

The conventional emphasis on gray matter

The growing problem of Alzheimer's Disease (AD) overshadows the entire field of dementia, and indeed attracts well-deserved attention as a medical and societal menace that extends far beyond the confines of neuroscience. The widely accepted neuropathology

of AD, memorized by medical students as featuring the familiar neuritic plaques and neurofibrillary tangles, naturally directs attention to the cerebral cortex in the investigation of etiopathogenesis, clinical phenomenology, and treatment (Querfurth and LaFerla, 2010). At the same time, the prominence of thinking about higher cortical function – regularly taught in many medical and graduate schools as the province of behavioral neurology – further draws investigators toward the cerebral cortex in an almost irresistible fashion. But many other dementias result from neuropathology in regions other than the cortex, and the understanding of dementia cannot be complete without inclusion of these disorders. Indeed, it can be plausibly stated that the field has been held back by the somewhat uncritical acceptance of the cortex as the only important mediator of cognition, a view that to some extent impedes innovative thinking about the phenomenology and etiopathogenesis of dementia syndromes.

The long-standing emphasis on cortical gray matter as the source of higher functions has its roots in the nineteenth century, when advances in neurology and neuroscience fostered the development of a hierarchical conceptualization of the brain (Parvizi, 2009). According to this view, the brain is composed of "lower" structures in caudal regions that subserve involuntary behaviors, with "higher" structures added rostrally in the course of evolution as humans acquired more voluntary control over instinctual behavior. At the summit of the brain's evolved structural hierarchy is the cerebral cortex, particularly the frontal lobes, which is thought to endow humans with distinctive cognitive capacities. An early impetus to corticentrism was manifest in the work of Franz Joseph Gall (1758–1828) and his collaborator Johann Kaspar Spurzheim (1776–1832), whose misguided ventures into phrenology nevertheless focused attention on the cerebral cortex as the substrate of the higher functions (Gall and Spurzheim, 1810–1818). A corticocentric focus was then prominently advanced by the English neurologist John Hughlings-Jackson (1835–1911), who maintained that higher brain centers operated for the purpose of governing lower ones (Parvizi, 2009). Hughlings-Jackson's seminal studies of epilepsy also stimulated interest in the cortex, as it was clear that a diversity of neurobehavioral experiences were associated with certain kinds of seizures. Sigmund Freud (1856–1939), who began his career as a neurologist and was an admirer of Hughlings-Jackson, followed later in a similar manner with his proposal of the id, ego, and superego forming the structure of personality; these categories, like all psychic processes, would presumably be found someday to correspond to specific areas of the brain (Parvizi, 2009). All of these ideas proved highly influential, and whereas much has been learned since the days of Gall, Hughlings-Jackson, and Freud, the hierarchical view of the brain and cognition continues to inform much contemporary thinking in neuroscience.

With the coming of the twentieth century, brain–behavior relationships were largely ignored as Freudian psychoanalysis and holistic psychology held sway for some 50 years. Still, Alzheimer's discovery of plaques and tangles in the cerebral cortex of his demented patient Auguste Deter (Alzheimer, 1907) helped keep alive the focus on the cerebral cortex. In subsequent years, as brain–behavior relationships began to attract neuroscientific interest once again, the influential neuropsychologist Alexander Luria further supported the bias toward the cerebral cortex by studying Russian soldiers who had sustained penetrating head injuries in World War II. This work culminated in the publication of his masterwork *Higher Cortical Functions in Man* (1966), a book that highlighted the term still commonly used to describe the interests of behavioral neurologists. Roughly contemporaneous with Luria, the Canadian neurosurgeon Wilder Penfield (1891–1973) presented remarkable observations from awake patients to show convincingly that conscious experiences could be elicited by stimulation of the cerebral cortex (Penfield, 1975).

As neurology gained momentum as a medical specialty in the mid-twentieth century, an unquestioned assumption about the hegemony of the cortex in the organization of cognition steadily became commonplace. One factor supporting this assumption was that laboratory studies using animal models are necessarily limited with respect to the examination of the other major portion of the brain, its white matter. As will be discussed in Chapter 3, nonhuman animals have far less white matter than humans have; in rodents, for example, the laboratory animals studied most often, only about 14% of brain volume is occupied by white matter (Goldberg and Ransom, 2003), whereas in humans this figure is about 50%. Thus the extrapolation of data from rodent studies to humans has led to serious underestimation of the

importance of white matter involvement in human disease (Matute and Ransom, 2012). Another development fostering the corticocentric perspective was that, as the technology of clinical neuroscience improved to quantify many aspects of brain structure and function, most methods that came into widespread use – electroencephalography, magnetoencephalography, single photon emission computed tomography, positron emission tomography, and functional magnetic resonance imaging – were not generally applied to the examination of any brain areas except the cerebral cortex (Parvizi, 2009). The oldest of these technologies, electroencephalography, can in fact be employed to study white matter because of the disruption in electrographic coherence caused by white matter lesions (Nunez, Srinivasan, and Fields, 2015), but the primary application of electroencephalography has clearly been in the study of cortical function. Thus the use of available methods for studying the brain further exacerbated the bias toward the cortex and away from other regions. Because the instruments available to study the brain were not developed to probe any region except its outermost layer, it is not surprising that the underlying tissue remained to a large extent understudied. This situation persists to a considerable degree today; despite structural neuroimaging techniques that allow detailed views of subcortical regions, functional imaging studies of the cerebral cortex dominate the field.

A related problem unique to the world of dementia research also deserves comment. As will be discussed in more detail later in this book, the assumption that cortical neuropathology underlies the dementia of AD is so pervasive that it has come to dominate thinking about how dementing disease produces clinical dysfunction. The striking postmortem appearance of cortical neuritic plaques and neurofibrillary tangles in a person who was known to have dementia is indeed compelling, and, drawing from experience with other neuropathological lesions such as atherosclerosis, neoplasia, and viral inclusions that clearly cause clinical illness, neurologists are predisposed to conclude that plaques and tangles cause dementia. Even though this conclusion cannot be indisputably supported, as will be discussed in subsequent chapters, the powerful influence of plaques and tangles further reinforces the view that the cortex is the most essential, or even only, site of cognitive function. Thus a certain circularity of

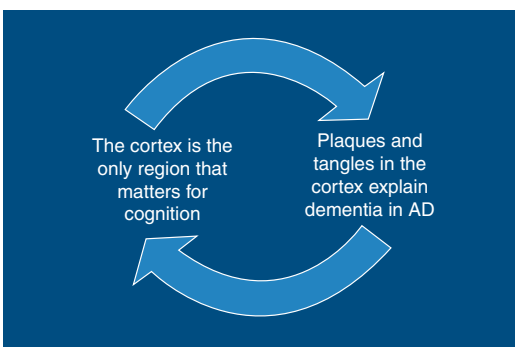

Figure 1.1 Circular reasoning on the structural basis of dementia.

reasoning develops, by which it is claimed that because plaques and tangles in the cortex explain the dementia of AD, the cortex is the only region that matters for cognition (Figure 1.1). Whereas the cortex is undoubtedly important for cognition, to invoke the neuropathology of AD as proof that only the cortex matters runs the risk of oversimplifying the complexity of dementing illness.

In sum, all of these factors have conspired to concentrate research efforts on the cerebral cortex in the overwhelming majority of current studies in cognitive neuroscience, particularly those devoted to the study of dementia. This situation would seem to be in need of an adjustment that will serve to extend investigation to other regions of the brain that play a key role. It is in this light that the present state of cognitive neuroscience suffers from what has been justifiably termed corticocentric "myopia" (Parvizi, 2009).

If the undue concentration on the cerebral cortex is to be rectified, a comprehensive effort to examine regions subjacent to the cortical mantle is clearly warranted. This directive immediately implicates the impressive array of noncortical structures, which include the deep gray matter of the thalamus, basal ganglia, the cerebellum, and of course the white matter. The subcortical dementias, the most familiar being Huntington's Disease (HD) and Parkinson's Disease (PD), are classically associated mainly with neuropathology in the basal ganglia, and despite some criticism, the concept of subcortical dementia has endured as a useful contrasting clinical syndrome to the cortical dementia of AD (Bonelli and Cummings, 2008). White matter disorders are often included in the subcortical dementias, alternatively known as

frontal-subcortical dementias (Bonelli and Cummings, 2008), but uncertainty has lingered about the importance of white matter damage in producing neurobehavioral effects. In part because white matter changes on contemporary neuroimaging are so common, and at times present in normal people of all ages, patients with dementia and white matter lesions are frequently assumed to have coexistent cortical neuropathology to explain their cognitive loss. White matter is not traditionally discussed as a specific foundation of cognitive or emotional operations in curricula or textbooks considering the neural organization of human behavior, and it is not surprising that until recently it has figured only incidentally in research on dementia.

Why white matter matters

White matter merits focused and systematic consideration as a brain component critical not only to the field of dementia but to all of behavioral neurology (Filley et al., 1988; Filley, 2011, 2012). At first glance, it should not be a novel realization that the roughly one half of the human brain occupied by white matter may be important for behavior (Nolte, 2002; Schmahmann and Pandya, 2006). Nature has little use for tissues with no functional significance, and white matter provides the essential macroconnectivity of distributed neural networks coursing within and between the hemispheres to subserve information processing speed and a range of related neurobehavioral functions. Evolution has in fact produced an expansion of white matter volume exceeding that of gray matter in *Homo sapiens*, as will be elaborated in Chapter 3. From a clinical perspective, modern neuroimaging has revealed that white matter lesions with a predilection for the frontal lobes are present in a large proportion of the entire population, and in the vast majority of older adults (Launer, 2004), observations that not only implicate white matter dysfunction in the pathogenesis of cognitive impairment but also underscore the prominence of frontal white matter as a feature of human neuroanatomy (Schoenemann, Sheehan, and Glotzer, 2005). The gray matter, meanwhile, contributes at the level of the synapse via an intricate web of microconnectivity, and is the major locus of much investigation describing the mediation of memory, language, praxis, perception, and other instrumental functions, and, of course, the cognitive impairment related to neuropathology in these regions. White matter functions in parallel with gray matter to expand the operational capacity of neurons by enabling the rapid and efficient transfer of information that complements the information processing of synapses and neuronal cell bodies (Turken et al., 2008; Bartzokis et al., 2010; Kochunov et al., 2010; Kerchner et al., 2012).

These ideas have recently coalesced to foster a new development in neuroscience centered on the concept of the "connectome," generally defined as the totality of neural connections in the human brain (Sporns, 2011). These connections include synaptic contacts in gray matter, often called the microconnectome, and the longer connections made by white matter tracts, which are known as the macroconnectome (Kaiser, 2013), the collection of macroscopic tracts that form the basis of this book. Whereas the history of neuroscience is replete with efforts by many distinguished investigators to map the brain, these attempts most often focus on the cerebral cortex, and the power of advanced neuroimaging now enables the study of what has come to be called connectomics as never before (Catani et al., 2013). Exciting as the prospect may be, however, it is wise to put the topic in perspective: whereas the complete connectome of the nervous system in the nematode *Caenorhabditis elegans* was mapped almost 30 years ago (White et al., 1986), this project involved the analysis of just 302 neurons and 5,000 synapses, and it is a far more daunting task to take on the roughly 100 billion neurons and 100 trillion synapses of the human brain (Catani et al., 2013). Nevertheless, the extraordinary connectivity that subserves the highly integrated phenomena of cognition and emotion calls out for exactly this kind of investigation. To that end, the Human Connectome Project has been launched in the United States, with the assistance of federal funding, with the goal of producing a comprehensive, publicly available map of human brain connectivity (Toga et al., 2012). Impressive progress has already been made in advancing the understanding of connectivity as neuroimaging techniques continue to evolve at a rapid pace.

As will be demonstrated throughout this book, and can be reviewed in a previous monograph (Filley, 2012), the neurobehavioral study of white matter discloses a host of cognitive and emotional deficits that can plausibly be related to tract damage in the subcortex and, to some extent, within the cortex

itself. These observations are crucial for clinical neuroscience, including the daily tasks of accurate diagnosis and informed patient care. But it is also worth considering the role of white matter in health, and studies are showing that the functions of white matter as determined by modern neuroimaging correspond well with the loss of functions observed with lesions of those same systems. With the availability of astonishing neuroimaging techniques that can identify regions of white matter and correlate their structure and function with normal cognitive operations, it is becoming clear that cerebral white matter is centrally engaged in cognitive processing speed (Kerchner et al., 2012), mathematical ability (Matejko et al., 2013), measured intelligence (Jung et al., 1999), several traditional neurobehavioral domains such as executive function (Sasson et al., 2013), memory (Fields, 2011), language (Friederici, 2015), and visuospatial skills (Umarova et al., 2010), and in more recently considered areas, including social cognition (Parkinson and Wheatley, 2014) and creativity (Takeuchi et al., 2010). Far from the often expressed view that white matter simply "follows" gray matter as a mere extension of the neuronal cell bodies and synapses in the cerebral cortex that primarily generate the phenomena of higher function, white matter makes its own unique contribution to the multiple distributed neural networks subserving behavior. Moreover, the importance of white matter is apparent across the life span as developmental changes exert selective age-dependent effects (Bartzokis et al., 2001; Bartzokis, 2005). The myelinated tracts of the brain participate in all normal neurobehavioral functions, and their breakdown or dysfunction under abnormal conditions may have profound clinical consequences.

The behavioral neurology of white matter

The many advantages offered by the advent of neuroimaging techniques over the past three decades have allowed clinicians and investigators to examine the white matter using a time-honored approach known as the lesion method. Originating with the work of nineteenth-century neurologists who correlated neurobehavioral deficits seen in life with brain damage seen at autopsy (Benson, 1993), the lesion method has been and remains the major source of information at the core of behavioral neurology (Damasio, 1984; Benson, 1993; Filley, 2011). Yet the data gathered by this method largely focused on gray matter, especially that of the cerebral cortex, and white matter was traditionally not given equal consideration. Conventional magnetic resonance imaging (MRI) directly addresses this deficiency with its remarkable capacity to depict the white matter of the brain in health and disease (Aralasmak et al., 2006). With MRI, white matter findings can be correlated in life with neurobehavioral deficits just as securely as changes within gray matter, and in some cases even more so. Since then, an impressive database has been generated to support the role of white matter in cognition and emotion.

One of the most durable tenets of behavioral neurology, and indeed a principle central to all of neurology, is that the location of a lesion is more clinically revealing than its etiology. That is, the understanding of altered behavior in people with brain damage is fundamentally determined by the site of the damage rather than its cause. Once the correlation of the behavioral change with the area(s) of damage is established, then the critically important tasks of defining the neuropathology as precisely as possible and then treating the problem can proceed. But from a neurobehavioral perspective, localization is paramount. Nonfluent aphasia in a right-handed individual, for example, implies left inferior frontal cortical injury, and similarly, a cerebral disconnection syndrome suggests damage to the corpus callosum; in each case, neuropathological lesions ranging from infarction and trauma to infection and neoplasm may all be responsible.

With the emergence of modern neuroimaging invigorating the study of brain–behavior relationships, interest in white matter steadily mounted. As MRI led to better understanding of old diseases and the discovery of intriguing new ones – many associated with obvious neurobehavioral dysfunction – it became ever more difficult to ignore the impact of white matter lesions on normal cognition and emotion. A good example of this trend was apparent in the understanding of multiple sclerosis (MS); whereas cognitive impairment of any severity was thought to be present in only around 5% of patients in the pre-MRI era (Kurtzke, 1970), careful study of this issue in later years disclosed cognitive impairment in 43% of MS patients (Rao et al., 1991), and figures higher than this are often cited.

MRI, therefore, offered the novel opportunity to examine white matter–behavior relationships. As with cortical diseases, white matter disorders can be investigated by use of the lesion method, and combined with neuropathological methods, MRI and its derivative techniques are steadily establishing the selective role of white matter dysfunction in disturbing normal behavior. Studies of this kind are also helping find a solution to the issue of the potential role of concomitant gray matter neuropathology that may complicate the relationships between white matter and behavior (Stadelmann et al., 2008). Reports have now appeared that demonstrate selective white matter dysfunction – with minimal gray matter involvement, or none at all – that has compelling neurobehavioral relevance. Examples can be found in cases of focal damage detected by MRI (Arnett et al., 1996; Van Zandvoort et al., 1998), volumetric MRI studies demonstrating macrostructural disruption (Juhasz et al., 2007; Northam et al., 2011), advanced neuroimaging with magnetic resonance spectroscopy (MRS; Filley et al., 2009), magnetization transfer imaging (MTI; Iannucci et al., 2001), and diffusion tensor imaging (DTI; Gold et al., 2010) disclosing microstructural disturbances, and neuropathological study of white matter (Filley, Halliday, and Kleinschmidt-DeMasters, 2004; Al-Hajri and Del Bigio, 2010; Del Bigio, 2010). In all of these examples, the relative contributions of white and gray matter have been considered, and the conclusion has been reached that neurobehavioral significance can be attributed to disordered white matter alone. While not likely to come as a surprise to many neurologists and others who examine brain–behavior relationships, the demonstration that white matter by itself disrupts neurobehavioral competence has been uncommon until recently. Studies of this kind are most welcome, as the information generated is crucial for understanding the unique contribution of white matter to behavior.

It has thus become apparent that a behavioral neurology of white matter can be plausibly considered (Filley, 2012). Historically, the development of such a body of knowledge would not be possible without the work of Norman Geschwind (1926–1984; Figure 1.2), recognized as the founder of behavioral neurology, whose most important paper (Geschwind, 1965) emphasized the role of cerebral disconnection in the pathogenesis of neurobehavioral syndromes. The idea of disconnection, which prominently involves cerebral white matter damage or dysfunction, had been introduced by many prominent nineteenth-century European neurologists, and Geschwind vigorously revived and expanded the concept while launching the discipline known as behavioral neurology. Classic syndromes such as conduction aphasia and alexia without agraphia were highlighted as clearly implicating white matter, setting the stage for the detailed analysis of many other syndromes related to white matter lesions that would become possible with neuroimaging. Today the behavioral neurology of white matter includes not only the classic disconnection syndromes of Geschwind and his predecessors, but also a variety of neuropsychiatric conditions, and the syndromes of cognitive impairment that are the subject of this book.

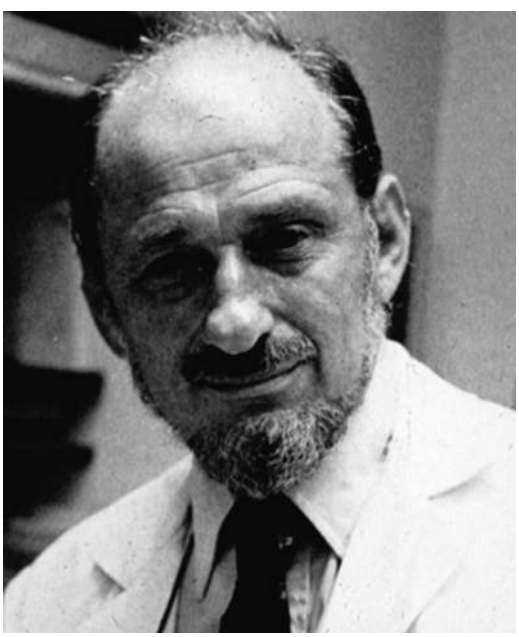

Figure 1.2 Norman Geschwind.

Despite its traditional position as a minor contributor to the mediation of cognition and emotion, white matter can be seen to have a particularly noteworthy position in the study of dementia. Once investigation turns its attention to this part of the brain, a spectrum of intriguing data and implications becomes evident. The neuropathology of white matter disorders is typically

diffuse or widespread, thus disrupting many networks simultaneously and producing a multidomain syndrome that merits the term "dementia." Whereas focal neurobehavioral syndromes and various neuropsychiatric syndromes may occur with white matter lesions, dementia is also being recognized as demanding attention, and its importance in behavioral neurology may extend to a broad spectrum of disorders. This book describes the origin and development of the syndrome of white matter dementia, a term introduced nearly three decades ago (Filley et al., 1988) to call attention to the cognitive sequelae of white matter disorders affecting the brain.

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