Contents

CHAPTER 1

Neurobiological Bases of Cognition, Emotion, and Behavior

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That brain and behavior are inseparable and that mental events are brain events are the physicalist philosophical foundations of neuropsychiatry (Arciniegas et al. 2006). Biological, social, and environmental factors, as well as their reciprocal interactions, are appreciated as influences on brain function in health and disease, and neuropsychiatrists recognize all of these factors as necessary elements of any account of mental (i.e., neuropsychiatric) function. Their influences on cognition, emotion, and behavior and the combined mechanisms by which they engender neuropsychiatric disorders, however, are understood and described in terms of their effects on brain structure and function.

The Joint Advisory Committee on Subspecialty Certification of the American Neuropsychiatric Association and the Society for Behavioral and Cognitive Neurology (Arciniegas et al. 2006) directs subspecialists in Behavioral Neurology & Neuropsychiatry (BNNP) to elicit and construct comprehensive patient histories that emphasize neurodevelopmental and environmental influences on cognition, emotion, behavior, and elementary neurological function. Clinical assessment of these neuropsychiatric functions requires that practitioners understand brain-behavior relationships and possess the assessment skills needed to apply that understanding in clinical practice. The clinical assessment in BNNP employs, and is made systematic by, the use and interpretation of standardized, validated, and reliable metrics of neuropsychiatric function. Neuropsychological testing, neuroimaging, and electrophysiological and other laboratory measures

that clarify the structural and functional neuroanatomy of illness, refine differential diagnostic considerations, and inform prognosis, treatment selection, and treatment response expectations are also employed, where appropriate (see Chapters 2 through 5). Interpreting clinical signs, symptoms, and syndromes in relation to structural and functional neuroanatomy (i.e., the neurobiological bases of behavior) therefore supersedes conventional (i.e., *Diagnostic and Statistical Manual of Mental Disorders* [DSM]–based) psychiatric diagnoses. This neuropsychiatric approach to clinical assessment and treatment is designed to avoid the practice of "mindless neurology" and "brainless psychiatry" that was pervasive during much of the twentieth century (Abraham 1999). It also eschews the historical dichotomization of clinical conditions into strict "psychiatric" or "neurological" types in favor of a more integrative approach. A comprehensive account of neuropsychiatric health and disease therefore demands a detailed understanding of the neurobiological bases of cognition, emotion, and behavior.

A life span, or neurodevelopmental, perspective adds another dimension to understanding behavior: brain structure and function change dramatically with age—from fetal development through infancy, childhood, adolescence, adulthood, and old age. Physiological functions vary more widely in elderly people than in young people, tolerance of injury and potential for recovery are diminished in elderly patients, and the neurobehavioral consequences of brain dysfunction often differ as a function of the age of the patient.

This chapter is intended to introduce readers of this volume to the neuroanatomical and neurochemical bases of cognition, emotion, and behavior. First, we present a synoptic model of behavioral neuroanatomy as a framework for the remaining discussion. The model divides the nervous system into three behaviorally relevant zones: an inner zone surrounding the ventricular system, a middle zone encompassing the basal ganglia and limbic system, and an outer zone composed primarily of the neocortex. We present the anatomy of each zone and describe the behavioral consequences of injury to each. Next, we describe two distributed systems; these cross the three zones to allow information to enter the brain (thalamocortical system) and allow impulses mediating action to exit the brain (frontal-subcortical circuits). We also present neuropsychiatric syndromes associated with abnormalities of these systems. Finally, we integrate the biochemical bases of neuropsychiatric function with structural and functional neuroanatomy. Readers seeking complementary and comprehensive syntheses of this information intended specifically for subspecialists in BNNP are referred to recent reviews (Arciniegas et al. 2013; Hart 2016).

A Model of Behavioral Neuroanatomy

Paul Yakovlev developed a comprehensive model of the nervous system in terms relevant to behavior (Yakovlev 1948, 1968; Yakovlev and Lecours 1967). He adopted an evolutionary perspective and noted that the brain consists of three general regions: a median zone surrounding the ventricular system, containing the hypothalamus and related structures; a paramedian-limbic zone consisting primarily of limbic system structures, basal ganglia, and parts of the thalamus; and a supralimbic zone containing the neocortex.

In this chapter, we present the Yakovlev approach—updated with informa-

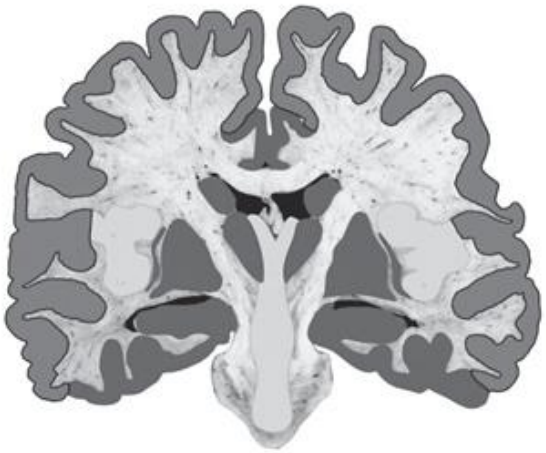

FIGURE 1–1. Updated version of Yakovlev's model of the nervous system demonstrating the median zone (*yellow*), paramedian-limbic zone (*blue*), and supralimbic zone (*red*).
See Plate 1 to view this image in color.
Source. Based on Yakovlev and Lecours 1967.

tion from more recent anatomical studies (Benarroch 1997; Filley 2012; Hart 2016; Mesulam 2000)—as a foundation for understanding brain-behavior relationships (Figure 1–1). The median zone is immediately adjacent to the central canal, is poorly myelinated, and has neurons with short axons that synapse on nearby cells, as well as on cells with longer axons that project to more distant nuclei. The median zone contains the hypothalamus, medial thalamus, and periventricular gray matter of the brain stem as well as functionally related areas of the amygdala and insular cortex. The system mediates energy metabolism, homeostasis, peristalsis, respiration, and circulation. The median zone contains the reticular activating system and the thalamocortical projections that maintain consciousness and arousal in the awake state and that participate in sleep initiation and maintenance. No lateralization of function is evident in the median zone. This system is fully functional at birth and is responsible for the early survival of the infant.

The *paramedian-limbic zone* contains neurons that are more fully myelinated than those of the median zone. Neurons here are grouped in nuclear structures that are connected in series. Many of the thalamic nuclei, the basal ganglia, cingulate gyrus, insula, orbitofrontal region, hippocampus, and parahippocampal gyri are included in this zone. The paramedian-limbic zone includes the structures composing the limbic system (Papez 1937). Structures of this zone mediate posture, are essential for generation and expression of emotion, and contribute to emotional experience. There is little lateral specialization of the paramedian structures. Phylogenetically, this level of brain development is present in reptiles (MacLean 1990). The paramedian-limbic zone is partially functional at birth, and its emerging integrity becomes evident in smiling and crawling. Disorders of motivation, mood, and affect are associated with paramedian-limbic dysfunction, and this zone is the anatomic site of structures involved in many neuropsychiatric disorders. Parkinson's disease, with

its depression, apathy, akinesia, masked facies, hypophonic voice, and marked postural changes, is an example of a common disease of elderly people affecting the paramedian-limbic zone.

The *supralimbic zone* is outermost in the brain and includes the neocortex and the lateral thalamic nuclei. The neurons of this zone have long, well-myelinated axons that project via white matter tracts to more distant targets. The supralimbic neocortex contains the neurons mediating higher cortical (association) functions, as well as the pyramidal neurons that project to limbs, lips, and tongue. It mediates highly skilled, fine-motor movements evident in human speech and hand control. Ontogenetically, this zone first finds expression in the pincer grasp and articulate speech. Phylogenetically, the supralimbic zone first appears in mammals and is most well developed in humans (MacLean 1990). The supralimbic zone is expressed in human cultural achievements, including art, manufacture, speech, writing, and science. The supralimbic zone exhibits lateralized specialization of structure and function, with marked differences between the functions supported by each cerebral hemisphere.

The supralimbic zone is vulnerable to some of the most common neurological disorders associated with aging, including stroke and Alzheimer's disease. For example, the expansion of the neocortex has been at the expense of a secure vasculature. The enlarged association areas have created border zones between the territories of the major intracranial blood vessels that are at risk of stroke because of limited interconnections and poor collateral flow; reduced cerebral perfusion with carotid artery disease or cardiopulmonary arrest regularly results in border zone infarctions at the margins between these vascular territories. In addition, penetrating branches form arterial end zones that have no collateral supply as they project through the white matter to the borders of the ventricles. This vascular anatomy creates an area of vulnerability to ischemia at the margins of the lateral ventricles. Periventricular brain injury has been associated with depression (Smagula and Aizenstein 2016; Sneed et al. 2008), "vascular cognitive impairment, no dementia" (VCIND; Stephan et al. 2009; see also Duncombe et al. 2017), vascular neurocognitive disorder (Kirshner 2009; Tomimoto 2015), and Binswanger's disease (Filley 2012). Along with the hippocampus, the supralimbic zone is the major site of pathological changes in Alzheimer's disease (Savioz et al. 2009). Focal lesions of the neocortex also result in neurobehavioral domain–restricted deficits such as aphasia (language), apraxia (skilled purposeful movements, i.e., praxis), and agnosia (recognition).

This model of behavioral neuroanatomy provides an ontogenetic life span perspective showing the emerging function of these structures in early life and their disease-related vulnerability in later life. The model reflects an evolutionary perspective of the brain, emphasizing its development through time and its increasing complexity in response to evolutionary pressures. From a clinical point of view, the median zone is responsible for basic life-sustaining functions; accordingly, disturbances in this zone are reflected in disorders of consciousness and abnormalities of metabolism, respiration, and circulation. By contrast, most neuropsychological deficit syndromes, such as disorders of language, prosody, praxis, recognition, visuospatial function, calculation, and executive function, are associated with disturbances of the structure and/or function the supralimbic neocortex. Disorders of emotion (i.e., mood disorders, disorders of affect), anterograde amnesia (impairments in new

learning), disorders of motivation, and personality alterations are more likely to occur with abnormalities in the paramedian-limbic zone or disturbed interactions between this zone and the median and supralimbic zones (Arciniegas 2013a; Gardini et al. 2009; Javitt 2007; Mayberg 2003). Thus, neuropsychiatric disturbances occur in characteristic patterns that correspond to brain evolution, development, structure, and function.

Neocortex (Supralimbic Zone)

Histological Organization of the Cortex and Behavior

Brodmann's maps remain the classic guide to the histological organization of the cerebral mantle. Within Brodmann's areas (abbreviated BA followed by the number of the area), three types of cortex relevant to understanding behavior have been identified: a three-layered allocortex, a six-layered neocortex, and an intermediate paralimbic cortex. The limbic system cortex (e.g., the hippocampus) has a three-layered allocortical structure, whereas the sensory, motor, and association cortices of the hemispheres have a six-layered structure (Mesulam 2000). In the neocortex, layer I is outermost and consists primarily of axons connecting local cortical areas; layers II and III have a predominance of small pyramidal cells and serve to connect one region of cortex with another; layer IV has mostly nonpyramidal cells, receives most of the cortical input from the thalamus, and is greatly expanded in primary sensory cortex; layer V is most prominent in motor cortex and has large pyramidal cells that have long axons descending to subcortical structures, brain stem, and spinal cord; and layer VI is adjacent to the hemispheric white matter and contains pyramidal cells, many of which project to the thalamus (Mesulam 2000) (Figure 1–2). Layers II and IV have the greatest cell density and the smallest cells; conversely, layers III and V have the lowest density and the largest cells. Cell size correlates with the extent of dendritic ramification, implying that cells of layers III and V projecting to other cortical regions have the largest dendritic domains (Schade and van Groenigen 1961).

Functional Organization of the Neocortex

The neocortex is highly differentiated into primary motor and sensory areas and unimodal and heteromodal association regions (Mesulam 2000) (Table 1–1). Figures 1–3 through 1–5 illustrate the anatomical distributions of the different cortical types in the cerebral hemispheres. Primary motor and sensory areas account for only 16% of the neocortex (Figure 1–3), whereas unimodal and heteromodal association cortices collectively occupy 84% of the human neocortex (Figures 1–4 and 1–5). The differences in these proportions reflect the marked importance of association cortex in the functions that are characteristic of higher mammalian brains and particularly human functions like language, executive function, humor, and creativity (Rapoport 1990). The neocortex is organized in a mosaic of cortical columns, and local circuit neurons (confined to the cortex) compose approximately 25% of the cellular population (Rapoport 1990). Cortical regions receive and send information via white matter tracts.

Primary motor cortex occupies the motor strip in the posterior frontal lobe and serves as the origin of the pyramidal motor system (Figure 1–3, *green*). Lesions