Introduction

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Neuropsychology is the science and practice of evaluating and understanding brain-behavior relationships and providing recommendations for intervention that can be implemented in the daily lives of persons when brain dysfunction compromises functioning at home or school, on the job, or in the community at large. The associated target behaviors and skills can range from specific cognitive abilities to emotional and psychosocial functioning. This specialty has advanced significantly over the past several years, but recent well-respected published works about common neuropsychological disorders have tended to focus primarily or exclusively on either children or adults, or have provided separate discussions of conditions that are traditionally seen more commonly at either end of the age spectrum (e.g. Morgan and Ricker [1], Snyder et al. [2]). Similarly, there is a dearth of comprehensive discussions in the available literature to date of various neuropsychological syndromes in their different manifestations across the lifespan, and the longitudinal development and longer-term outcomes of such conditions. This has contributed to a sometimes unwarranted bifurcation within the field, where developmental course has been left out of the diagnostic and treatment equation. In response, the primary goal of this volume is to provide an integrated review of neuropsychological function and dysfunction from early childhood through adulthood and, where possible, old age, to support the understanding and consideration of the role development plays in the presentation and outcome of neuropsychological disorders across the lifespan.

Each chapter in this volume was written by one or more authors who specialize in clinical practice as well as research with the disorder being discussed. As a result, these experts give the reader an up-to-date account of the state of the art of the field at this time, and make suggestions for improvement in approaches toward assessment, intervention, and empirical investigation of the disorders as they present across the lifespan. We hope that this book will provide a vantage point from which to explore lifespan developmental aspects of a wide range of commonly encountered neuropsychological disorders. We anticipate that it will be of interest not only to pediatric neuropsychologists but also to professionals in rehabilitation, neurology, and various allied health fields.

References
The structure of the brain is in constant flux from the moment of its conception to the firing of its final nerve impulse in death. As the brain develops, functional networks are created that underlie our cognitive and emotional capacities. Our technologies for evaluating these functional systems have changed over time as well, evolving from lesion-based case studies, neuropathological analyses, in vivo neurophysiological techniques (e.g. electroencephalography), and in vivo structural evaluation (CT scan, magnetic resonance imaging (MRI), diffusion tensor imaging (DTI)), to in vivo functional methodologies (functional magnetic resonance imaging (fMRI), positron emission tomography (PET)). And with these rapidly developing technologies, we are able to more thoroughly test some of the earlier hypotheses that were developed about the nature and function of the brain.

Although attempts to localize mental processes to the brain may be traced to antiquity, the phrenologists Gall and Spurtzheim may have initiated the first modern attempt, by hypothesizing that language is confined to the frontal lobes [1]. While these early hypotheses were largely ignored as phrenology fell in ill-repute, they were resurrected in the early 1860s by Paul Broca, who, inspired by a discussion of the phrenologists’ work, sparked a renewed interest in localization of brain function with his seminal case studies on aphasia [2]. Broca’s explorations were among the earliest examples of lateralized language dominance.

Recently, high-resolution structural MRI was applied to preserved specimens taken from two of Broca’s patients, to examine the localization of damage on the surface and interior of the brains. This modern technology revealed extensive damage in the medial regions of the brain and highlighted inconsistencies with previous hypotheses in the area of the brain identified by Broca, which is now identified as Broca’s area [3]. This is interesting, both from a historical perspective and also with respect to our current understandings of the brain systems involved in the behavioral presentations Broca described (beyond the articulatory functions of the inferior frontal gyrus); specifically the extent of behavioral changes identified by Broca is now more accurately reflected by the apparent neuropathology.

A contemporary of Broca’s, John Hughlings Jackson, offered a different perspective regarding localization. While Jackson had no problem with the notion of probabilistic behavior profiles with specific brain lesions (e.g. a left inferior frontal lesion most likely will affect expressive speech), he did not agree with the prevailing idea at the time that these lesion/behavior observations represented a confined center of function [4]. Jackson proposed a vertical organization of brain functions, with each level (e.g. brain stem, motor and sensory cortex, and prefrontal cortex) containing a representation, or component of the function of interest. Though this idea was at the periphery of opinion at the time, when strict localizationist theory was gaining momentum, it has come to form the basis of modern thought regarding the mechanisms of brain and behavior relationships.

Holes and gaps in the models of strict localization of behaviors to specific, contained brain regions became more salient to the mainstream neuroscience community over time (cf. the disrepute of phrenology and conflicting findings from lesion/behavior studies). In response, Karl Lashley’s search for the memory engram typified another era in the exploration of brain–behavior relationships. Using an experimental approach rather than the classic case study method, Lashley, famously unable to localize memory function in rats (through progressive brain ablation), introduced the constructs of equipotentiality and mass action [5]. Equipotentiality is the concept that all brain tissue is equally capable of taking over the function of any other brain tissue (demonstrated in the visual cortex) and, relatedly, mass action references the idea that the behavioral impact of a lesion is dependent on its size, not its location. Also, although less popularized,
Section I: Theory and models

he suggested that, at any given time, the pattern of neural activity is more important than location when understanding higher cognitive functions [6]. Although plasticity in the human brain does not conform to notions of equipotentiality, recent research on stem-cell treatments in neurodegenerative diseases has reinvigorated the construct in an albeit new form. Guillaume and Zhang [7] review the use of embryonic stem cells as a neural cell replacement technique and strides in functional integration, axonal growth, and neurotransmitter release (e.g. the development of dopamine-producing cells in mouse brains after stem cell implantation).

Historically, political and social influences on the philosophy of science trended Western societies away from the study of brain structures in the understanding of behavior after World War I [8]. In contrast, researchers in the former Soviet Union continued that approach. For example, while in opposition to the idea of equipotentiality, Filimonov (cited in Luria, 1966 [9, 10]), a Soviet neurologist, presented the concepts of functional pluripotentialism and graded localization of functions. Specifically, he postulated that no cerebral formation is responsible for one unique task, and that the same tissue is involved in multiple tasks, given the right conditions. These concepts signaled a move from strict localization approaches to understanding brain–behavior relationships to a dynamic functional systems approach (i.e. back to a Jacksonian view), most notably attributed to Alexandr Romanovich Luria. His approach to neuropsychological investigation stood in contrast to Western psychometric methods, by instead focusing on the effect of specific brain lesions on localized/adjacent functional systems (syndrome analysis) [10].

Luria stated that simple to more complex behavioral operations are not localized to a particular brain region, but instead managed by an “elaborate apparatus consisting of various brain structures” [11]. Though other definitions of functional systems, or even neural networks, have since been posited, this early view eloquently described the construct. Luria proposed that all functional systems must involve three core blocks including (1) the arousal block, (2) the sensory input block, and (3) the output/planning unit. Structurally, the arousal unit referenced reticular formation and related structures that impact cortical arousal; the sensory input unit referenced post central-fissure structures and the integration of cross-modal sensory data; and the output/planning unit referenced primarily the frontal lobes and involved planning and execution of behavior [12].

Luria presented a theory of functional systems development based on these three functional units. He suggested that the three functional units develop hierarchically in the form of increasingly complex cortical zones. These zones correspond to primary, secondary, and tertiary motor and sensory areas, which develop in order of complexity, with the tertiary planning unit (anatomically demarcated by prefrontal areas) appearing last [12]. Luria’s developmental theory mirrors Jackson’s proposal that neuro-anatomical development proceeds upward from the spinal cord to neocortex and from the posterior to anterior [4].

Functional systems, of course, are organized within a far more complicated web than Luria’s original three-tiered theory. Still, modern brain researchers have “run” with the idea of the functional system. Recent research has explored questions of the nature of top-down control (vertical integration), with some investigators arguing for specific areas within the stream as primary originators (e.g. lateral prefrontal cortex [13]), while others argue for different cortical systems as top-down controllers (e.g. fronto-parietal and cingulo-opercular control networks [14]).

Functional neuroanatomy is the basis of our understanding of the human condition, as is an understanding of how that anatomy interacts with the body and its environment; a complex dance. What we do know is that almost any behavior, even a slight deviation in heartbeat interval, may be influenced by myriad factors within the nervous system. A deviation of heartbeat interval can be influenced by fluctuations in physical activity, thinking, and emotional status [15, 16]. Our exploration of brain–behavior relationships is further complicated by language, and more specifically the definition of constructs that are chosen to define these relationships. Take, for example, our understanding of a change in heartbeat interval and its relationship to emotion. Constructs such as fear, anger, sadness, and happiness describe rather large subsets of behavior. In order to capture these emotions at a brain level, Arne Ohman has suggested that emotion is a “flexibly organized ensemble of responses, which uses whatever environmental support is available to fulfill its biological function” [17].

This is a noticeably loose definition. It has to be with constructs such as emotional memory [18], expressive aprosodia and receptive aprosodia [19], emotional intelligence [20], approach and withdrawal [21], and terms such as melancholy, wistfulness, euphoria, mirth, and doldrums floating around in the collective consciousness of researchers and the lay public. To understand that
minute shift in heartbeat interval, we need to understand the emotional state of our subject. To evaluate the functional systems involved in that heartbeat shift, we need to understand the interconnecting pathways involved in vagal (cranial nerve X) control of the heart (direct parasympathetic nervous system influence is necessary in a beat-to-beat change in heart rate). What structures connect to the vagus? What structures connect to those structures? Are there afferent feedback loops? How do these control systems develop? The so-called “decade of the brain” has extended and we have an ever-developing complexity in our understanding of the brain’s role in defining what it means to be human. It is an exciting time to be a neuropsychologist.

The development of functional neuroanatomy across the lifespan is a complicated topic. This chapter, necessarily, is not a comprehensive review of the subject, but is instead a detailed introduction. As such, the purpose of the following sections is to discuss current research and our current knowledge regarding the neuroanatomical structures that are of particular interest with regard to understanding cognitive and emotional development. The chapter is therefore organized as follows: (1) Brain structure. In this section, we cover cellular structures and brain areas in their prototypical forms, discussing general associated functions. (2) Brain development across the lifespan. This section covers the mechanism of brain development and notable changes over time in anatomy and function.

Brain structure

The nervous system is composed of central (CNS), peripheral (PNS), and enteric branches. The brain and spinal cord form the CNS. Nerves that connect the spinal cord and brain to peripheral structures such as the heart compose the PNS. The enteric nervous system controls the gastrointestinal system primarily via communication with the parasympathetic and sympathetic nervous systems.

Brain cells

The brain has two classes of cells, neurons and glia. There are many different types of cells within each class, although they all share characteristics that distinguish these nervous system cells from other cells in the body. Generally stated, neurons are specialized electro-chemical signal transmitters and receivers. Glia serve a supporting role in the brain (e.g. nutritional and scavenger functions, growth factors, blood–brain barrier components, and myelin–white matter creation) and have a role in neurogenesis during development (e.g. radial glia as neuron progenitors [22]).

Neurons

Within the adult neocortex, there are billions of neurons and 10 to 50 times more glia. The total number of synapses is estimated to be approximately 0.15 quadrillion. Myelinated white matter is estimated to span between 150 000 and 180 000 kilometers in the young adult [23, 24].

Neurons are composed of a cell body, axon, and dendritic fields. The cell body contains less than a tenth of the cell’s entire volume, with the remainder contained within the axon and dendrites [25]. Synapses are interaction points between neurons. An individual neuron communicates via action potential. Action potentials are all-or-none electrical events which are excited (promoted) or inhibited (prevented) based on the nature of synaptic stimulation (e.g. the nature of chemical and electrical stimulation via neurotransmitters and graded potentials). A single neuron may be in direct contact (via synapse) with thousands of other neurons. The firing rate of a neuron is influenced by the summation of inhibitory and excitatory events along the axon and dendritic–synaptic interactions among the numerous connections. Speed of transmission is a function of white matter width and myelination.

White matter may be myelinated or unmyelinated. Myelination increases transmission speed. Myelin sheaths (covering axons) are generated by specialized glial cells in the brain called oligodendroglia, and in the periphery by cells called Schwann cells.

Neurons may be classified as unipolar, pseudounipolar, or bipolar depending on the cell body form and number and arrangement of processes. Functional characteristics are also used in classification (e.g. afferent neurons that conduct signals from the periphery to the CNS are also called sensory neurons, and efferent neurons that conduct signals from the CNS to the periphery are also called motor neurons). Further, neurotransmitter receptor types are also used to describe neurons. For example, neurons containing serotonin or glutamate are referenced as serotonergic or glutaminergic neurons [26].

Neurotransmitters

Neurotransmitters are chemical agents that bind to specialized receptors on neurons. Neurotransmitters...
specifically relevant to neuropsychology include, but are not limited to, serotonin (e.g. depression/anxiety), acetylcholine (e.g. memory), dopamine (e.g. motor), norepinephrine (e.g. depression), glutamate (e.g. memory), and gamma-aminobutyric acid (e.g. anxiety). The effect of a particular neurotransmitter on a functional system is largely determined by receptor types. Each neurotransmitter can bind to multiple receptor types. The distribution of receptor types is not even throughout the brain and may influence emotional state/traits, disease outcomes in mental health, and response to psychopharmacologically active medications. For example, protein expression of serotonin receptors in the prefrontal cortex differentiates successful suicidal patients and controls [27]. Asymmetry in serotonin receptors is found in depressed patients with greater right prefrontal receptor density than left compared with controls [28]. Moreover, higher baseline binding potential in chronic depression pharmacological treatment is associated with worse outcomes [29]. For a more comprehensive review of neuronal structure and function, see Levitan and Kaczmarek [30].

Cranial nerves
There are 12 cranial nerves. A solid understanding of the effects of cranial nerve lesions, or the effects of upstream lesions on cranial nerve activity, is an important tool for neuropsychologists in evaluating patient presentation. Cranial nerves have both sensory and motor functions. For example, cranial nerve level control of the muscles of the eye is distributed across three nerves (the oculomotor, trochlear, and abducens nerves), whereas sensory information from the eye is transmitted via the optic nerve. The optic nerve projects from the retina, to the thalamus, through the temporal and parietal cortices, and to the calcerine cortex in the occipital lobe. Processing is not performed at the level of the cranial nerves, which only serve to connect/transmit information from processing centers. Testing cranial nerve function can, however, give clues as to the nature of a lesion. For example, the optic radiations of the optic nerve travel close to the surface of the cortex of the temporal lobe. A unilateral lesion of the temporal lobe can cause a contralateral visual field cut. Examining associated behavioral changes can suggest a location for a functional lesion. For a more detailed review of cranial nerve functions and assessment see Monkhouse [31].

Rhombencephalon
The rhombencephalon, or hindbrain, is composed of the medulla oblongata, the pons, and the cerebellum. Functionally, the hindbrain contains several structures involved in neural networks regulating autonomic nervous system (ANS) function and arousal. Cranial nerves regulating the ANS (vagus), and movements of the mouth, throat, neck, and shoulders (glossopharyngeal, hypoglossal, trigeminal, spinal accessory) are found in the hindbrain. Additional structures include the reticular formation (basic autonomic functions, respiration), nucleus of the solitary tract (in actuality, this refers to several structures) and the nucleus ambiguus. The nucleus ambiguus and the nucleus of the solitary tract are the primary interface junctions for the vagus nerve, which enervates the viscera. In thinking about the development of brain structures and functional systems relevant to emotional and cognitive behaviors, it may be helpful to consider phylogeny and lessons from comparative neuroscience.

Transitioning from reptiles to mammals, we see the emergence of myelinated vagus. Returning to our earlier example of emotion and changes in heartbeat intervals, Porges [32, 33] discusses the impact of this system and its development on social engagement behaviors in humans with his polyvagal perspective, contrasting and elucidating the interactions of brainstem structures, peripheral afferents, cortical and subcortical top-down control, and myelinated vagal efferents. Regulation of the autonomic nervous system is a complex component of social behaviors and emotional response. Cortical, subcortical, and other brain structures such as the amygdala, hypothalamus, orbitofrontal cortex, and temporal cortex all interact via direct and indirect pathways with these hindbrain structures to influence parasympathetic and sympathetic nervous system response. Further, the nucleus of the solitary tract receives afferent input from the periphery (e.g. baroreceptors, which monitor and relay changes in blood pressure), which is in turn distributed to subcortical and cortical structures for processing.

These hindbrain structures should be considered as output and input nuclei for a range of supportive behavioral features in the human (e.g. facilitating appropriate arousal levels for performing cognitive, exertional, and social functions). Also contained within the rhombencephalon are the pons and cerebellum. Functionally, these structures contribute to fine motor control via postural and kinesthetic feedback to volitional areas.
(e.g. premotor and motor cortex). This includes facilitating motor movements in speech.

In addition to fine motor control, lesions of the cerebellum have a wide range of behavioral and cognitive consequences. The cerebellum has reciprocal connections to brainstem nuclei, hypothalamus, and prefrontal and parietal cortices (among other areas). Behavioral effects of cerebellar lesions observed in the literature include autonomic disregulation [34], flattening of affect, distractibility, impulsiveness, stereotyped behaviors, depression [35], memory and learning dysfunction, language problems, and visuospatial effects [36]. Though these problems in cognition and behavior are clearly less severe than lesions in associated areas of neocortex and some reported issues have not been replicated, the variety of impacts suggests an important role for the cerebellum in some of these functional systems. There are some interesting clues as to what that role may be.

Recent research has shown additional roles of the cerebellum in speech with lesion effects beyond dystaxic motor impairments in speech formation. Ackerman et al. [37] review recent clinical and functional imaging data as they pertain to speech syndromes and potential connections to other cognitive functions following cerebellar lesions. They argue that connections to language areas in the cortex function as conduits to subvocalization (self speech) which is involved in verbal working memory (a right cerebellar/left frontal interaction). This subvocalization argument is also present in other modalities (e.g. imagined movements). These connections, along with the hypotheses of planning and rehearsal components attributed to cerebellar activity, may explain the increasing evidence of wide-reaching cognitive and behavioral effects with cerebellar lesions.

**Mesencephalon**

The midbrain includes the substantia nigra (linked to dopamine production and Parkinson disease), the superior and inferior colliculi (visual and auditory system actions), and a large portion of the reticular activating system (RAS). The reticular activating system, formed in part by nuclei in the midbrain tegmentum, plays a role in consciousness. The discovery of the RAS was critical for understanding coma. It serves as a modulator of sleep and wakefulness via connections to the diencephalic structures, the thalamus (thalamic reticular nucleus) and hypothalamus. These connections ascending from the reticular formation are part of the ascending reticular activating system. Also nested within the midbrain are projections from the dorsal raphe nucleus (from the hindbrain structure, the pons). The raphe is a source of serotonin and is also involved in the regulation of sleep cycles.

The substantia nigra is functionally linked to the basal ganglia, specifically the caudate nucleus and the putamen (referred to collectively as the striatum). It is divided into two sections, the pars compacta and the pars reticulata. The pars compacta projects to the striatum and the pars reticulata projects to the superior colliculus and thalamus. The substantia nigra provides dopamine to the basal ganglia and it is part of the extrapyramidal motor system. Lack of dopamine in the striatum leads to parkinsonian symptoms (rigidity, tremor, slowing); the system still functions without the substantia nigra as long as the level of dopamine is regulated properly.

The superior and inferior colliculi are interconnected small structures in the midbrain that are involved in visual and auditory orientation and attention. The superior colliculus receives projections from the frontal eyefields (premotor cortex) and controls saccadic movements. The interconnection and functional relationship to the prefrontal cortex has led to the use of saccadic eye movement models in evaluating the neural circuitry of schizophrenia and other psychiatric illnesses thought to involve prefrontal cortical systems [38].

**Telencephalon**

The telencephalon includes the entirety of the cerebral hemispheres including the diencephalon, limbic system, basal ganglia, and other structures. We will continue working our way through the brain from the ventral to the dorsal and the caudal to the rostral. We begin the discussion of the telencephalon with the thalamus and hypothalamus.

**Thalamus and hypothalamus**

The thalamus and hypothalamus, among other structures, compose the diencephalon. The thalamus is a complex bilateral structure with extensive reciprocal connections to major structures throughout the brain, including efferent fibers to cortical regions (thalamocortical axons) and afferent fibers from cortical regions (corticothalamic axons). There are 11 thalamic nuclei that are classified as either relay or association nuclei based on their target projections. These are specific nuclei. There are also nonspecific nuclei, stimulation of which yields activations along a large area of cortex. The thalamus has nuclei with projections to all major areas in the cortex, including e.g. premotor and motor cortex).
sensory areas except for olfaction. Further, it is a projection site for the RAS (important role for arousal and sleep; logical, given the sensory connections). For a comprehensive review of thalamic nuclei and function, please see Jones [39].

Because of the heterogeneity of nuclei, associated functional systems, and projections of the thalamus, it can be difficult to understand which systems are involved in the neuropsychological sequelae of thalamic lesions. One approach is to use functional imaging technologies, such as PET scan, to evaluate diaschisis effects of a localized thalamic lesion [40].

The thalamus is the most likely location for a strategic infarct (e.g. from a stroke) to cause a dementia. This is probably a consequence of the role of the thalamus in regulating higher-brain activity. As a subcortical structure with dense connections throughout both hemispheres, the thalamus reflects the lateralization of function of involved cortical areas. For example, contralateral attentional neglect occurs with right-sided thalamic lesions. A similar presentation is also evident with right parieto-temporal lesions [41].

Developmentally, abnormalities in thalamic nuclei (e.g. massa intermedia), have been associated with future manifestations of psychiatric conditions such as schizophrenia. The massa intermedia is detectable early in development, within 13 to 14 weeks of gestation [42]. There is some evidence that the medial dorsonuclei reduces in volume as schizophrenia progresses, an area rich in connections to prefrontal cortex (an area implicated in the expression of schizophrenia) [43]. Shimizu et al. [44] find evidence of a developmental interaction between the massa intermedia and medio-dorsonuclei in schizophrenic patients.

The hypothalamus is primarily involved in visceral, viscerosensory, and endocrine (oxytocin and vasopressin) functions. It directly modulates autonomic nervous system activity. It functions as one connection point for limbic structures (involved in emotional regulation) to control of the autonomic nervous system. The stria terminalis, an afferent white matter tract, connects the amygdaloid bodies to the hypothalamus. The hypothalamus then has direct efferent connections to brainstem nuclei, including the output nuclei for vagal control (nucleus ambiguous) and sympathetic neurons in the spinal cord. These connections make the hypothalamus a critical component in functional systems involved in rage and fear responses.

The interaction of three structures, the hypothalamus, pituitary gland, and adrenal gland, is important in the regulation of mood, sexuality, stress, and energy usage. The so-called hypothalamic-pituitary-adrenal (HPA) axis has been implicated in social bonding and mate-pairing in comparative neuroscience and human research. Developmentally, it has been found in prairie voles that exposure to oxytocin (a hormone produced in the HPA) early on is associated with capacity for social bonding in adult animals [45, 46].

Further connections also involve the hypothalamus in memory functions (e.g. the hippocampus and mamilary bodies are connected via the fornix). Lesions to the mammillary bodies, a hypothalamic structure, can cause severe anterograde memory deficits. Deterioration of this system is associated with the development of Alzheimer’s disease.

### Basal ganglia

The basal ganglia are a set of subcortical grey matter structures most often associated with aspects of motor control, though recent research demonstrates additional roles in functional systems, including cognitive domains such as attention. Unlike primary motor cortex lesions, paralysis does not occur with basal ganglia damage. Instead, abnormal voluntary movements at rest, and initiation and inertia deficits are typical.

The structures included in the basal ganglia vary by nomenclature, but commonly reference the caudate and putamen (i.e. dorsal striatum or neo-striatum), globus pallidus (internal and external segments), substantia nigra, and subthalamic nucleus. Other nomenclatures include the amygdala (discussed here with limbic system structures), and the nucleus accumbens and olfactory tubercle (ventral striatum).

There are two pathways of activity in the basal ganglia with opposing behavioral outcomes, the indirect and the direct pathways. These pathways facilitate and inhibit the flow of information through the thalamus and operate simultaneously (the overall effect is a function of the current balance of activation pattern between the pathways). Activation of the direct pathway increases thalamic activity and activity of the cortex. Activation of the indirect pathway decreases thalamic activity and activity of the cortex. Damage to the basal ganglia can either decrease or increase movement depending on which structures/neurotransmitters are impacted within the direct and indirect pathways.

Several neurodegenerative disorders are associated with basal ganglia structures including Parkinson disease, Huntington disease, Wilson disease, and various multisystem atrophies (MSAs). Psychiatric disorders
that appear in childhood including attention deficit hyperactivity disorder (ADHD) and Tourette syndrome are also associated with abnormalities in the basal ganglia. Recent studies have shown reduced overall caudate volumes and lateralized differences in caudate and globus pallidus volumes (left greater than right) in children diagnosed with ADHD. Further, fractional anisotropy, a measure of apparent white matter integrity using a structural imaging technique called diffusion tensor imaging (DTI), is reduced in ventral prefrontal to caudate pathways in children with ADHD. Behaviorally, this prefrontal/caudal circuit is thought to relate to inhibitory control (e.g. a go–no go task). As for etiological factors, there is recent evidence that early diet can influence future caudate volumes and intellectual aptitude, suggesting a potential avenue for environmentally multi-factorial. Aron et al. present converging evidence on the role of a fronto-basal ganglia network in inhibiting both action and cognition. They review both comparative and human data using go–no go tasks and conclude that the fronto-basal ganglia systems are critical in determining individual differences in a variety of human behaviors, stating, “Variation to key nodes in this circuitry (or to their connections) could produce important individual differences, for example, in aspects of personality, in the response to therapy for eating disorders, and in liability toward and recovery from addiction. Developmental, traumatic, or experimentally induced alterations to key nodes in the control circuit lead to psychiatric symptoms such as inattention, perseveration, obsessive thinking and mania, and could also have relevance for movement and stuttering.”

**Limbic system**

The limbic system is a network of structures involving subcortical, cortical, and brainstem regions that play a role in emotional behaviors including emotionally related memory/learning and social interactions. Important subcortical gray matter structures of the limbic system include the amygdala, nucleus accumbens, and hypothalamic nuclei (as illustrated above in the HPA), among others. Cortical structures include aspects of the prefrontal cortex (orbitofrontal), cingulate gyrus, and the hippocampus.

The amygdala, probably the most central structure (conceptually) of the limbic system, is almond-shaped and located deep in the anterior temporal lobe. There are multiple nuclei which can be divided into two groups, a basolateral group and a corticomedial group. The amygdala is rich with connections to cortical areas including the orbitofrontal cortex and temporoparietal cortex, subcortical structures including the basal ganglia, thalamus, hypothalamus, brainstem structures including autonomic output nuclei, and the hippocampus (a phylogenetically older area of cortex involved in memory consolidation).

The amygdala is involved in functional systems of emotion, reward, learning, memory, attention, and motivation. Though researchers have strongly focused on fear conditioning and negative emotions in the amygdala (the role of the amygdala in fear startle reflex), it also has a role in positive emotion. For a review of the role of the amygdala in positive affect see Murray. Direct stimulation of the amygdala via electrodes has been shown to most probably elicit fear or anger responses. In rats, electrical stimulation of the amygdala elicits aggressive vocalizations. In humans, in a study of 74 patients undergoing presurgical screening for epilepsy, fear responses were most frequent with amygdala stimulation (higher rate for women than men). Functionally, in addition to a central role in emotional processing, the amygdala has a role in olfaction (the corticomedial cell group is directly connected to the olfactory bulbs), though there are also interconnections to other sensory areas. The amygdala appears to respond to threatening sensory stimuli via mobilization of fight or flight responses, but it also responds to positive sensory stimuli. The key is not the modality of the sensory input or the valence, the amygdala will respond to all, but whether the sensory data contain affective content. The amygdala also enhances cognitive performance in the context of emotional stimuli (e.g. emotional memory formation via linkages to the hippocampus).

Developmental disorders such as autism have been linked to abnormal changes over time in the amygdala. In addition to increased white matter volumes and overall head size early in autism, in a study of young children with autism (36–56 months of age), the amygdala was enlarged by 13–16%. Amygdala volume differences, both larger and smaller, are found in many psychiatric conditions, including schizophrenia, depression, bipolar disorder, generalized anxiety disorder, and borderline personality disorder. Sometimes, conflicts appear with one study showing increased amygdala volume in depression and another showing decreased amygdala volume. Tebartz et al. suggest
a resolution to such conflicting results may be a function of the “dominant mode of emotional informational processing.” They hypothesize that an enlarged amygdala may relate to depressed mood, anhedonia, phobic anxiety, and rumination and that a smaller amygdala may relate to emotional instability, aggression, and psychotic anxiety.

Another limbic structure, the hippocampus, is located ventrally and medially in the temporal lobe, and can be divided into four regions, designated CA1, CA2, CA3, and CA4. CA stands for cornu ammonis. A major input pathway to the hippocampus stems from the entorhinal cortex and the main output pathway from the fornix. The hippocampus is a critical structure to learning new information. Damage to the hippocampus can cause severe anterograde learning deficits such as in Korsakoff’s syndrome, a condition caused by vitamin deficiencies in chronic alcohol abuse that damages hippocampal structures. Classically, the role of the hippocampus in memory was brought to the attention of the scientific community via a case study in 1957 [57] of a patient who underwent bilateral temporal lobe resections, referred to as HM. HM had intact remote and autobiographical memory until the surgical procedure, but was unable to learn new information subsequently. Corkin [58] reviews 45 years of research on HM.

Laterality and extent of peripheral involvement determine the type and severity of memory impairment with hippocampal lesions. Involvement of projection areas such as the entorhinal cortex increases the severity of anterograde deficit. This is the system that deteriorates in cortical dementias such as Alzheimer’s disease. Bilateral lesions produce dense anterograde memory deficits. A unilateral left or right hemisphere lesion will produce verbal or spatial memory deficits, respectively.

Normal development of the hippocampus can be interrupted by environmental factors. Hippocampal volumes are reduced in victims of childhood abuse [59]. Pediatric temporal lobe epilepsy can also have a significant impact on hippocampal development. Hippocampal atrophy in children with epilepsy has been shown to relate to reduced neuropsychological performance [60].

Cerebral cortex

The cortex is divided into four lobes, the frontal, temporal, parietal, and occipital. As was discussed earlier in the chapter on top-down control and the organization of functional systems, the cortex is the most highly organized and complex aspect of brain management. The cortex is thought to be necessary for conscious behaviors (thalamo-cortical relationships), though recent research suggests that some level of consciousness can exist without the cortex [61]. There are two hemispheres divided by a large fissure called the longitudinal fissure. They are generally superficially symmetrical and structures are mirrored across the two. Though there are individual differences in brain structure, on average it is known that the right frontal lobe tends to be wider than the left and the left planum temporale of the superior temporal cortex is larger than the right (thought to be related to language development). Recent neuroimaging research has also demonstrated substantial differences in white matter connectivity; for example, in systems underlying language functions between the left and right hemisphere using diffusion tensor imaging [62].

Several helpful mapping systems have been created to identify various brain regions. Brodmann’s map is one of the best-known systems and it is based on cellular architecture (see Fig. 1.1).
The motor and sensory areas of cortex are divided by a large fissure called the central sulcus (also known as the Rolandic fissure and cruciate fissure). This divides frontal and parietal areas and represents a steep functional boundary. The regions on either side of the fissure are the primary motor cortex (Brodmann’s area 4, anterior of the fissure) and primary somatosensory cortex (Brodmann’s areas 3, 1, and 2, posterior of the fissure). Organizationally, it is helpful to think in terms of primary, secondary, and tertiary association cortex. Functions progress from simple to complex, from unimodal to multi-modal.

Each sensory system is composed of a primary projection area and secondary and tertiary association areas. Functionally, the primary projection areas are the first area of cortex to receive information from a specific sensory system. Sensory data reaching the primary projection area are necessary for conscious perception. Lesion of primary sensory cortex can result in a loss of awareness of the afferent modality; however, the individual may still respond reflexively to the modality (e.g. blindsight). Further sensory processing occurs in secondary association cortex, but it is still limited to one modality. Finally, tertiary association cortex (e.g. Brodmann’s area 7 in the parietal lobe) integrates data from multiple sensory modalities.

The primary sensory projection areas are as follows: (1) vision = occipital cortex (calcerine cortex, Brodmann’s area 17), (2) audition = superior temporal gyrus, temporal lobe (Brodmann’s areas 41 and 42), (3) somatosensation = postcentral gyrus, parietal cortex (Brodmann’s areas 3, 1, and 2), (4) gustation = parietal operculum (Brodmann’s area 43), (5) olfaction = anterior tip of the temporal lobe (Brodmann’s area 38). The secondary and tertiary association cortices surround and extend from the primary projection areas (e.g. visual association areas roughly correspond to Brodmann’s areas 18 and 19).

In a normally organized brain, the left hemisphere is dominant for language functions. Around 90% of the population is estimated to be right-handed. Sinistrality is a clue that a brain is not normally organized. Recent neuroimaging studies have demonstrated different activation patterns in left-handers when processing language, with greater bilateral activations and shifts towards right-hemisphere language processing [63]. Assumptions about localization and lateralization of function should be treated with greater caution in these cases. The occurrence of sinistrality appears to be a combination of genetic and environmental factors. Sinistrality is over-represented in several neurological/psychiatric conditions such as epilepsy, autism, and schizophrenia. A recent study demonstrates a potential genetic link between sinistrality and schizophrenia [64].

The hemispheres are functionally specialized to deal both with different kinds of information and the same information in different ways. Although an in-depth review of laterality is well beyond the scope of this chapter, a few common areas of study include language, neglect (attentional space), memory (non-verbal versus verbal), and emotion.

In a normally organized brain, different aspects of language functions are divided across the hemispheres with semantic content, production, and rhythm localized to the left hemisphere, and expressive and receptive prosody/melody localized to the right hemisphere. Further, there is evidence that the right superior temporal lobe is instrumental in the identification of individual voices [65]. Lesions, depending on laterality and position relative to the central sulcus (anterior or posterior), will have expressive or receptive consequences, or both (e.g. a right frontal lesion may produce an expressive aprosodia, or inability to modulate the tone of speech output in a meaningful way, whereas a left frontal lesion may produce an expressive aphasia, inability to produce speech fluently).

In emotion, laterality is not a simple matter. For example, a model of aspects of emotional experience that has been applied across the lifespan is proposed by Fox and Davidson [66]. They present a view of emotional expression with emphasis on right and left frontal modulation. Much of Fox’s work has consisted of developmental EEG research. Specifically, Fox infers right and left frontal activation from localized alpha bandwidth (~8–12 Hz) suppression. Two constructs are proffered as indicative of left versus right frontal activation respectively, approach and withdrawal.

Approach and withdrawal behaviors as recently conceptualized refer to social interactions. Approach behaviors are associated with positive affect and withdrawal behaviors are associated with negative affect. These behaviors are evident, at least in some form, as early as infancy. In one study, with a group selection criterion of motor reactivity and a disposition component (assessed through parent report and observation) infants with high motor reactivity and a disposition component of approach and withdrawal were found to be more likely to evidence greater right frontal EEG asymmetry, supporting the notion of right frontal mediation of approach and withdrawal behaviors as recently conceptualized refer to social interactions. Approach behaviors are associated with positive affect and withdrawal behaviors are associated with negative affect. These behaviors are evident, at least in some form, as early as infancy. In one study, with a group selection criterion of motor reactivity and a disposition component (assessed through parent report and observation) infants with high motor reactivity and a disposition component of approach and withdrawal were found to be more likely to evidence greater right frontal EEG asymmetry, supporting the notion of right frontal mediation of negative emotion [67].