4

Brain Networks and the Human Mind

Armed with background information about intrinsic connectivity networks (ICNs), we will now consider how brain systems are thought to create the mind and how dysfunction within and across brain networks may contribute to psychiatric symptoms and psychiatric disorders. For this discussion, we will continue to use the definition of "mind" outlined in earlier chapters and championed by Joseph LeDoux in his book *Synaptic Self*. According to LeDoux, the mind is the result of activity in brain circuits that allows humans to do three things: think (cognition), attach value to things (emotions), and set and achieve goals (motivation). It is our premise that all major psychiatric disorders involve defects in each of these three aspects of mind but that dysfunction in a given aspect of mind does not necessarily imply that there is specific pathology localized to that system. Rather, effective processing in interlinked systems depends upon appropriate and accurate inputs from other networks, and pathology in one system can result in dysfunction in another. Two examples cited earlier highlight this. First, in disconnection syndromes such as hemineglect, the lack of appropriate input from a damaged system results in peculiar interpretations by the remaining undamaged systems. This concept that healthy brain regions may make peculiar interpretations when confronted with problematic input from other regions seems to be a basic principle underlying the way the brain works. Second, illnesses like Alzheimer's disease may initially result from a preferential attack on a specific ICN early in their course, although clinical manifestations, even at very early time points, involve more widespread defects in cognition, emotion, and motivation. These latter concepts have been extended recently in studies examining connectivity in brain networks that have sustained damage from focal lesions. It appears that damage that is confined to a single network (e.g., a cognitive control network) results in dysfunction and altered connectivity in intact nodes within the damaged system but does not result in rearrangements within a closely related but undamaged network. Nonetheless, interactions between the two networks are altered because of defective processing within the damaged system.

COGNITION (THINKING)

Working Memory and Prefrontal Cortex

There is little doubt that human cognition is extremely powerful. It gives us the ability to process distinct inputs from the external world and to combine these inputs

with our personal internal world, including evaluation of our current state of well-being and memories. Such integration requires coordinated activity in regions of the brain that are highly connected, the "convergence zones" in LeDoux's terminology. For us to become aware of what we are thinking, we must hold those thoughts "on-line" in conscious awareness. Thus, it is no surprise that the brain has networks devoted to this process. Cognitive scientists refer to this as "working memory." While working memory does not result from activity in a single brain region, the prefrontal cortex (PFC), particularly the dorsolateral PFC (dlPFC), plays a major role. When we are consciously thinking about something (like what we had for lunch today or what we have to do this evening), dlPFC is dealing with this information.

Working memory may represent the most basic aspect of what it means to think consciously. This function has several key features. First, working memory is not a storage device. Rather, it seems to be a series of operations that pulls information from multiple sources and keeps track of that information while it is being used—a kind of "scratch pad" processing. Second, working memory has limited capacity, and it must be continuously updated for a person to remain conscious of current thoughts and stay on track with a task. It is estimated that working memory can hold about five to nine items at a time. In psychology, this is referred to as the "seven plus or minus two" (7 ± 2) rule, and it is thought to be the cognitive basis for the use of seven-digit phone numbers and the fact that humans are not particularly efficient at handling multiple tasks at the same time, given that most tasks have multiple subcomponents. Recent work has shown that even though humans believe they are good at multitasking, individuals who are frequent multitaskers, particularly those who use multiple types of media, are actually highly distractible and have more difficulty completing tasks than people who try to do fewer things at a given time using a more limited repertoire of media. In part, this distractability reflects overloading of working memory and the way our PFCs seem to work naturally. Although working memory capacity is limited, it can be frequently updated, and this updating may be important for the ability to maintain a stream of thoughts while "thinking." How working memory is continually updated is a matter of active study; some evidence suggests the importance of inputs acting on NMDA-type glutamate receptors and the involvement of dopamine D1 receptors as a filtering device. Persistent neural activity in dlPFC is also likely to contribute.

How Does the Brain Select Thought Content?

While the network involved in working memory is critical for conscious thinking, the brain must figure out how to choose the content of our thoughts—how to select what to include in our thinking and what to exclude. It appears that at least two other ICNs play a major role in this process—the default-mode ICN and an ICN (or ICNs) regulating attention. Working memory is closely associated with attention networks and appears to involve at least two essential operations that draw upon this association: a mechanism for "selecting" items that engages the rostral superior frontal sulcus, posterior cingulate cortex, and precuneus, and an "updating" operation that involves the caudal superior frontal sulcus and posterior parietal cortex. This latter system helps to change the focus of our attention (see the Appendix for locations of key brain regions).

As described in Chapter 3, functional imaging studies indicate that human brains are never really idle or at rest. When we are not engaged in an active task, certain regions of the brain are very active in terms of metabolism and blood flow; this is one of the primary reasons the brain uses so much energy. Task-dependent energy use is a relatively small contributor (5% or less) to overall brain energy demand compared to this baseline activity. When a person's attention is directed to a task of interest, activity in the regions with high baseline use diminishes while brain activity in the regions required for the specific task increases. When we shift away from the focused attention required for a specific task to a more "relaxed" brain state, activity in the brain regions required for the task decreases and the background activity once again increases. Various functional imaging studies examining how humans process different types of information have found the same set of brain regions to be involved in this high baseline (background) activity. As mentioned in Chapters 2 and 3, this led Marc Raichle and colleagues to refer to this brain network as a "default system." The default-mode network involves a distributed collection of connected brain regions that includes the ventromedial PFC, the posterior cingulate and retrosplenial cortices, the precuneus and parts of the ventromedial temporal lobe, the hippocampus, and the inferior parietal lobule (see Fig. 2-1). Importantly, some of these same default regions overlap with the working memory system; this is not surprising given that when we are awake we are usually thinking about something, even when not doing a specific task.

When we focus attention on a task (e.g., doing a math problem or reading this sentence), we must engage working memory and shift out of the default state into a mode that engages the ICNs required to perform the job at hand. A key component of this attention-shifting process is an ICN that Maurizio Corbetta refers to as a "reorienting system." In the visual system, this involves cortical circuits in the right (nondominant) hemisphere that link frontal and parietal lobes. It consists of at least two pathways: a *ventral* circuit that interrupts current thinking and resets attention to the new task and a *dorsal* pathway that selects the new objects of attention and links them with ICNs appropriate for the needed computations. Figure 4-1 presents a diagram of the dorsal and ventral reorienting networks.

The ventral path acts like a type of "circuit breaker" that allows us to change our cognitive focus and shift our attention. It is triggered by task-relevant stimuli and allows us to switch from the internal focus of the default system to operations that address specific external demands. The dorsal pathway helps to select the specific items of focus and to evaluate the nature of the external variables in order to determine the content of working memory that relates to the specific stimulus at hand. In other words, the dorsal system seems to prioritize external (world) demands while the default system prioritizes internal (self) information. Perhaps because of the limited capacity of working memory, we usually don't perform both of these tasks at the same time, or at least we don't perform both efficiently at the same time. Put another way, daydreaming doesn't usually help with getting one's job done.

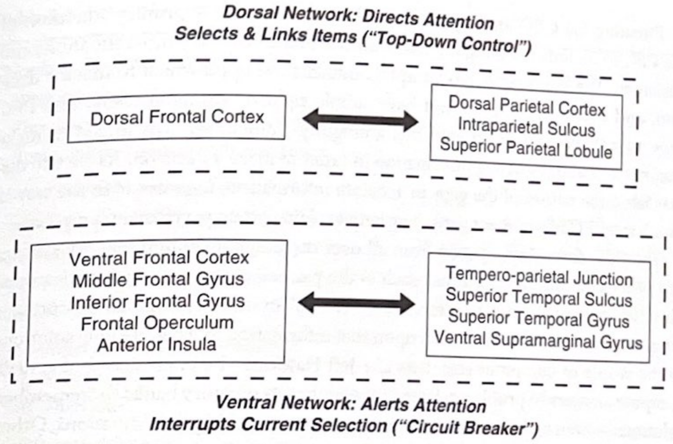

Figure 4-1 Attention and frontoparietal reorienting networks. The diagram depicts key brain structures thought to be important in reorienting and attention networks as described by Maurizio Corbetta and colleagues.

PFC Does More than Working Memory

In addition to its roles in working memory and attention, the PFC is also critical for many other cognitive tasks, including planning and decision making, drawing inferences, determining cause-and-effect relationships, and making predictions about things, people, and events by determining regularities and patterns. These are some of the so-called "executive" functions of the brain and represent the highest-order levels of cognitive processing.

Using this executive function analogy, Elkhonon Goldberg has described the PFC as the "chief executive officer" (CEO) of the brain. As is true of corporate CEOs, this analogy indicates that the PFC is probably not the site where all jobs (computations) are performed or even the site with the skills needed to solve a given problem. Rather, the PFC knows "who" in the organization has the abilities required for a given task and refers the "job" to those regions for processing. The results are then fed back to PFC for further analysis, evaluation, and decision making. The various subdivisions of the PFC are among the most highly connected regions of the brain—convergence zones where inputs from many sources are combined, integrated, and then used to signal other brain regions in order to generate responses. The great expansion in size and connectivity of the PFC over the course of human evolution is thought to be one of the major contributors to the advanced cognitive capabilities exhibited by humans compared to other species.

Pursuing the CEO analogy further, some view one of the primary functions of the PFC to include handling the uncertainties that accompany most situations and decisions. The brain rarely has complete information upon which to make a decision, and most problems do not have simple right or wrong answers. The PFC appears well suited to deal with this ambiguity. Sometimes, it is forced to make assumptions about missing information in order to make a decision. As we will discuss later, the nature of the gaps in accurate information, together with the way in which the PFC fills in these gaps, may help explain certain psychiatric symptoms.

The PFC draws information from all over the brain, including sensory systems and other key convergence zones such as the parietal cortex and the hippocampus. The PFC also has access to information "stored" in other regions of neocortex in long-term memory, and it can call upon that information to generate new solutions. In the words of computer scientists like Jeff Hawkins, the brain does not actually compute answers to problems. Rather, it searches its memory banks to "remember" solutions—even to "remember" solutions to new and ambiguous situations. Others refer to this as the ability of the PFC to "remember the future." Although the future really doesn't mean anything to our stored memories, the PFC, often working in conjunction with the hippocampus, tries to utilize prior information and apply it to new situations.

One can imagine that the various functions of the PFC make this brain region extremely complicated in terms of its internal anatomy and its inputs and outputs. To avoid getting lost in too much detail, we will use a simple scheme that divides the PFC into three major subsections: lateral, medial, and ventral. Lateral PFC, particularly the dorsolateral aspect, appears to contribute significantly to working memory; it is most developed in higher-order primates and humans. The medial PFC includes anterior cingulate cortex and is involved in decision making and selecting outputs to be implemented. This may be the true "executive" region of the brain. The ventral (orbital) PFC is coupled to the brain's emotional-processing systems; it provides a way for emotions to affect decision making and, in turn, helps to regulate emotions. The PFC has diverse efferent (outflowing) connections throughout the brain that allow generation of a complex array of responses. Table 4-1 and Figure 4-2 present a description of subregions within the PFC and their proposed cognitive functions.

One of the key PFC connections is a close coupling with specialized ICNs for language in the dominant (usually left) cerebral hemisphere. This coupling to sophisticated language ICNs is most highly developed in humans, and it provides humans with the ability to think in terms of language. Language provides the basis for generating conceptual metaphors, analogies, and categories—types of thinking that allow humans to move beyond simple perceptions into the realm of complex concepts. Interestingly, many of these higher-order abstractions are tied to the operations of simpler sensory systems, leading us to express abstract ideas (like affection and love) in sensory terms (warm, hot, cold). This type of abstraction is so natural for us that we largely take it for granted, and it pervades many of our abstract ideas, including concepts in math and science (e.g., the idea that numbers are points on a line or values of positions in a game). Understanding human thought often requires deciphering the metaphor being used to express a concept. In some psychiatric disorders, defects in this type of abstraction can result in "concrete" (rigid) thinking and problems in communication. Psychiatrists sometimes try to assess this by having patients interpret simple analogies or proverbs. Misunderstanding the metaphor or abstraction can lead to a total inability to understand the message an individual is trying to communicate.

Table 4-1 Frontal Cortex: Subdivisions and Proposed Functions

Dorsolateral prefrontal cortex (dlPFC)

- Working memory
- Top-down control of attention, emotions, and impulses
- Reasoning and dealing with ambiguity

Anterior cingulate cortex (ACC)

- Conflict monitoring

Dorsomedial prefrontal cortex (dmPFC)

- Error detection
- Reality monitoring

Ventromedial prefrontal cortex (vmPFC)

- Emotional regulation
- Self-reflection

Orbitofrontal cortex (OFC)

- Affective value of stimuli and reward expectation
- Impulse control

In addition to generating responses via interactions with language ICNs, the PFC has the ability to direct other regions in their responses. This is referred to generically as "top-down processing," reflecting the fact that this mode of control uses the highest levels of the brain to regulate more primitive systems, like emotions, motivation, and motor function. For the PFC to exert top-down control, several ICNs have evolved that utilize different time scales in order to accomplish PFC-mediated cognitive control. One such ICN involves a frontoparietal system that provides a means

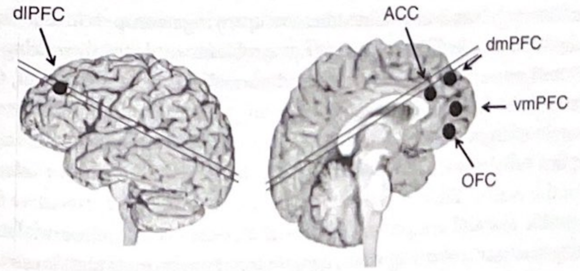

Figure 4-2 Key regions of frontal cortex. The diagram shows the approximate locations of key regions of the PFC that are listed in Table 4-1. See Table 4-1 for abbreviations. (Adapted from Damasio, 2005, with permission.)

for rapidly altering focus and adjusting control (not unlike the operations involved in attention). A second ICN involves the opercular regions of the PFC and the cingulate cortex; this cingulo-opercular system plays a role in more persistent control by providing stable maintenance over the duration of a task. (The frontal "operculum" is the most posterior part of the inferior frontal gyrus and includes Broca's speech area in the dominant hemisphere.) Both of these systems take advantage of structures in the PFC that are involved in working memory as well as other regions involved in decision making. There is also evidence that the cerebellum, a structure primarily involved in motor function, may participate in mediating interactions between the frontoparietal and cingulo-opercular control systems. This latter observation is an indication of how complex neural circuitry can be and how defining a brain region as "motor," "sensory," or "cognitive" can be a bit arbitrary and function-dependent.

These two cognitive control systems utilize a number of strategies to regulate function. Two examples are referred to as "proactive" and "reactive" strategies. Proactive strategies bias attention, perception, and action toward a goal, while reactive strategies respond only when they detect a need for changes, a type of error correction. Interestingly, age may affect which strategy is used for cognitive control, with older persons being more reactive and younger persons being more proactive. It also appears that individuals can be taught to adapt and change their preferred mode of control, and this may provide a target for psychotherapy and rehabilitative strategies. It is important to emphasize that top-down control over emotions and motivation can be extremely difficult and energy-demanding. The more primitive centers of the brain are not designed for this type of control, and it is clear that they can generate responses and behaviors independent of the PFC. As noted by LeDoux, this may be a reason that knowing and doing the right thing can be difficult. Figure 4-3 presents a diagram highlighting how several forms of top-down processing are thought to operate.

PFC and Neuropsychiatric Disorders

Complex higher-order information is processed in the PFC, and as a result this brain region is often implicated in dysfunction accompanying neuropsychiatric disorders. While abnormalities in PFC function (e.g., problems in decision making or top-down control over emotions) may suggest abnormalities in the PFC itself, this may not necessarily be the case. Rather, the PFC may perform poorly because it receives misinformation from other regions or because it is disconnected from key inputs and outputs. Problems with input or output to the PFC may result in clinical symptoms. For this reason, Elkhonon Goldberg has likened defects in executive function to nonspecific physical symptoms like "fever." In other words, abnormal executive processing says that something is wrong with brain function; it just doesn't tell you what is wrong or where the primary problem is located.

Difficulties in dealing with ambiguity may be one of the earliest manifestations of PFC dysfunction in psychiatric illnesses. Ambiguous or confusing information, for example, may lead to actions that appear bizarre. Problems in dealing with uncertainty can lead the PFC to instruct lower brain regions to respond with outputs that are not appropriate for the task. For example, the PFC may receive erroneous information that all of a person's shoes are missing. The response may be accusations that family members or unknown intruders stole the shoes. In reality, the person has impaired memory and forgot that she hid her shoes under the bed. The output has a delusional quality but likely results from the fact that the PFC received only part of the data necessary to come to a correct conclusion. Similarly, the PFC may direct stereotyped behavioral responses (e.g., outbursts of temper) to deal with uncertain and stress-provoking situations. Individuals who are "stressed" tend to use habitual (implicitly learned) responses in preference to higher-order goal-directed behaviors when confronted with new challenges. This is an energy-saving strategy in that habitual responses require little forethought or planning; nonetheless, these responses can be inappropriate in many settings. This may be a particular problem in individuals who have certain types of personality disorders, where over-learned and stereotyped responses seem to rule the day, particularly when the individual is stressed.

One of the major problems in detecting defects in PFC function is that current clinical tests of its higher-order processing are relatively crude compared with assessments of motor, sensory, or language function. Clinical tests as well as more sophisticated neuropsychological tests are better at monitoring defects in working memory and attention than at determining how patients respond to and make decisions in

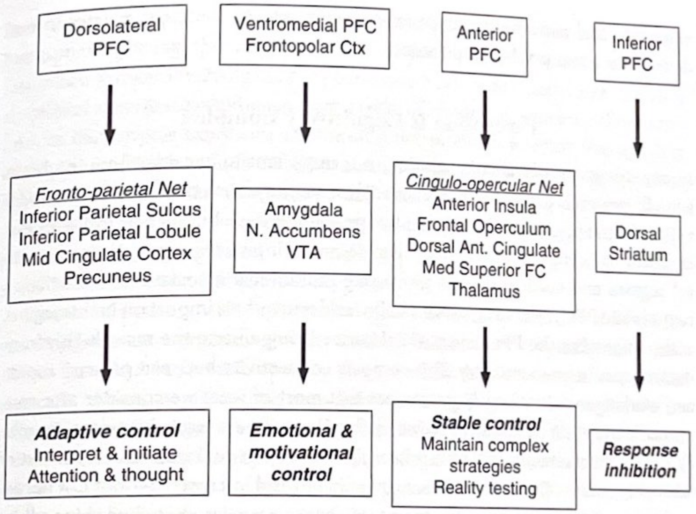

Figure 4-3 Top-down processing: prefrontal cortex and control networks. The diagram depicts some of the key PFC regions and networks providing top-down control over mental processing. Included are the adaptive control and stable-set control networks discussed in the text and described by Steve Petersen and colleagues. See the Appendix for location of key structures.

real-world and ambiguous situations. We will return to these issues later in our discussions about psychiatric disorders.

Perception Is Cognitively Complex

In any discussion of human cognition, it is important to consider how the brain actually perceives input. The brain has sophisticated systems that process unimodal types of input (e.g., input from individual primary senses), but higher-level processing involves a complex interplay between unimodal inputs to primary thalamocortical regions and cortical regions processing multimodal associations (association cortices and PFC). The structure of small-world networks is important in this regard, with regions like the PFC and parietal cortex being among the most highly connected areas in brain circuitry. This complex connectivity between primary inputs and working memory largely guarantees that most of what we consider as a conscious "perception" is highly processed information. Some cognitive scientists conclude that there is really very little primary perception in our brains and that most of what enters conscious awareness is highly filtered and interpreted—but not necessarily correct from a factual standpoint. Michael Gazzaniga described this well by referring to the brain as a "self-concerned interpreter." What we believe is happening around us and to us is actually an amalgam of sensory inputs, memories, context, and internal state (emotions and motivations) interpreted by the PFC with abstracting techniques to pigeonhole and simplify incoming data. Examples of the latter include the use of abstract categories (e.g., "plants," "animals," or "sports"), metaphors, and analogies that help to channel and organize thoughts about a new experience. In fact, as a result of the costly energy demands of higher-order processing, the brain, particularly the PFC, must take shortcuts and use its memories to make predictions about what it is experiencing. The brain rarely takes in a complete picture at one time, but rather focuses on part of a scene and makes "guesses" about the rest. As noted by Gregory Berns, these shortcuts represent a way for the brain to avoid overload. Using this type of processing, the brain changes a perception only when it realizes it has made a mistake. Recognizing mistakes and generating "error signals" are very important parts of the process of perception, and to the extent that error correction is defective, misperceptions can dominate conscious experience (e.g., bad moods, delusions). Internal error correction is a form of cognitive "reality check" and is fundamental for dealing with complex situations.

Lateralized Brain Function and Cognition

The brain uses different modes of processing to make predictive interpretations about the world, and the two cerebral hemispheres seem to process information in complementary but distinct ways. This concept is important when considering how different functions are lateralized in cortex. It is clearest with regard to language functions, which are processed in the left (dominant) hemisphere. In contrast, spatial information is processed preferentially in the right (nondominant) hemisphere.

Emotions also appear to be differentially processed in neocortex, with the right hemisphere playing the major role in interpreting and generating emotional responses. Strokes involving the right hemisphere can be associated with defects in emotional experience resulting in several types of aprosodias, which are clinical syndromes that involve expressive and/or receptive problems in emotional signaling. Examples of defects include inability to express specific emotions (e.g., appearing bland or blunted rather than sad) or difficulties in interpreting the emotions of others (mistaking anger for another emotional state or failing to even recognize that an emotion is being expressed). Both types of problems can lead to major defects in social communication and interpersonal interactions.

Studies of patients with "split brains" have been highly instructive for understanding lateralized processing in the cerebral hemispheres. Typically, these individuals have had intractable epilepsy and have had their corpora callosa severed surgically in order to prevent seizures from spreading from one hemisphere to the other. The corpus callosum is a large fiber bundle in the middle of the brain that connects the two cerebral hemispheres. Studies of split-brain individuals have yielded unique insights into how the hemispheres operate in isolation. The left hemisphere appears to seek logic and cohesiveness in its responses. It does not appear to be concerned with being factual or correct, but only with giving a coherent story. It generally doesn't admit that it doesn't know something, and it will "make up" an answer if needed. For example, in the hemineglect disconnection syndrome resulting from damage to the right hemisphere, the undamaged left hemisphere generates the story that the paralyzed hand belongs to someone else. In contrast, the right hemisphere seems concerned with accurate details and has difficulties dealing with inconsistencies. Unfortunately, this hemisphere does not have a direct language module, so it tends to express itself through emotions and feelings. These differences between the two hemispheres may contribute to the observation that strokes involving the anterior left hemisphere are more commonly associated with depression than lesions of the right hemisphere. When the left side is damaged, the right hemisphere recognizes there is a problem and becomes "worried," expressing its concerns through negative emotions. In the presence of similarly placed anterior lesions of the right hemisphere, the left hemisphere typically has no problem going about its business, but it is not held in check by the emotional control imposed by the right hemisphere. This may result in the development of manic-like (or impulsive) behaviors in some cases.

Why these differences in hemispheric function evolved, particularly with regard to logic and emotion, is not clear, but it may reflect, in part, the way information from the autonomic nervous system is processed in the brain. Input from the sympathetic nervous system conveying data about arousal and survival is preferentially processed in the right forebrain, while input from the parasympathetic nervous system involving relaxation and affiliation is processed on the left. Interestingly, these different inputs and modes of processing appear to have different energy requirements, with left (holistic) processing being more energy-sparing and right (detail-oriented) processing being more energy-intensive.

Intelligence and Cognitive Flexibility

Before leaving this initial discussion about cognition, we would like to make a few comments about human intelligence and its potential relevance to psychiatric disorders. "Intelligence" is a difficult and politically charged concept to define precisely. It reflects the contributions of a variety of brain regions and ICNs and is something of an emergent property of the brain. Although debated, it also appears that there may be different types of intelligence and that individuals can vary significantly across these domains. These include abilities involving language, mathematics and logic, music, movement/athletics, spatial relationships, and social function. Social intelligence reflects the ability to understand one's own mind and the minds of others. Emotional understanding and empathy might constitute a separate form of intelligence, although this may be a subset of general social intelligence. These various forms of intelligence can be difficult to measure, and many clinically used instruments based on verbal and nonverbal intelligence quotients (IQ) are subject to cultural biases and leave a lot to be desired. Nonetheless, defects in IQ performance can be important for identifying areas of functional impairment that can impede educational, social, and occupational activities. Also, while high performance on IQ tests is not protective against neuropsychiatric disorders, low intellectual performance is associated with increased risk for several major disorders, including depression, substance abuse, and psychosis. Similarly, intellectual capacity may be important for predicting persons at greatest risk for dementing illnesses as well as the course of dementia. An example of this comes from the Nun Study, a longitudinal study that examined the long-term outcomes of women living in a cloistered religious order. In early adulthood, those entering the convent were asked to write autobiographies. Women whose writings demonstrated more advanced and complex writing styles fared better as they aged in terms of cognitive performance and risk of dementia. The reasons for the differences are not certain but are consistent with a "cognitive reserve" hypothesis in which greater intellectual capacity may help to buffer illness. Top-down processing and emotional control also appear to benefit from greater intellectual capacity. Nonetheless, being "smart" in one domain does not necessarily predict intelligence in the other spheres, and it is unclear whether different forms of intelligence result in different abilities to top-down process and control emotions and motivation. It is also clear that the brain circuits underlying "intelligence" involve multiple cognitive processes and that these functions often involve computations in frontal, parietal, and temporal cortices and the interconnections among these regions. In particular, high intelligence may reflect the benefits of small-world network processing outlined earlier.

Humans are inherently social animals, and our ability to relate to others has a lot to do with life satisfaction. Defects in a person's social network and support system can have significant impact on the outcome of mental disorders as well. Thus, the area of social intelligence is important in psychiatry. In particular, the ability of an individual to recognize that others have their own minds (experiences and agency) and to draw inferences about the mental states of others based on facial expressions, speech, verbal tone, and nonverbal cues is important in connecting socially with others and in developing satisfying interpersonal relationships. Understanding this ability has led to the concept of "theory of mind" (TOM); that is, we develop a "theory" about what others are actually thinking and meaning. TOM implies that humans are often (if not always) trying to "read" the minds of others. This is an interesting concept when one considers how bothersome such thoughts can be to individuals with psychosis, who often struggle with the notion that people are reading their minds or putting thoughts into their heads. Reading each other's mind is a basic tenet of how we relate and develop understanding of the intentions, actions, emotions, and words of others. Activity in the medial and inferior PFC and superior temporal sulcus, likely including the face area in the fusiform gyrus, appears to contribute significantly to TOM processing. Interestingly, some parts of the PFC have neurons (called "mirror neurons") that seem particularly adept at TOM-type processing. These neurons fire in response to perceived actions of others and initiate actions that mimic what is perceived in the other person's behavior, including his or her movements. Defects in TOM have been observed in multiple psychiatric disorders, but they may be most prominent in autism, where major defects in social attachment and reciprocity are cardinal features. Individuals with autism-spectrum disorders appear to have diminished capacity to perceive agency (planning, intention and self-control) in others. Similarly, misattributions about mental states may represent a type of cognitive defect in other disorders. For example, attribution of agency to inanimate objects is observed in schizotypal thinking (called "magical" thinking).

EMOTIONS: COMPUTING VALUES AND MEANING

What Values, What Meaning?

Emotional processing, the second component of the mind in LeDoux's scheme, allows humans (and other animals) to attach value to the things they encounter. The brain systems involved in emotion are evolutionarily old compared to the PFC; even rodents have emotional-processing systems that are organized in a fashion similar to the networks found in primates and humans. There is little doubt that these systems play an important role in survival: emotions allow us to assess a situation rapidly and unconsciously, and determine whether it is safe or a threat. These are the computations that allow us to make "gut" decisions. Emotional systems are also designed to take control of brain function and drive behavior when activated. For example, we have all had the experience of becoming startled upon hearing a sudden noise, taking defensive postures before we ever become consciously aware of what is happening. The initial sensory input (vision or sound) is processed subcortically and activates key survival systems. Cortex is involved secondarily and can then put conscious constraints on motor behavior (called "response inhibition" in cognitive terms). For example, we may move away from a snake before we consciously realize that we are even doing so. After moving away from the snake, we then understand the danger and consciously decide to move to even safer ground.

There is some agreement that humans have six "primary" emotions: happiness, sadness, fear, anger, surprise, and disgust. Contempt is also included in some schemes. These are considered primary emotions for two reasons: they appear to occur in all human populations and they are expressed in a similar fashion (using similar facial expressions) by people of different cultures. Human emotional life is much richer than the primary emotions, however, and we also have many secondary emotions that relate to social interactions. These include guilt, shame, embarrassment, jealousy, pride, and love, among others. Although these secondary emotions have major impacts on our lives, it is not clear that they are processed in the same way as the primary emotions or how they may derive from the primary emotions.

Given that primitive brain systems underlie emotional processing, it is also useful to think about emotions from the perspective of other animals. Jaak Panksepp has described the existence of seven major emotional systems in animals. These include networks for lust (sexual approach), care (maternal nurturing), joy (play), fear (danger), rage (anger), panic (separation distress), and seeking (exploration). Similar to emotions in humans, Panksepp views these systems as rapidly encoding information about whether an encounter is life-sustaining or life-threatening and driving adaptive and instinctual responses to appropriate action. Panksepp has further argued that these primary systems in animals extend to humans and could serve as potential "endophenotypes" for describing the underpinnings of psychiatric disorders. Endophenotypes are observable (and usually quantifiable) traits that are likely tied much closer to genes and neural systems than complex illness phenotypes (such as disorders and syndromes).

How Are Emotions Processed?

All emotions represent brain computations that include an analysis of incoming information and a subsequent output based on that analysis. In this model, a stimulus is initially perceived either consciously (in the cortex) or unconsciously (in subcortical structures). Specific brain systems process this perception and generate a bodily response. This response is often a change in the output of the autonomic nervous system, the system regulating basic body physiology (e.g., heart rate, blood pressure, respiration, and temperature). These bodily changes are also detected by the brain and can be incorporated into the computational mix. For example, becoming afraid increases heart rate. This in turn can be perceived by the brain, leading to further increases in heart rate in a positive feedback loop. At the point when bodily sensations and context are recognized consciously in working memory, we experience what Antonio Damasio calls a "feeling," the conscious representation of an emotional state. At several places along this processing path, we can take behavioral action in response to the emotion. This might occur once we become consciously aware of the "feeling." At that point, the PFC can drive voluntary behavior. Alternatively, and perhaps more interestingly, a behavioral response can occur before or simultaneous with changes in heart rate and respiration, before neocortex has become involved and before we are conscious of what is going on. This is one of the major principles of emotional systems: they do not need cortex to do their computations and to effect behavioral change. This makes them both powerful and potentially problematic.

How does this happen? It appears that there are several subcortical and cortical networks that contribute to emotional processing. As a result of work by LeDoux, Michael Davis, Michael Fanselow, and numerous others, the system that is understood in most detail is the one involved in processing fear, a primary emotion experienced as clearly in rodents as it is in humans. In fear processing, the amygdala, a complex walnut-shaped brain structure with multiple sub-nuclei deep within the temporal lobe, is a principal player. When a fear-generating stimulus is encountered, information is routed initially through the thalamus, a subcortical way-station for processing sensory and other inputs. The thalamus connects directly to the amygdala for rapid assessment of inputs and also sends input to sensory neocortex for more detailed assessment and interpretation. This simple routing allows the amygdala to drive defensive action via its own direct connections to stress and alerting systems in the hypothalamus and brain stem as well as to the striatum and motor system before cortex ever gets involved. The nature of synaptic contacts and synaptic delays ensures that the amygdala gets the information before the cortex, given that more synapses are required to get the data to cortex and distributed within cortex to working memory. Adding to this, recent studies indicate that the amygdala also has direct chemo-sensing properties of its own and uses acid-sensing ion channels (ASICs) to detect changes in brain carbon dioxide levels or acid–base balance. Thus, the amygdala can do its own direct sensory processing; in turn, this can generate rapid emotional responses, including fear. This may be one of the reasons why changes in respiration (hyperventilation) are so closely intertwined with emotions. Figure 4-4 highlights neural circuitry involved in fear processing (and anxiety) and the central role of the amygdala.

The direct input from the thalamus (or cortex) flows to the lateral nucleus of the amygdala for initial processing. The lateral nucleus connects directly to the central and basolateral amygdaloid nuclei, which regulate emotional processing and generate output to regions controlling alertness, defensive behaviors, and hormonal responses, with the central nucleus playing the key role as a driver of outputs to other brain regions. These output regions include brain-stem nuclei governing arousal and motivation (e.g., the norepinephrine, serotonin, and dopamine transmitter systems) as well as systems regulating neuroendocrine hormonal responses in the hypothalamus and systems mediating freezing responses (behavioral inhibition) in periaqueductal gray. The amygdala is an important activator of stress hormones like cortisol via its connections with the paraventricular nucleus (PVN) of the hypothalamus, resulting in the release of corticotrophin-releasing factor (CRF), which in turn stimulates the pituitary to release ACTH (adrenocorticotrophic hormone). ACTH acts on the adrenal glands to promote secretion of cortisol. Cortisol does many things to mediate stress responses, including acting on the brain in a feedback fashion. Interestingly, changes in the regulation of cortisol secretion (altered diurnal

There is some agreement that humans have six "primary" emotions: happiness, sadness, fear, anger, surprise, and disgust. Contempt is also included in some schemes. These are considered primary emotions for two reasons: they appear to occur in all human populations and they are expressed in a similar fashion (using similar facial expressions) by people of different cultures. Human emotional life is much richer than the primary emotions, however, and we also have many secondary emotions that relate to social interactions. These include guilt, shame, embarrassment, jealousy, pride, and love, among others. Although these secondary emotions have major impacts on our lives, it is not clear that they are processed in the same way as the primary emotions or how they may derive from the primary emotions.

Given that primitive brain systems underlie emotional processing, it is also useful to think about emotions from the perspective of other animals. Jaak Panksepp has described the existence of seven major emotional systems in animals. These include networks for lust (sexual approach), care (maternal nurturing), joy (play), fear (danger), rage (anger), panic (separation distress), and seeking (exploration). Similar to emotions in humans, Panksepp views these systems as rapidly encoding information about whether an encounter is life-sustaining or life-threatening and driving adaptive and instinctual responses to appropriate action. Panksepp has further argued that these primary systems in animals extend to humans and could serve as potential "endophenotypes" for describing the underpinnings of psychiatric disorders. Endophenotypes are observable (and usually quantifiable) traits that are likely tied much closer to genes and neural systems than complex illness phenotypes (such as disorders and syndromes).

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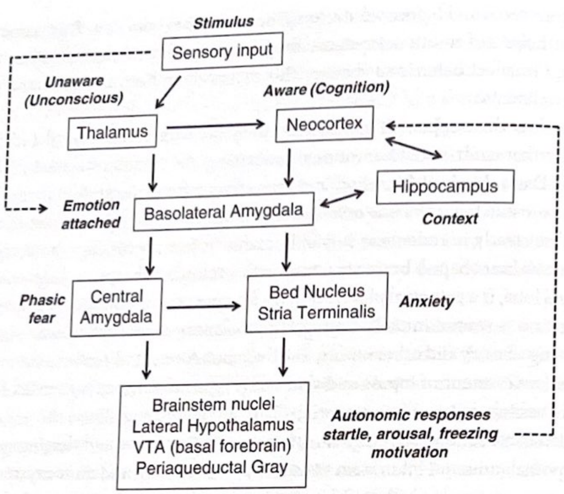

Figure 4-4 Fear and anxiety. The diagram depicts neural circuitry involved in processing fear and anxiety and highlights the central role of the amygdala. While much of this circuitry is shared between fear and anxiety, it is currently thought that the circuitry involved in anxiety engages the extended amygdala, including the bed nucleus of the stria terminalis. See the Appendix for location of key structures.

variation and diminished suppression with dexamethasone) are among the most replicated biological findings in major depression and stress-related disorders.

The amygdala is also capable of synaptic plasticity, and thus it can "learn" to be afraid. Repeated exposure to a fearful stimulus can result in a type of conditioning that leads to an otherwise innocuous stimulus becoming associated with a fear-producing stimulus. This is the basis for Pavlovian conditioning, and similar implicit effects in humans may play a role in certain mood and anxiety disorders. The amygdala also has strong bidirectional connections with the hippocampus, a brain region that is critical for declarative memory formation and that helps to process novelty and context. These connections can lead to even more complex forms of emotional learning that can have adverse effects on behavior. For example, a person can become conditioned to be afraid of paired stimuli via the amygdala (e.g., becoming afraid of a bell that is paired with a shock); one can also become conditioned to be afraid of the place where a bad thing happened (e.g., being stressed in a classroom). When "context" is added to the conditioning, the hippocampus likely plays a role in the learning. This is called "contextual fear conditioning" and can result in excessive and inappropriate responses when one re-enters the conditioned place—for example, generalizing a bad classroom experience to all classrooms. The importance of the interplay between amygdala and hippocampus in emotional processing has been highlighted in a recent study demonstrating the contributions of these regions to anxious temperament as a predisposing risk for mood and anxiety disorders. In primates, hippocampal metabolic activity contributing to anxious temperament is heritable whereas amygdala activity is not. This suggests different roles for genes and environment affecting different brain regions in this behavioral phenotype.

The important point to remember is that there are different components to fear-generated memories, and these different components have implications for how the memories can be controlled or eradicated. Interestingly, studies in rodents indicate that animals can also be conditioned to recognize safety signals and environments where bad things will not happen (e.g., being conditioned to a place where a shock will never occur). This type of learning could contribute to the effects of certain forms of psychotherapy in humans and may help to form the basis of desensitization (deconditioning) therapies as well as extinction learning and conditioned inhibition. Importantly, such learning is not necessarily "unlearning," but more likely is an alternative type of learning that involves amygdala, striatum, and possibly hippocampus.

The amygdala also has connections to the PFC, with strong ties to the ventral (orbital) PFC and the medial (midline) PFC. It is interesting to note that the amygdala does not have strong connections to regions involved in working memory in the dorsolateral PFC, again highlighting the idea that conscious thinking is not really critical for amygdala function. In fact, when the amygdala is in control, working memory is temporarily suspended. Think how difficult it is to perform well on an examination when anxiety levels are running high; things that we ordinarily know well sometimes cannot be consciously recalled when anxiety is in control. Lateral PFC and working memory, however, can override the amygdala (i.e., you can think your way out of being afraid). The relationship of working memory to amygdala processing and the ability of the amygdala and its connections to serve as learning devices have major implications for psychiatry and are the basis for psychotherapies used to treat mood and anxiety disorders.

Other Emotions and Other Brain Regions

The amygdala is only one part of the "limbic system," a distributed subcortical brain system that is thought to play the conductor's role in emotional processing. The concept of the limbic system is sometimes debated—not because subcortical systems aren't involved in emotions, but because defining what constitutes a "limbic" structure can be difficult based on complex connectivity. While the amygdala is a key player in emotional processing, it is not the only structure involved. It is also clear that the amygdala participates in processing more than fear. For example, the amygdala plays a substantial role in rage (the "fight" part of the "fight-or-flight" response) and may also trigger positive emotions, including sexual behaviors. Different nuclei of the amygdala may be involved in different primary emotions. The medial and posterior nuclei are thought to be involved in processing sexually oriented emotions and behaviors, while, as noted previously, the lateral and central nuclei are involved in processing fear. There is also evidence that the amygdala, particularly its medial portion, is part of a basic "threat" system that appears to regulate aggressive behaviors.

Importantly, the amygdala itself is only one component of an extended system that includes the bed nucleus of the stria terminalis (BNST), the striatum (particularly the ventral striatum), hypothalamic nuclei that regulate hormone output via the pituitary, and brain-stem nuclei that regulate the output of monoamine neurotransmitters. Examples of these brain-stem nuclei include the locus coeruleus (site of norepinephrine synthesis), the dorsal raphe nucleus (serotonin), and the ventral tegmental area (dopamine). The connections and involvement of these structures in distributed emotion-processing networks provide a framework for understanding how catecholamines, indoleamines, peptide transmitters, and hormones are involved in psychiatric disorders. Interestingly, studies in rodents and humans suggest that anxiety, a more persistent state of unease with less well-defined triggers than fear, differs from primitive acute fear responses in engaging an extended amygdala network, including the BNST (see Fig. 4-4). Also, involvement of the nucleus accumbens and dopamine in emotional processing provides a link for understanding how emotions relate to motivation. We will discuss this in greater detail later.

Work on the fear-processing network has been greatly aided by the fact that there are well-characterized rodent models of fear conditioning. This has allowed anatomical pathways and synaptic mechanisms to be mapped in considerable detail. Similar models for other emotions are less well developed. Nonetheless, growing evidence indicates that specific regions in cortex are involved in emotional processing and in the generation of conscious awareness of feelings. These cortical regions include the anterior insular cortex (AIC), the rostral anterior cingulate cortex (ACC), and somatosensory cortex. AIC and ACC are deeper cortical structures that receive multimodal inputs from emotional systems and work in concert with the emotional systems. They appear to be critical for conscious awareness of several emotions, including disgust, affective components of pain, and motivation. Disgust is a particularly interesting example. This primary emotion reflects a visceral (gut-level) response to a perception and may have evolved as a mechanism to assess whether something in the environment is edible or noxious. This "gut feeling" eventually may have taken on other meanings of social importance, such as determining "right and wrong" (our moral standards). In other words, the level at which we experience a twinge of disgust may be the level beyond which we will not proceed with an act. Human neuroimaging studies of moral decision making strongly suggest that our initial assessment in these decisions involves our emotional networks, including brain regions involved in disgust. The AIC plays a key role in these experiences and is adept at pulling together information about homeostatic state (state of the autonomic nervous system, hormonal levels, and arousal), emotional state, hedonic conditions, and social situations. The concept that moral standards are closely related to emotional processing demonstrates the amazing integration of cognitive and emotional systems. Figure 4-5 shows the location of the AIC in the human brain.

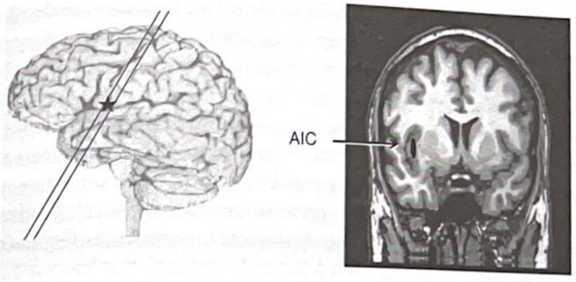

Figure 4-5 Insular cortex. The figure depicts the location of insular cortex. This region plays a role in higher-level processing of several emotions. Abbreviation: AIC (anterior insular cortex). (Adapted from Damasio, 2005, with permission.)

In concluding this discussion of emotional processing we also want to highlight the key role of the hypothalamus, a part of the diencephalon located below the thalamus (hence the name; see the Appendix for location). This region, like the amygdala, is a collection of multiple small nuclei that, in effect, connect the brain and endocrine systems via the pituitary gland. The various hypothalamic nuclei regulate many behavioral and homeostatic processes, including food intake, metabolism, sexual behaviors, circadian rhythms, stress responses, and the autonomic nervous system (blood pressure, respiration, temperature). Even more complex behaviors such as maternal and social affiliation appear to have strong ties to hormones regulated by the hypothalamus (e.g., oxytocin). The details of hypothalamic function and its regulation are complex, with more than 15 subnuclei involved. The importance of the hypothalamus is highlighted by the notion that some neuroscientists liken its actions to those of a thermostat, adjusting bodily function to meet demands. Other scientists go a step further and suggest that most of the higher brain is designed to keep the hypothalamus under control. The importance of the hypothalamus to behavior and psychiatric disorders cannot be overemphasized. In recent years, some illnesses have been directly linked to hypothalamic dysfunction. A clear example is the finding that narcolepsy, a disorder characterized by sleep attacks and cataplexy (loss of muscle tone), involves the loss of specific hypothalamic neurons that release the peptide orexin (also known as hypocretin). It is possible that similar findings will be discovered in other neuropsychiatric disorders in the future.

What Triggers Emotional Responses in the Brain?

Emotions are incredibly dynamic and powerful aspects of our mental lives. They are capable of taking control to help us survive. Thus, it would seem that the stimuli that trigger these responses are critical for us to recognize quickly. While there is still much to be learned about what triggers emotions in humans, there is evolving evidence that effective triggers seem to involve "error" detection in our brains—rapid (and not necessarily conscious or correct) assessments of whether a stimulus (or an action) meets expectations or not. When there is a mismatch between expectation and perceived (or experienced) outcome, emotional systems can be activated to make rapid adjustments. As you might guess, the most intense emotions are triggered by negative assessments. Furthermore, the computations that activate emotions can be quite crude, reflecting perhaps not much more than educated guesses (predictions) about what is going on around us. Thus, they are also prone to error and require their own error correction to adjust inappropriate responses.

In his book *Iconoclast*, Gregory Berns, a cognitive neuroscientist and psychiatrist, discusses categories of things that trigger human anxiety. Berns describes several types of human fears, and his assessment provides interesting food for thought that may also be relevant to how other negative emotions (e.g., anger, sadness) are activated. At its most base level, fear is triggered by perceived harm: threats to our well-being. These are fairly straightforward interpretations, although learning and memory can generalize these responses to less appropriate circumstances (e.g., becoming afraid of things that really can't harm us). Berns also indicates that fear responses can be triggered by perceptions of loss or failure, which in many cases can be accompanied by a fear of personal humiliation. This might lead to a fear of rejection or of being isolated and ostracized from a social network. Humans are highly social animals and loss of contact with our "herd" is bad for our well-being. The final trigger for fear responses described by Berns may be the most interesting and the one that provides deepest insight into how our brains process abstract information: this is the fear of the unknown. We have already emphasized the concept that our brains don't tolerate uncertainty very well. This is particularly true of our left hemispheres, which tend to make up answers if things don't seem coherent. Similarly, dealing with ambiguity and the fact that most decisions don't have clear-cut right or wrong answers is a major challenge for the PFC. In the absence of certainty, emotional systems can be used to provide more definitive responses—though not necessarily correct or useful responses. Some cognitive scientists believe that difficulties in dealing with ambiguity may be one of the earliest manifestations of serious dysfunction involving higher brain centers. Again, this doesn't necessarily mean that there is pathology in those centers, only that they are struggling with the data they are confronting.

From a neuroscience perspective, it is not clear why different emotions are triggered under different circumstances or why different emotions are triggered in the same individual when confronted by relatively similar circumstances. It is also not known why some individuals are prone to anxiety and others to anger or sadness when confronted with similar situations. At one level of analysis, the computation that a perceived (or real) outcome does not meet expectation might trigger anxiety if the perception is one of harm, sadness if the perception is one of loss or defeat, or anger if the perception is one of unfairness. The factors that bias individuals toward one or another of these determinations may have a lot to do with how our motivational system works and how our expectations are determined by our brains.

MOTIVATION: THE IMPORTANCE OF HAVING GOALS

How Does Motivation Work?

Motivation is the third component of LeDoux's mental trilogy. It involves the computations that determine how we set and achieve goals. Motivation is closely

coupled to our concepts of reward and the factors that dictate our expectations. The motivational (and reward) system, like the emotional systems, is old from an evolutionary perspective, and it is closely entwined with the subcortical emotional systems. For example, in Jaak Panksepp's scheme, the emotion called "seeking" may reflect some of what is considered motivation since it involves the computations that drive animals to explore their environment. Also, the way that certain incentives pique our interest may involve activation of emotions. These incentives can be innate or learned. Some seem to be basic drives (e.g., food, sex, survival) while others are more complex and are derived from our learning and environment. Interestingly, humans have a unique ability to use their own abstract thinking as an incentive (or at least as a motivator). As noted by Read Montague, humans are probably the only animals that are willing to die for abstract beliefs—religious or political ideas, for example. He sums this up well by saying "sharks don't go on hunger strikes." As we will discuss in more detail later, almost all abused drugs modulate and usurp the activity of our motivational system via effects on the neurotransmitter dopamine.

Our motivational system involves a subcortical network that includes the nucleus accumbens, the ventral pallidum, and the midbrain ventral tegmental area (VTA) (Fig. 4-6). This system interacts strongly with thalamocortical systems, including the PFC, and appears capable of computing both motivation and reward, although these are not necessarily the same thing from a processing perspective. The VTA is a region that synthesizes dopamine, and the dopamine released by projections from the VTA is a key modulator in the nucleus accumbens. Dopamine's influence also

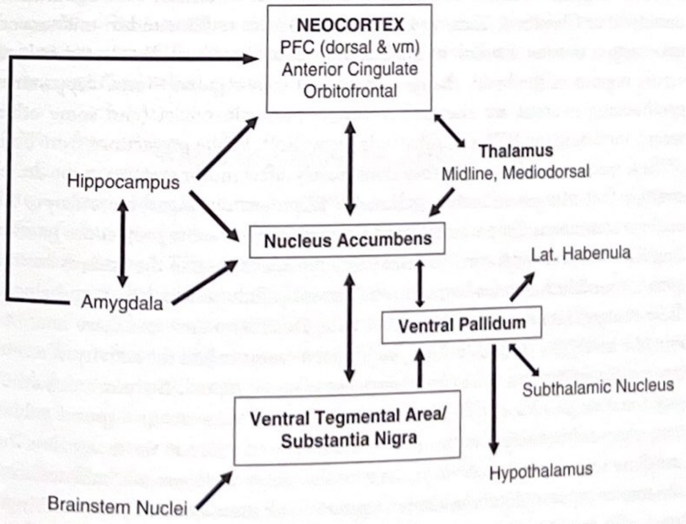

Figure 4-6 Reward circuit. The diagram depicts key structures and connections within the motivational system, highlighting the central role of the ventral tegmental area, nucleus accumbens, and regions of neocortex. See the Appendix for location of key structures.

spreads beyond the nucleus accumbens to connected areas in the rostral cingulate cortex that are important for error detection and areas in the PFC that regulate working memory. Based on imaging studies, it appears that anticipation of a reward activates the nucleus accumbens and VTA, while experiencing a reward seems also to involve the medial caudate nucleus, putamen, and eventually dorsal caudate and supplemental motor cortex. Dopamine helps to drive initial responses and to recruit the more distributed circuit involved in behavioral outcomes.

How does the motivation system work? It appears that the nucleus accumbens is a key region that integrates input about goals, emotions, and memories, and then generates signals that act via the ventral pallidum to help drive motor output and behavior. In this system, dopamine seems to play a major role as an error-detection signal. Some have considered dopamine to be a reward signal, but current thinking suggests it plays a different role. Dopamine seems to help determine whether a perception meets expectations, and it helps other regions in the network direct their attention to important (salient) activities. What this means in practical terms is that the firing of dopamine neurons in the VTA reflects a computational comparison of observations and expectations. When outcomes are better than expected, dopamine neurons in the VTA fire action potentials at increased rates, resulting in more dopamine being released in the nucleus accumbens, cingulate cortex, and PFC. When outcomes fail to meet expectations, firing diminishes and dopamine levels drop. Thus, it is the firing of these specific neurons and the release of dopamine that serves as a "critic signal," in the words of Montague.

What makes dopamine "motivating?" To answer this, it is important to understand how dopamine acts as a neurotransmitter. It a slow monoamine transmitter as described in Chapter 3. Thus, its actions do not drive millisecond-to-millisecond information transfer. Instead, it acts in a more protracted and distributed fashion across regions of the brain, changing inter- and intra-regional "tone." Dopamine-synthesizing neurons are clustered in several midbrain nuclei (and some other areas), including the VTA and substantia nigra (SN). While projections from both of these nuclei are diffuse, SN projections mainly affect motor systems in the dorsal striatum (called nigro-striatal projections). VTA projections distribute widely to the nucleus accumbens, hippocampus, and amygdala (mesolimbic projections) and to cingulate and prefrontal cortices (mesocortical projections). In the nucleus accumbens, dopamine facilitates output to the ventral pallidum, which in turn helps to drive changes in motor activity and behavior. Dopamine does not drive neuronal firing by itself (like glutamate does), but rather it seems to bias the activity of receiving (postsynaptic) neurons to fire in response to strong inputs. Therefore, dopamine may function as a kind of "volume control" that tells neurons to respond only to strong inputs (meaning that the neurons should pay attention to those signals). This translates into dopamine serving as a factor that helps to determine "salience" (i.e., whether an input is of sufficient importance to merit attention). In the rostral cingulate cortex, this signaling mediates error prediction, while in the lateral PFC it helps to focus attention and working memory. In the PFC, this can also be viewed as a type of "filtering" function. Under pathological conditions, where there is too much or too little dopamine, the brain can have trouble determining whether a stimulus is important or irrelevant. This may be a big problem for patients with schizophrenia, where changes in dopamine transmission are thought to contribute to defects in working memory and cognition.

Dopamine transmission in the motivational system also appears to be critical for reinforcement (incentive-based) learning, a type of experience-dependent processing that helps us update and select goals. According to Terry Sejnowski and colleagues, reinforcement learning is the mechanism that allows us to use an ancient prediction system (dopamine) to engage with the modern world and to learn from that world what works and what doesn't work. Montague describes this process as a series of computational steps. First, a perception (either internal or external) generates an immediate signal that is compared to a stored value function in longer-term memory. This comparison results in a "critic signal" (dopamine cell firing) as described earlier. The product of the critic signal (dopamine) is then used to guide choices and to select the next goal by biasing the responses of receiving neurons. This so-called "reward prediction error signal" not only biases subsequent decision making but also influences what is learned from the experience and is used to set future expectations. The learning part of this experience likely reflects the involvement of the hippocampus, where dopamine inputs play a modulating role and seem to be important for the generation of certain long-term memories. Recent imaging studies in humans have focused on understanding how the brain distinguishes between error detection and reward processing. It appears that errors strongly activate the posterior medial PFC (including pre-supplemental motor areas and the rostral cingulate zone) regardless of whether the perceived error is being made by us or by others. The latter is an example of how we learn from the behaviors of others. In contrast, activity in the striatum (particularly ventral striatum) is engaged by reward regardless of error status.

What Determines Our Expectations?

Comparisons of expectations to outcomes play a major role in reinforcement learning—but what sets our expectations? Clearly, they are not static and are often context-dependent. Thus, they are subject to modifications from our emotions and our memories. Nonetheless, our expectations often reflect core and longstanding aspects of our selves, aspects that likely fall under the broad heading of "personality." Personality refers to enduring patterns of how we think about ourselves and the world. It can be described in a number of ways, but one that we find helpful from a brain systems perspective has been championed by C. Robert Cloninger. According to Cloninger, there are two major dimensions to personality: temperament and character. Temperament reflects basic habits and skills that influence how we interact with and respond to the world. Cloninger defines four aspects of temperament: novelty seeking, harm avoidance, reward dependence, and persistence. Character traits determine how we participate in the world and include cooperativeness, self-directedness, and self-transcendence.

Genetics plays a large role in determining a person's temperament and character traits, although both are also modified by experience. Temperament traits appear to be particularly important in determining things that catch our attention and that are important to us. Thus, it appears that these traits also help to determine salience and to set our internal expectation barometer. Are we happiest when things are static or changing? Do we prefer safety over riskier undertakings? How much does the approval of others mean to us? Neuroimaging studies are helping to elucidate the neural systems that contribute to and help to drive these traits. For example, novelty seeking appears to involve a network that includes the hippocampus, amygdala, and nucleus accumbens, while reward dependence appears to engage regions of the PFC and striatum. Persistence involves lateral orbital and medial prefrontal cortices as well as the nucleus accumbens. The role of the nucleus accumbens in these traits is intriguing in light of its apparent role in motivation, error detection, and reinforcement learning. Also, studies of novelty seeking indicate that persons with high exploratory tendencies have diminished expression of a specific class of dopamine receptors (D2 receptors) in ventral midbrain dopamine neurons. These individuals also have enhanced dopamine responses to novel stimuli compared to individuals with low novelty seeking.

These observations are important for thinking about the role of personality in psychiatric disorders as well as potential strategies to help individuals with personality disorders deal with difficulties arising from their temperament and character. According to Cloninger, defects in character traits are the features that indicate the likely presence of a personality disorder, while differences in temperament traits determine the form the disorder takes. For example, uncooperative behavior and lack of self-directedness is observed in many personality disorders. However, the presence of high novelty seeking and low harm avoidance in the face of these character problems correlates with exhibiting antisocial behaviors (lying, poor school and job performance, sexual promiscuity, and fighting). Similar analyses can be applied to other personality disorders.

We want to end this discussion by emphasizing further the important role that motivation plays in brain function and how motivations, cognition, and emotions are intimately intertwined. Karl Friston has hypothesized that all of us have an internal representation of the world against which we compare things to determine whether they meet or don't meet expectations. He argues that motivation based on this stored "model of the world" helps the brain quickly overcome disorder (and the second law of thermodynamics). It forms the basis for biased attention and competition among inputs, allowing values assigned by ascending modulators (emotions) to regulate how inputs are handled and outputs are generated. This goes a long way toward sharpening executive function and minimizing "surprises" to the brain (a bane for higher-order cognitive function), but this also ensures that what is sampled and how it is sampled is biased, as are the strategies used for processing. An example of the latter is the finding that highly reward-dependent individuals exhibit greater improvement in working memory performance when in an environment where they are rewarded for performance, but, interestingly, the improvement in working memory typically occurs during tasks that are not directly rewarded. They improve their performance by adopting a proactive cognitive control strategy (see earlier sections of this chapter) that enhances the likelihood of reward. This again highlights how motivation and cognition are intertwined.

Appetitive (approach) aspects of motivation are largely driven by ventral striatal circuits. Motivation can also be considered to have avoidance aspects, driven in large part by amygdala-based circuits, and regulatory components mediated by PFC networks, again highlighting how the three components of mind are intertwined.

SUMMARY: A SIMPLIFIED OVERVIEW OF BRAIN SYSTEMS AND MIND

We believe that conceptualizing the mind as a trilogy comprising interrelated brain networks is heuristically valuable for thinking about psychiatric symptoms and disorders. At the risk of oversimplifying these points, we will conclude this discussion by providing a more basic summary of what we have described in this chapter. Admittedly, the descriptions below are unsophisticated from scientific and brain processing perspectives, but we think such simplification can help clinicians think practically about how brain systems contribute to psychiatric problems and how to approach those problems therapeutically.

The brain networks underlying thinking, emotions, and motivation interact strongly, and defects across these spheres occur in all major psychiatric disorders. Conscious thinking is the purview of the neocortex, and the PFC is central to this process. It is the moderator, decision maker, and interpreter of everything that happens in the conscious brain. While the PFC may not be able to solve all problems by itself, it has the best handle on where in the brain problems can be solved. Just like the way other small-world networks self-organize and operate, the PFC contains very highly connected nodes and has long-range connections to influence many other brain regions. It is also subject to dysfunction and error generation when it gets defective information from other systems.

The amygdala is critical for emotional processing. It might be considered a bit like a "watchdog" that detects challenges and then works with the hypothalamus and other homeostatic systems to alert the individual and rapidly correct things when deemed appropriate. The dopamine-nucleus accumbens system along with key parts of the PFC is important in motivation and can be viewed a bit like a behavioral "thermostat." When mismatches between expectation and outcome occur, this system helps the brain adjust and reset its compass. We will deal with the hippocampus in future chapters, but for now it is important to understand its key role in handling convergent inputs. It functions a bit like an "integrator" and binds a lot of things together, including our memories and emotions, resulting in even richer associations and memories based on experience. Almost all processed information eventually finds its way to the hippocampus and it, in turn, is capable of sharing its own processing with multiple brain systems. The hippocampus is also critical for novelty detection, so things that are considered "new" end up in this system. Finally, the anterior insula and rostral cingulate cortex serve important roles as "interpreters" helping to bring interoceptive (internal) representations and subjective experiences to awareness and thus to influence behavior. These two areas help to interpret the activity of the ancient evolutionary systems for the more recently evolved PFC. While we have singled out a few key regions, it is also important to keep the general ICN concept in mind: these regions do not function in isolation and are all parts of distributed brain circuits that interact and guide mental processing. Furthermore, our understanding of the complexities of interactions within and across brain systems remains in its infancy and as new information is gained systems neuroscience advances. For example, the cerebellum contains more than 50% of all brain neurons and has largely been thought to regulate motor function. Some evidence suggests that this is overly simplistic and this region may also participate in networks underlying language, mood, and executive control.

It is also important to realize that these brain systems do not result in anything akin to a computer or camera. They make mistakes by taking energy-saving shortcuts, but in healthy brains, they do an amazing job of correcting those mistakes, leading to coherent thinking, feeling, and behavior. This is even more amazing when we take into account the fact that our brains combine ancient systems (amygdala and nucleus accumbens) with intermediate (hippocampus) and relatively modern (neocortex) additions. In his book *The Accidental Mind*, David Linden refers to such an arrangement as a "kludge," a term that loosely means a bunch of things piecemealed together that somehow seem to get the job done. From an engineering perspective, it is not clear that this is the optimal way to design a great computational device, yet this system does more than even the most sophisticated computers in terms of pattern recognition, abstraction, and concept generation. It is amazing how well it works . . . most of the time.

Points to Remember

Psychiatric disorders are brain disorders and reflect dysfunction across all aspects of mind—cognition, emotion, and motivation.

Certain symptoms may predominate in certain illnesses (e.g., emotional problems in mood or anxiety disorders), but problems with cognition, emotion, and motivation are almost always comorbid. The way the brain is wired as a global network almost ensures comorbid symptoms across these three domains when things go wrong.

While the brain is a complex organ, mental processing can be effectively described and understood in terms of systems neuroscience and ICNs. As we will discuss further in subsequent chapters, defects in specific ICNs can predict psychiatric symptoms and can serve as targets for rehabilitative efforts and psychotherapies. Defects in molecular mechanisms are more likely to be amenable to specific pharmacological interventions.

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