CHAPTER 1

How the Brain Works

A BASIC SKETCH

In order to understand how medications work, it is important to have a basic understanding of the nervous system as well as an understanding of how it normally operates so a person can flourish. This is a bit like journeying to a new country and starting by learning where the largest cities and major roadways are on a map (see Figure 1.1). Our analogous list of major sites in the human nervous system will involve only the following components:

1. The **prefrontal cortex** and the **executive functions** and **social cognition** networks that it supports.
2. The **salience network** and its components—most important of which are the **amygdala, insula,** and **ventral anterior cingulate gyrus**.
3. The **autonomic nervous system** and its two divisions, the **sympathetic nervous system** and the **parasympathetic nervous system**.
4. The **monoamine systems,** three of which we will discuss in detail based upon their utilization of **norepinephrine, serotonin,** or **dopamine** as their primary **neurotransmitters**.

In this chapter, we will discuss how all these components work together to enable a human being to live and thrive in an ever-changing environment that regularly poses challenges and threats. This discussion will help you understand how most mental health problems are problems of **dysregulation** for which strengthening **top-down regulation**

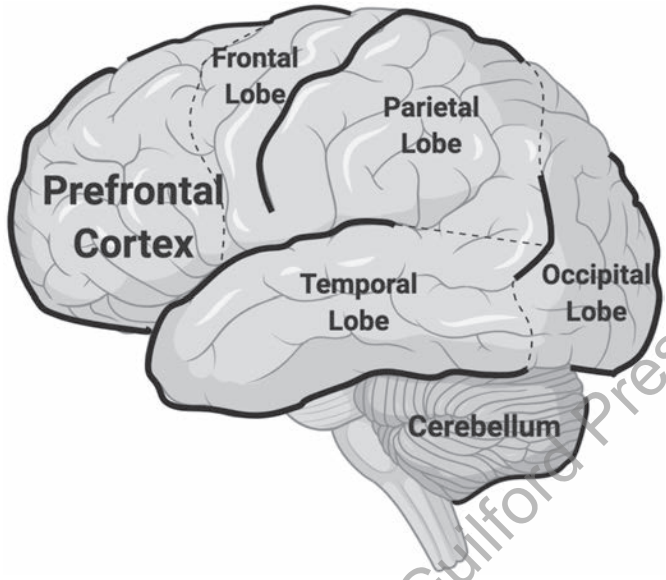

FIGURE 1.1. The parts of the brain.

of **bottom-up information processing** is often the needed solution. This paradigm underpins not only how medications work, but also how psychosocial interventions work by strengthening emotion regulation. These include such treatment programs as dialectical behavioral therapy, acceptance and commitment therapy, and the incorporation of yoga, mindfulness practices, or exercise into treatment programs.

If you do not have familiarity with the functional organization of the human nervous system, it may be helpful to read in more detail about each of the bolded terms as you encounter them. We begin by discussing how our biological evolution reshaped the architecture of the human brain into a social brain built for relationships (see Figure 1.2).

THE HUMAN BRAIN AS A PRODUCT OF EVOLUTION

Both psychotherapy and psychopharmacology rely upon brain circuits that evolved long ago and helped *Homo sapiens* to thrive in competition with other early hominids, such as the Neanderthals. Over the course of evolution, the human brain underwent two notable increases in size: 1.5–2.0 million years ago, and again 200,000–500,000 years ago (Mithen, 1996). These expansions in overall brain size were largely

due to enlargement of the human prefrontal cortex. The prefrontal cortex is small in most mammals, even among higher primates, such as macaque monkeys. In human beings, however, it has expanded to constitute about 20% of the entire brain. This large prefrontal cortex has mostly served the development of executive functions (planning, organizing, prioritizing, using self-talk to regulate one's behavior) and social cognition (noticing social cues, organizing into groups, making psychological sense of other people, feeling empathy for others).

In a social group where individuals cooperate, compete, and create alliances and coalitions, individuals with an ability to predict the behavior of others will achieve the greatest reproductive success. Social intelligence—powers of social forethought and understanding—is essential for maintaining social cohesion so that practical knowledge can be shared within the group. This "social brain" provided humans with capabilities for making psychological sense of each other, that is, to accurately imagine the contents and logic of each other's minds.

Not surprisingly, psychiatric disorders have their most disabling effects when they alter a person's capacities for social relatedness with others, such as an inability to notice social cues or to show empathy for another person's distress. All serious mental illnesses involve dysfunction in how the prefrontal cortex can effectively regulate other brain systems.

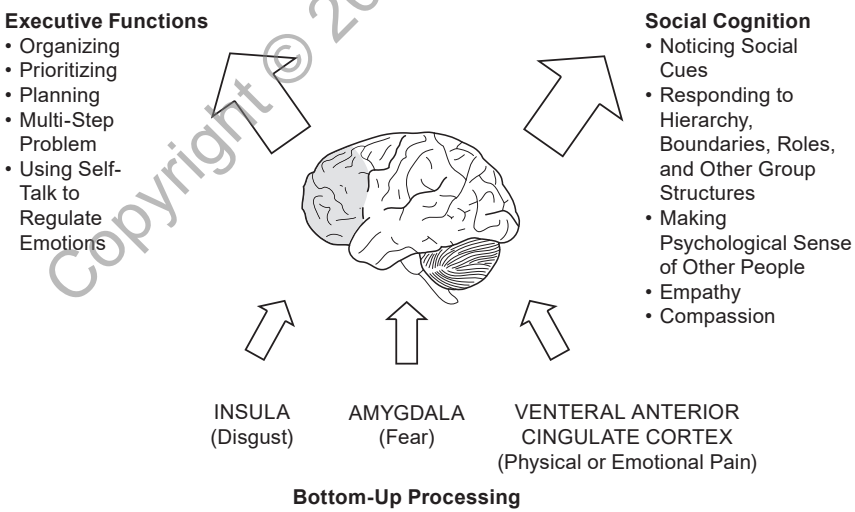

FIGURE 1.2. The evolution of the prefrontal cortex and the ascent of *Homo sapiens*.

NEURONS, NEUROTRANSMITTERS, AND NEUROTRANSMITTER RECEPTORS

Understanding how psychiatric medications work begins with a basic understanding of how the brain works. The human brain is made up of 100 billion cells called **neurons.** In addition, there are a similar number of **glial cells** that give a physical architecture to the brain and provide metabolic support for the neurons. Neurons in the brain differ from other cells in the body in that they are primarily designed for communicating with each other. Neurons are designed to pass an electrical charge along their surface from one end to the other, then to transfer the electrical charge to the next neuron, then to the next (see Figure 1.3). Transfer of the electrical charge from one neuron to the next is accomplished by dumping a molecule called a neurotransmitter into the cleft between neurons, called a **synapse.** The neurotransmitter drifts across

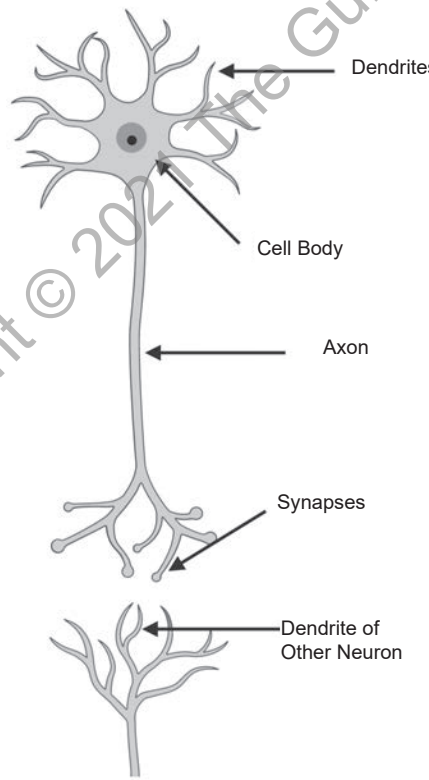

FIGURE 1.3. The neuron, or nerve cell.

the synapse to attach to a neurotransmitter receptor on the next postsynaptic neuron, where it activates another electrical charge that travels the length of the neuron to the next neuron, and so forth (see Figure 1.4). Often the traveling electrical charge is simply called an electrical impulse. An electrical impulse serves as the most fundamental unit of information in the nervous system.

At a physiological level, most psychiatric medications exert their effects by blocking access of neurotransmitters to receptors on postsynaptic neurons. Some medications strengthen the binding of neurotransmitters to receptors. Other medications block the **reuptake** for future reuse of neurotransmitters after their release into synaptic clefts. Each type of neurotransmitter will react with one specific type of receptor site and no other, similar to a lock and key. There are at least 40 different chemicals that have been shown to act as neurotransmitters; some of the most common are listed in Table 1.1.

Most synapses in the central nervous system (CNS) will conduct an impulse (usually via a neurotransmitter) in one direction only; that is, from the **axon** of the presynaptic neuron to the **dendrite** or cell body

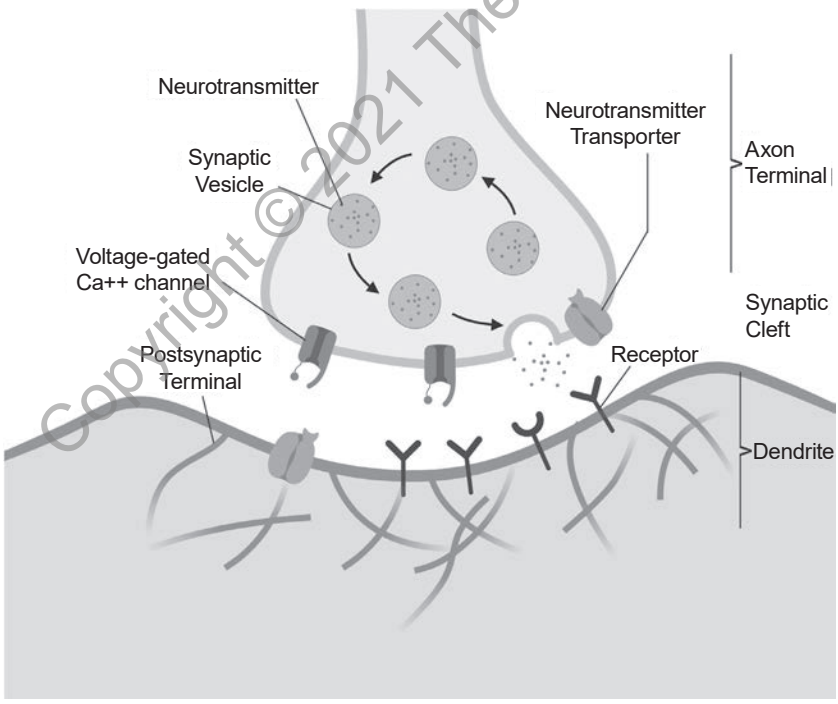

FIGURE 1.4. The nerve synapse.

TABLE 1.1. Some of the Most Common Neurotransmitters

Neurotransmitter	Function/biology	Disorder if malfunction	Medications used to influence this neurotransmitter
Acetylcholine	Usually excitatory, except for some parasympathetic nerve endings where it is inhibitory (such as the effect on the heart by the vagus nerve). Secreted by many neurons, including those in the motor area of the brain, basal ganglia, skeletal muscle motor neurons, all preganglionic autonomic nervous system neurons, all postganglionic parasympathetic neurons, and some postganglionic sympathetic neurons.	Complex, diffuse symptoms affecting all bodily systems. This is a complex, widespread neurotransmitter, the receptor sites of which are affected (usually adversely) by some psychotropic medications (anticholinergic side effects).	Very diffusely affected by many medications. In particular, antihistamines, anti-Parkinsonian drugs, and medications for dementia affect this system, as do numerous medications for general medical conditions. Many psychiatric medications have side effects that occur because of their influence on the acetylcholine receptors.
Dopamine	Usually inhibitory. Secreted by neurons in substantia nigra onto neurons of the basal ganglia, both subcortical areas of the brain.	Disorder in the dopamine system has been hypothesized to be important in psychotic disorders, and many antipsychotic medications work on dopamine receptors, of which there are several subtypes. Affects cardiovascular system and has other widespread effects.	Diffusely affected by many medications. Antipsychotic medications and some antidepressants have some dopaminergic effects; certain medications, used for general medical conditions also affect dopamine receptors.

GABA (gamma-aminobutyric acid)	Inhibitory. Secreted by neurons in the cerebral cortex, subcortical area, and spinal cord.	Anxiety states, also involved in chemical dependency.	Diffusely affected by many medications. Many antianxiety medications work on GABA receptor sites, especially in the frontal lobe of the brain. Alcohol, benzodiazepines, and barbiturates all affect GABA receptors, as do other drugs.
Norepinephrine	Mostly excitatory, but inhibitory in some areas. Secreted by neurons in the locus ceruleus (subcortical area) to widespread areas of the brain, controlling wakefulness, overall activity, and mood. Also diffusely secreted in the sympathetic nervous system.	Diffuse and widespread symptoms, including depression, changes in blood pressure, heart rate, and diffuse physiological responses, among many others. An important transmitter in the sympathetic branch of the autonomic nervous system.	Diffusely affected by many medications. Several antidepressants work specifically on this neurotransmitter and its receptor sites. Many medications for general medical conditions affect this neurotransmitter as well.
Serotonin	Usually inhibitory; helps control mood, influences sleep, and inhibits pain pathways in the spinal cord. Secreted by subcortical structures into hypothalamus, brain, and spinal cord. There are many subtypes of serotonin receptors.	Diffuse and widespread symptoms: depression, headache, diarrhea, constipation, sexual dysfunction, and other medical symptoms.	The selective serotonin reuptake inhibitors (SSRIs), the most commonly used antidepressants, work specifically on this neurotransmitter system.

(**soma**) of the postsynaptic neuron. A particular postsynaptic neuron will have anywhere from 10,000 to 200,000 terminals, or receptor sites, that interact with presynaptic neurons via release of neurotransmitters.

FUNCTIONAL BRAIN CIRCUITS

The neuron is the fundamental anatomical unit of the brain. However, the fundamental functional unit is not an isolated neuron but rather an entire circuit of interconnected neurons. A **functional brain circuit** can be thought of as a "family" of neurons that are interconnected. Like a medieval village family where Smiths are carpenters, Joneses are blacksmiths, and Kellys are tailors, each functional brain circuit carries out a specific sensory, cognitive, or behavioral action. Functional brain circuits are the building blocks of behaviors that involve thoughts, feelings, and actions. Functional brain circuits govern how the brain senses its surrounding world, processes information, and expresses adaptive actions in response.

A **signaling pathway** is the organized transfer of information between and within neurons so that the brain can sense changes in its environment, interpret those sensory stimuli, generate complex motor and behavioral responses, and store the information in memories. A signaling pathway can involve sensory receptors in body tissues that link to release of neurotransmitters that activate a sequence of brain circuits, which, in turn, prompt secretion of hormones that exert effects upon body tissues. Each of these steps serves as a link in a chain of command that connects sensing one's environment, to acting upon that environment to ensure survival and well-being of the species. For example, many mothers who nurse their newborn infants are familiar with the breast milk "let down" reflex. Sometimes just hearing the sound of her crying baby causes milk to be secreted from the mother's breast. How the sound of the baby can exert such an immediate effect upon the mother's body is an example of a signaling pathway. Its steps are as follows:

- The baby's crying sound is detected by the cochlea of the mother's ear.
- The cochlea activates nerve fibers that enter her brainstem to end within the nucleus of her eighth cranial nerve.
- The eighth cranial nerve nucleus activates a neural pathway that travels upward and, after several relays, activates neurons in the hypothalamus.

- The hypothalamic neurons release a small protein, oxytocin, into the bloodstream.
- When oxytocin travels to the mother's breast through the bloodstream, it causes contraction of the muscles surrounding the milk ducts, causing milk to be secreted.

Signaling pathways for specific human behaviors involving multiple functional brain circuits are linked together for a single common purpose. Some of the steps of a signaling pathway can involve types of tissues other than neurons, such as sensory receptors; release of hormones; or muscle contractions.

Intrinsic Connectivity Networks: Our "Clans" of Functional Brain Circuits

Complex domains of behavior, such as executive functions or detection of emotionally salient events, are subserved not by simple functional brain circuits, but by large networks that combine many different functional neural circuits into an integrated whole. **Intrinsic connectivity networks (ICNs)** are large-scale networks of brain circuits that have characteristic functions and behavioral correlates, such as executive functions, social cognition, or memory.

In comparison to single circuits, these ICNs might be likened to clans, or "families of families," of functional neural circuits (Laird et al., 2011). The prefrontal cortex on the left side of the brain houses ICNs that support executive functions, while the prefrontal cortex on the right side houses ICNs that support social cognition.

Executive Functions

Executive functions is an umbrella term for a number of cognitive processes, such as planning, organizing, prioritizing, selective focusing of attention, multistep problem solving, verbal reasoning, inhibiting impulses, mental flexibility, multitasking, and initiation and monitoring of actions. Executive functions represent the evolutionary achievement of functional brain circuitry anatomically located within the prefrontal cortex of the brain's hemisphere that is also dominant for language (usually the left hemisphere).

Executive functions enable humans to override responses that might otherwise be automatically elicited by environmental stimuli. Some of these executive functions include:

1. Planning for an envisioned future and decision making
2. Correcting or troubleshooting errors
3. Acting in situations requiring novel, unrehearsed solutions
4. Navigating technically difficult or high-risk situations
5. Managing situations that require overriding a strong habitual response or resisting temptation

Frank McCourt (1996), in *Angela's Ashes,* described his Ireland childhood, half-starved, disheveled, chronically ill, and lacking any adult encouragement; he nevertheless determined to go to the United States and gain an education. He made plans and backup plans. He secretly created a post office savings account where he could save a few pence at a time. Utilizing creativity and ingenuity, he worked from one odd job or money-making scheme to another. At age 19, he purchased a steamer ticket to the United States. Such pathways thinking and agency thinking is emblematic for how executive functions operate (Snyder, 2000): "Here I am, there is where I want to be, these are steps I can take to get there." Despite a childhood of extraordinary poverty and neglect, Frank McCourt's executive functions kept finding pathways to a future he could only envision with his imagination. His memoir won a Pulitzer Prize.

Social Cognition

Social cognition is the broad set of skills that enable a person to utilize relationships to cope with life's challenges. It includes perceptual skills for noticing social cues and patterns of interaction, as well as social processes such as rules of hierarchy or group boundaries. Social cognition enables emotional awareness of others and oneself. Whereas the dominant (for language) hemisphere houses the infrastructure for executive functions, the nondominant hemisphere provides the infrastructure for social cognition. The dorsomedial prefrontal cortex supports **mentalization** as the cognitive capacity to make psychological sense of other people, while the ventromedial prefrontal cortex supports the emotional perspective-taking of empathy. Executive functions and social cognition can be coordinated to enable the most sophisticated problem solving, strategic planning, and collaboration skills in all the animal kingdom.

Salience Network

The brain's salience network detects meaningful stimuli in a person's surrounding environment and generates appropriate emotions in response.

These emotions provide needed direction and motivation for taking action—to feel fear readies both mind and body for flight; to feel anger readies mind and body to fight; to feel shame readies mind and body to hide from sight; and so forth. The salience network operates both within and outside of conscious awareness. Brain circuits that constitute the salience network include those organized around the amygdala (to detect threatening stimuli), insula (to detect distasteful or disgusting stimuli), and ventral anterior cingulate cortex (to detect emotionally or physically painful stimuli).

The salience network alerts the prefrontal cortex that "there is work to be done." The salience network also sets in simultaneous motion two other systems whose roles are to get the body and mind ready for action:

1. The autonomic nervous system (ANS), which readies the various body organ systems for whatever path of action will be required. The sympathetic division of the ANS prepares for a fight-or-flight response—racing the heart, elevating blood pressure, releasing extra glucose into the bloodstream. The sympathetic nervous system is thus an accelerator that puts the entire body into crisis mode. The parasympathetic nervous system is a decelerator that puts a brake on the sympathetic system in order to fine-tune behavioral responses to environmental demands. The parasympathetic division readies the body for one of three options when facing adversity: to freeze death-like, to fight or flee, or to "tend and befriend," bonding with others to meet adversity together (Porges & Dana, 2018). For example, an unexpected loud explosion would immediately activate the sympathetic nervous system—speeding heart rate, raising blood pressure, shifting blood flow away from the visceral body organs to the muscles—readying the body for a possible need to flee. Simultaneous activation of the parasympathetic nervous system might lead a few people to freeze immobile, others to flee, and still others to seek other people who could help. Which parasympathetic action would be largely determined by the person's behavioral genetic history; by the extent to which the person did, or did not, feel both frightened and trapped; as well as by any personal history of past traumatic events (Levine, 2010; Porges & Dana, 2018).

2. The monoamine systems, which utilize serotonin, norepinephrine, or dopamine as neurotransmitters, prime the CNS for a rapid response (norepinephrine, serotonin) or more sharply targeted response (dopamine) when facing an adversity. For example, a mouse unexpectedly scurrying across the floor of one's office would likely produce

activation of norepinephrine into the cerebral cortex. For the next 20 minutes or so, information processing would be speeded within the cerebral cortex and a shift termed a *heightened signal-to-noise ratio* would occur in the brain's perceptual systems for how quick-moving objects are perceived. This bias also creates risks for overinterpretation of moving shadows as possible mice, when the same shadows would never previously have attracted attention.

The ANS and the monoamine systems typically activate in concert. Their dual mission is to prepare both mind and body to act upon plans put forward by the prefrontal cortex as it responds to the salience network's alert.

EMOTION REGULATION AND TOP-DOWN/BOTTOM-UP INFORMATION PROCESSING

In its quest for survival, *Homo sapiens* faced a dilemma. Safety meant staying in close touch with changing conditions in the environment. This awareness entailed letting sensations from seeing, hearing, touching, tasting, and smelling course freely into the nervous system. This was termed bottom-up information processing (Gross, 2007; McRae, Misra, Prasad, Pereira, & Gross, 2012).

However, the prefrontal cortex, for all its wonderful capabilities, was also the part of the brain most vulnerable to stress. When flooded with too much stimulation, the prefrontal cortex would stop functioning, leaving the person too frazzled to think or function. A method was needed to dampen arousal from incoming stimuli so that executive functions and social cognition could perform optimally. The solution was top-down regulation by the prefrontal cortex. The prefrontal cortex would send its descending fibers into the major components of the salience network (amygdala, insula, anterior cingulate cortex) to inhibit their transmission of sensory information into the brain. By deactivating these transmission centers, this top-down regulation could preserve a relatively quiet environment for the prefrontal cortex to focus on its work.

Emotion regulation refers to a person's ability to find the best balance between the brain's "need to know" (bottom-up processing) and its "need to think" (top-down regulation). Emotion regulation is the focus of clinical intervention both with medications and psychosocial interventions that strengthen top-down regulation.

Achieving Emotion Regulation through Attention Reallocation

The brain's attention systems enable awareness to be concentrated upon discrete stimuli in the environment while screening out extraneous "noise." Attention systems involve three different anatomic regions in the brain that subserve three different types of attention—alertness, vigilance for emotionally salient events in the environment, and "spotlight" executive attention that enables a person to focus on one target in the environment while screening out awareness of all else.

In the brain, "attention trumps emotion." That is, wherever attention is focused determines whether or not an emotional response can be generated in response to an environmental event. This fact underpins much of psychotherapy, particularly hypnosis, such that shifting focus of attention shifts a person's emotional state. For example, the old adage of athletes in training, "No pain, no gain," implicitly shifts focus of attention from the pain of training to the pleasure of winning in competition. In the American classic *The Adventures of Tom Sawyer,* Tom says a single sentence to his friends laughing at him for having to work on a Saturday morning: "Does a boy get a chance to whitewash a fence every day?" Soon his friends are joyfully whitewashing the fence, while Tom heads out to go fishing (Twain, Fishkin, Doctorow, & Stone, 1997). Interventions that reassign focus of attention are particularly valuable in enabling emotion regulation.

In summary, the brain's salience network conducts surveillance over the ever-changing environment, detecting meaningful stimuli and generating emotional responses to them. These emotional responses provide a direction and level of motivation for executive functions and social cognition to act. The ANS and monoamine systems are simultaneously activated to ready both the body organs and brain information-processing systems to align with the kind and intensity of emotion.

However, regulation of the emotional response is necessary. The prefrontal cortex is the part of the brain most sensitive to stress. An excess of stimulation can overwhelm the prefrontal cortex, leaving a person feeling "frazzled," flooded, unable to think clearly or to utilize relationships effectively. Top-down regulation from the prefrontal cortex and reallocation of attention by the dorsal cingulate cortex can dampen, or even suppress entirely, the initial emotional response. This top-down regulation of bottom-up information processing balances needed sensitivity of awareness for the environment with long-term commitments and social desirability. It enables humans to pause and think, rather than to respond immediately when something happens that is emotionally

upsetting. As Howard Thurman has stated: "The test of life is how much pain and disturbance we can absorb without spoiling our joy" (Thurman, 2010).

CONCLUSION

Functional brain circuits are the shared target for both medications and psychotherapeutic interventions. Psychotherapeutic interventions use language and relationship to shift focus of attention or to reframe meaning so that emotional activation changes. Medications produce changes in emotional activation through a different means. Generally, psychiatric medications do not intervene directly in the complex operations of prefrontal cortex ICNs for executive functions and social cognition. Rather, they alter functioning of the regulatory systems—sometimes the ANS, more often the monoamine systems—that ready the mind and body to respond to stressors. In subsequent chapters, we will examine how medications can modify regulatory symptoms in a manner that relieves the suffering of anxiety and depression.

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