

Circuits in Psychopharmacology

- Cerebral cortex
- Brodmann areas
- Functional brain areas
 - Areas within prefrontal cortex
 - Beyond prefrontal cortex to hippocampus and amygdala
- The planes of the brain
- Neurotransmitter nodes
 - Dopamine
 - Norepinephrine
 - Serotonin
 - Acetylcholine
 - Histamine
- Linking it all together into functional loops
 - Corticocortical circuits
 - Cortico-striatal-thalamic-cortical circuits
- Pyramidal cells as drivers of cortical circuits
 - Pyramidal cell excitatory outputs
 - Pyramidal cell inhibitory inputs
 - Pyramidal cell excitatory inputs
 - Fine tuning pyramidal cells with monoamine, acetylcholine, and histamine input
 - Regulating the monoamine “tuners”
- Summary

Psychopharmacology is moving beyond receptors, enzymes, and other molecules as the targets of drugs as well as mental illnesses. The issue now is *where* in the brain are drugs and illnesses targeting specific molecules, and specifically within which circuits? Circuits can now be imaged in patients in research settings, and this may soon be possible in clinical settings as well.

The good news is that brain imaging is transforming the fields of psychiatry and psychopharmacology, with the promise that this technology may allow much more precise assessments of psychiatric risk, of malfunctioning brain circuits, and of the effects of treatments not just on symptoms but on brain functioning. The bad news is that the modern psychopharmacologist who wishes to follow the current research literature and be

prepared to utilize these techniques in clinical practice must now become at least an amateur neuroanatomist.

Here we will review those aspects of brain anatomy most robustly linked to psychiatric symptoms and to the actions of psychotropic drugs. In general, this means an emphasis on the prefrontal cortex. This part of the journey into contemporary psychopharmacology may be a bit painful to some and may require reading of this chapter more than once. However, the reward that comes from a working knowledge of neuroanatomy is to open an entirely new paradigm of understanding psychiatric disorders and their treatments: namely, to know where in the brain psychiatric symptoms are hypothetically mediated and thus how best to select and combine drugs to reduce symptoms of psychiatric disorders in individual patients.

The various pathways and brain regions introduced here will be discussed repeatedly throughout this book and will be adapted to specific psychiatric disorders and drugs in the chapters on individual psychiatric disorders.

Cerebral cortex

The anatomical journey for a modern psychopharmacologist begins with the cerebral cortex (Figure 7-1). Cortical neurons form connections or networks with neurons in many brain areas. Such cortical networks are considered to be the “engines” of the brain because they

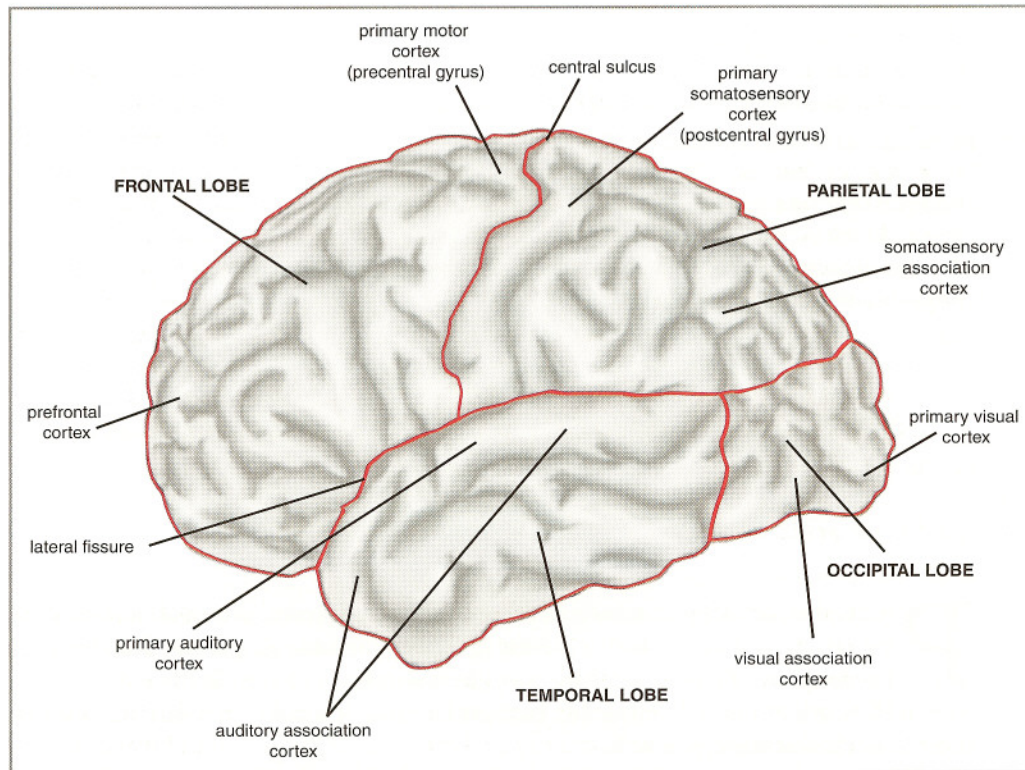


FIGURE 7-1 Key brain regions. This figure is a simple visual representation of the localization of several key regions of the cerebral cortex. The frontal lobe comprises the cortical area in front of the central sulcus, while the prefrontal cortex is the subregion of the frontal lobe in front of the primary motor cortex. The other lobes – parietal, temporal, and occipital – are also shown. Auditory areas are primarily located in the temporal lobe; visual areas are in the occipital lobe, and somatosensory areas in the parietal lobe.

have the capacity to transform simple inputs into complex outputs that ultimately mediate brain functions and behaviors. Each anatomical site in a cortical network can be considered a “node.” Various nodes in the cortex and in a few other key areas of the brain can now be imaged as they perform various brain functions or indeed as they malfunction in living patients. Because different functions live in different areas of the brain, or, more properly stated, are topographically localized, it is important to know the names and addresses of a few key brain areas.

A simple visual representation of where the prefrontal cortex is located on a realistic depiction of the lateral view of the brain is shown in Figure 7-1. The frontal lobe is, not surprisingly, in the front, specifically in front of the central sulcus, and the prefrontal area is that part of the frontal lobe in front of primary motor cortex located in the precentral gyrus. Other key areas of the cortex shown in Figure 7-1 include the parietal, temporal, and occipital lobes. Visual, auditory, and somatosensory areas are also indicated.

To better understand the localization of key brain regions, it is often useful to look at the same regions on several depictions of different brains, since there is variability from one brain to another and also from one neuroanatomist to another. Because this can be frustrating to those who seek a general idea of brain topography rather than detailed neuroanatomical explanations, we will often use cartoons and icons to show things schematically and conceptually but not necessarily completely accurately from a neuroanatomical point of view.

Brodmann areas

For the more serious neuroanatomist, cortical areas are designated by what are known as Brodmann areas, so named for the neuroanatomist who came up with them a long time ago (Figure 7-2). These often appear in modern literature as numerical designations of areas of activation with various functional neuroimaging techniques, so it may be useful to gain a passing familiarity with at least those Brodmann areas located in the prefrontal cortex. There is not, however, an exact overlap of specific Brodmann areas of Figure 7-2 with the anatomical designations shown in Figure 7-1 or with the functional divisions of the prefrontal cortex shown in subsequent figures. In fact, no two brains have the exact size, shape, and placement of Brodmann areas, since some views will not show areas tucked under a fold or gyrus in some brains. To avoid confusion, this text will mostly use the functional anatomic designations shown in subsequent figures; however, more precise designations are available by use of Brodmann areas for the informed anatomist interested in exact topographical designations for the cerebral cortex.

Functional brain areas

Areas within prefrontal cortex

Figure 7-3 is another realistic lateral view of the brain at the top, with a medial view included on the bottom. Shown here is how the front of the brain is basically divided from the back by the fissure called the central sulcus, and again, the frontal cortex is the entire area in front of that (Figure 7-3). Parts of the frontal cortex that will not be emphasized much in this book are the primary motor cortex (purple) and the area just in front of that called the supplemental motor area (light green).

Not only will the region in front of the motor areas – called prefrontal cortex and shown in yellow on both the lateral and the medial views – be emphasized here but so too will various important subdivisions of the prefrontal cortex that can have very different behavioral functions.

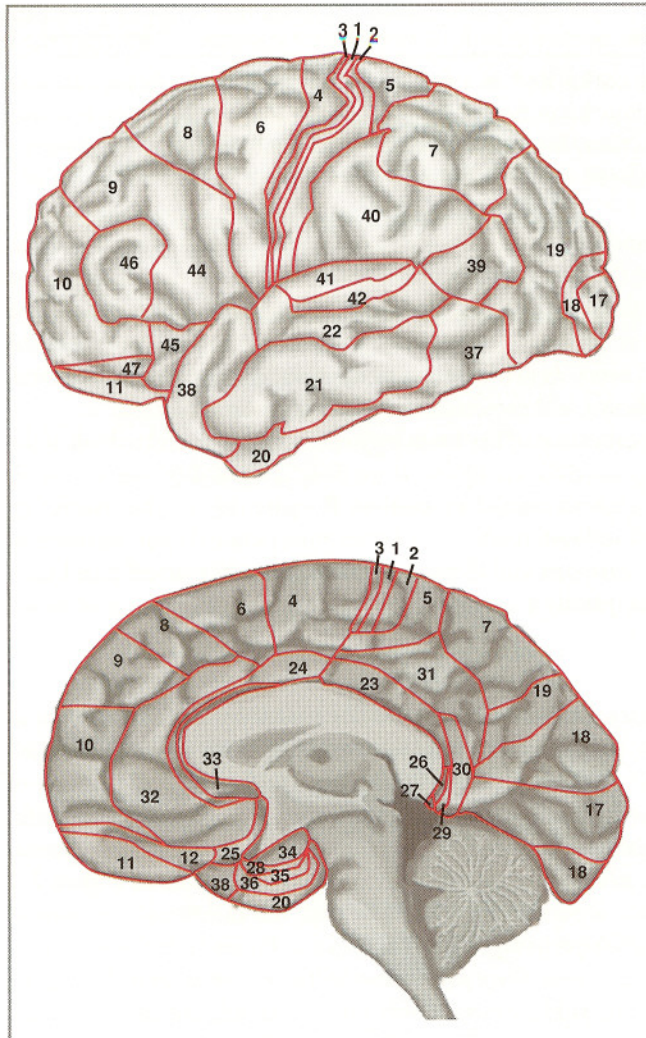


FIGURE 7-2 Brodmann areas. One way of identifying different brain regions is through the use of Brodmann areas. These areas are structurally though not necessarily functionally distinguishable regions of the brain, each of which is designated by a unique number. Lateral (top) and medial (bottom) views of the brain are shown here with the Brodmann areas indicated.

Dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex (DLPFC) is shown in the blue-green oval and seen only on the lateral view (Figure 7-3). This is an important region of prefrontal cortex whose cortical pyramidal cells are the engines for various types of cognitive functions, such as executive functioning, problem solving, and analyzing.

Orbital frontal cortex

The orbital frontal cortex (OFC) is the part of the prefrontal cortex that sits above the eye in its orbit and is seen both on the lateral and medial views of Figure 7-3 (blue). The OFC may regulate impulses, compulsions, and drives.

Anterior cingulate cortex

The anterior cingulate cortex (ACC) is the part of prefrontal cortex shown in light pink on the medial view of Figure 7-4. The top of the ACC, also called dorsal ACC, is thought

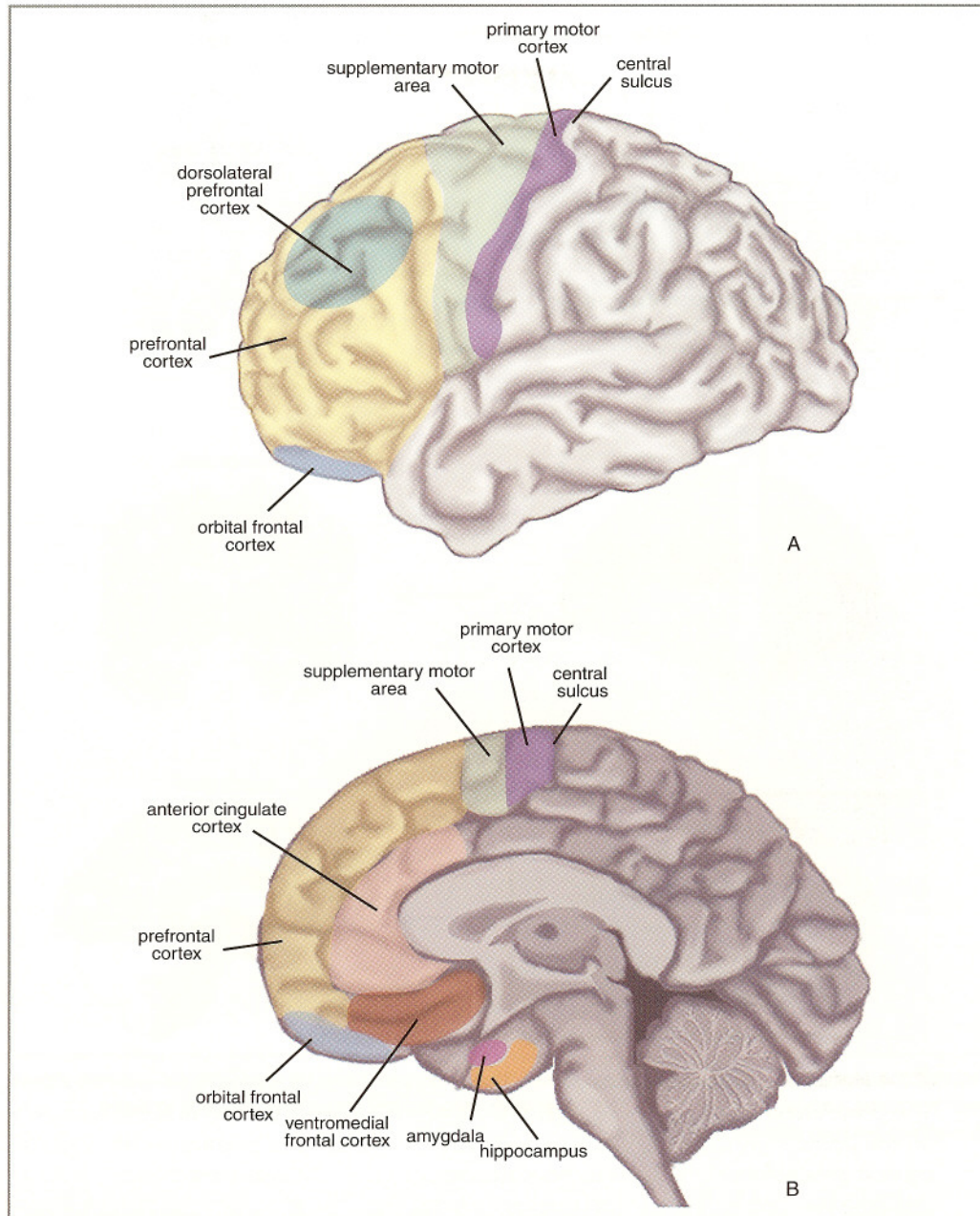


FIGURE 7-3A and B Key brain regions. Several functional anatomical divisions of the brain relevant to psychopharmacology are shown here, using both a lateral (**A**) and a medial (**B**) view. There are several subregions of the frontal cortex, including the primary motor cortex, supplementary motor area, and prefrontal cortex. The prefrontal cortex itself consists of functionally distinct subregions. These include the orbital frontal cortex (OFC), visible in both the lateral and medial views, which may regulate impulses and compulsions; the dorsolateral prefrontal cortex (DLPFC) (lateral view), which is integral to cognitive functioning; the ventromedial prefrontal cortex (medial view), which is involved in emotional processing; and the anterior cingulate cortex (ACC) (medial view), which is involved in both selective attention (dorsal ACC) and emotional regulation (ventral ACC). Two additional brain regions emphasized here are the amygdala and the hippocampus, which are important for fear processing and memory, respectively.

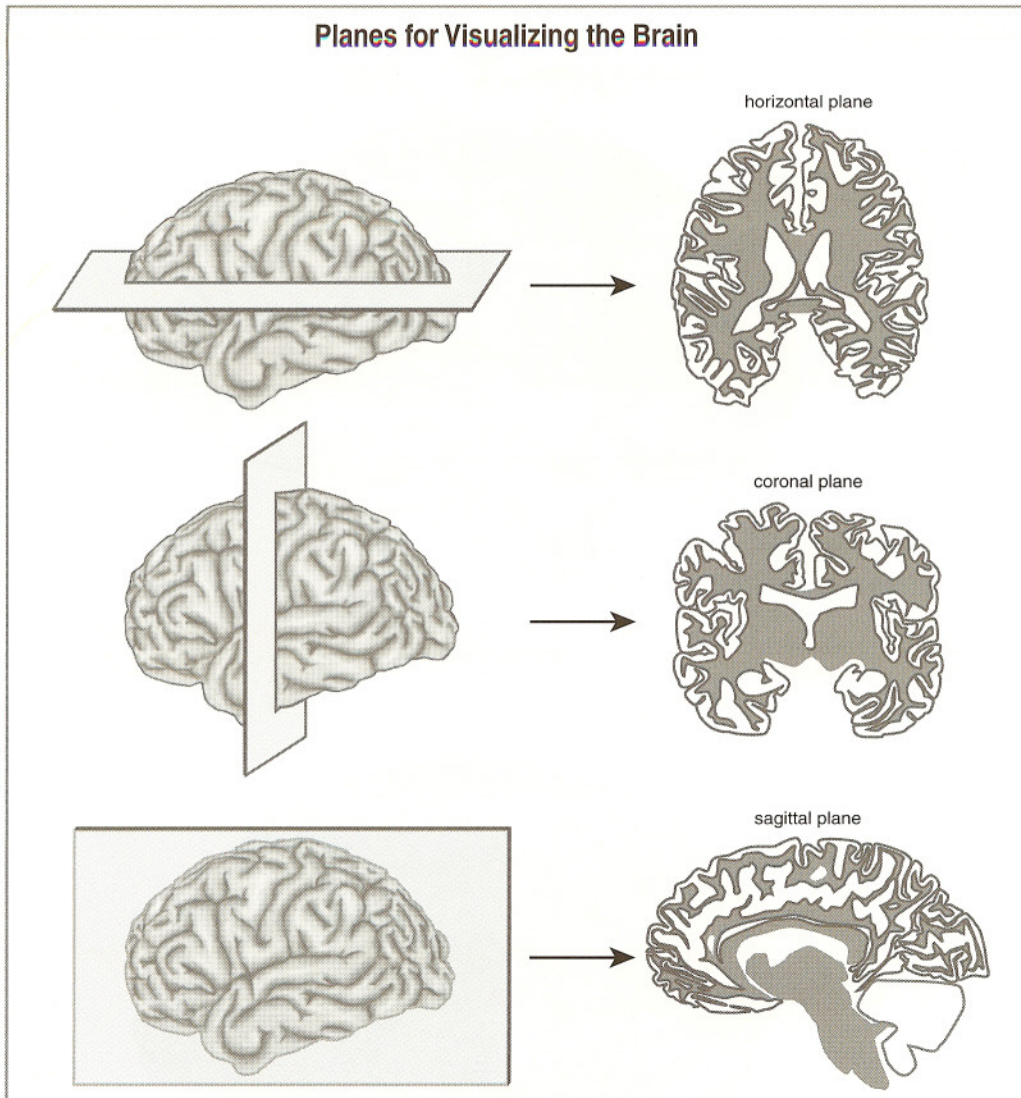


FIGURE 7-4 Horizontal, coronal, and sagittal planes. Three standard planes for visualizing the brain are shown here: horizontal, coronal, and sagittal. Each of these views may be used throughout this book to depict connectivity between different brain regions.

to play an important role in selective attention. The lower part of the ACC, called either the ventral ACC or the subgenual ACC, regulates various emotions such as depression and anxiety. The ACC is shaped like a C; some would say it bends like a knee. *Genu* is the Latin name for knee; thus the area of the C below the bend is sometimes called the subgenual area.

Ventromedial prefrontal cortex

The ventromedial prefrontal cortex, in brown, is the area between the OFC and the ventral ACC (Figure 7-3); it also plays a role in emotional processing.

Beyond prefrontal cortex to hippocampus and amygdala

Two other areas are shown on the medial view of Figure 7-3: the orange hippocampus, important for memory, and the magenta almond-shaped amygdala, buried in the temporal lobe near the hippocampus and involved very much in fear processing.

The planes of the brain

Those who are serious neuroimagers know how to slice and dice the brain, and understand the anatomical relationships of all the possible cuts that can be made through the brain by the various neuroimaging techniques available today. The modern psychopharmacologist should have some familiarity with the deeper structures of the brain so revealed by these techniques in order to interpret various brain images, especially those images showing areas that project to prefrontal cortex or receive projections from prefrontal cortex.

Thus, three standard planes for visualizing the brain are shown in Figure 7-4: the horizontal plane, the coronal plane and the sagittal plane. It may be useful to refer back to this picture when studying images throughout this book to remind yourself at times what cut of the brain you are looking at, and how the cut relates to the orientation of the whole brain.

One can also visualize the brain in some figures that attempt to show the structures underlying the cortex in a 3 dimensional perspective (Figure 7-5). The deep structures under the surface, such as the caudate, thalamus, hypothalamus, brainstem monoamine centers (VTA, ventral tegmental area; LC, locus coeruleus; raphe) can be seen here through a transparent cortex (Figure 7-5).

The brain can also be shown more as a cartoon with approximations of anatomic areas. For example, 11 key areas of the brain that will be discussed extensively in this text are shown with their rough anatomic localization and names in Figure 7-6. The hypothetical behaviors thought to be regulated by circuits running through each of these 11 nodes in various networks are indicated in Figure 7-7.

These will be important to remember, since alterations in neurotransmitters within these sites (Figure 7-6) are hypothesized to create inefficient information processing there and consequently the specific symptoms of psychiatric disorders indicated for each of these 11 areas (Figure 7-7). Also, the neurotransmitters within each of these 11 areas serve as targets for psychopharmacologic drug treatments, which are hypothesized to reduce symptoms in these specific areas by successfully altering neurotransmission and thus information processing there. Knowing where an individual patient's symptoms are hypothetically located, and the neurotransmitters that regulate them within those specific brain areas, can provide a rational basis for which drugs are chosen or combined. This theme will be emphasized repeatedly throughout the textbook and specific applications of this principle will be discussed for each of the specific psychiatric disorders in subsequent chapters.

Neurotransmitter nodes

Several different neurotransmitters have their cell bodies in the brainstem, and their axons project to prefrontal cortex and to many other areas of the brain (Figures 7-8 to 7-13). Although there is quite a bit of overlap of projection areas among the various neurotransmitters, no one neurotransmitter projects to all the same brain areas as another, and certainly not always to the same neurons in the brain areas where they project. Nevertheless, it is hypothesized that when a neurotransmitter does project to a specific area, it has the capacity to modulate the behavior or brain function thought to be associated with that area, as illustrated in Figure 7-7.

Important Functional Areas Within the Left Hemisphere

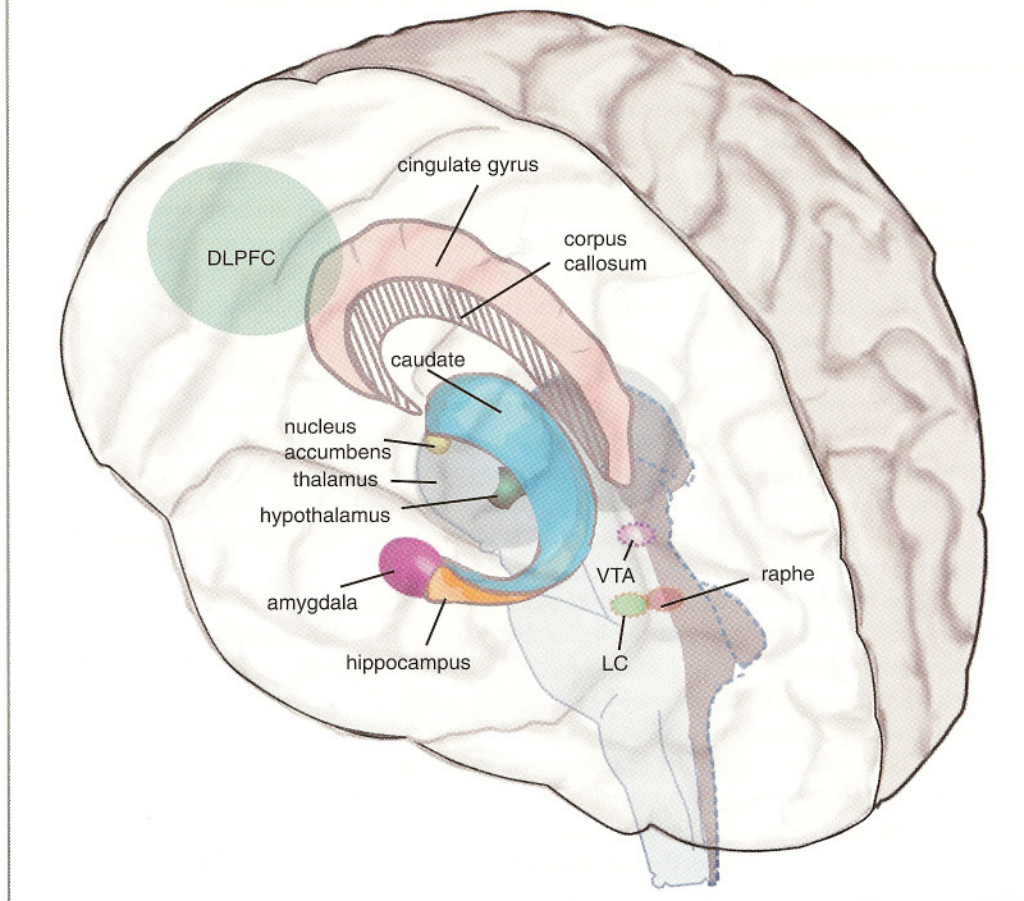


FIGURE 7-5 Key brain regions in three dimensions. This figure provides a somewhat three-dimensional depiction of the brain in which the cortex of the left hemisphere is transparent, allowing us to see the topographical relationships between structures such as the caudate, nucleus accumbens, thalamus, hypothalamus, amygdala, hippocampus, and brainstem monoamine centers. VTA, ventral tegmental area; LC, locus coeruleus; DLPFC, dorsolateral prefrontal cortex.

Neurotransmitter pathways form the molecular and anatomical substrates that “tune” neurons within circuits. This happens not only at the cortical level but at the level of all the nodes within the network of the various cortical circuits. Psychopharmacologists can rationally target these pathways and the functions they regulate by selecting and combining drugs that act on the specific neurotransmitters in the specific brain areas of interest for treatment of an individual patient. Thus, it is useful to know which neurotransmitters go where as well as the function of each brain area they innervate.

Dopamine

The major dopamine projections are shown in Figure 7-8. They arise predominantly but not exclusively from brainstem neurotransmitter centers, notably the ventral tegmental area and

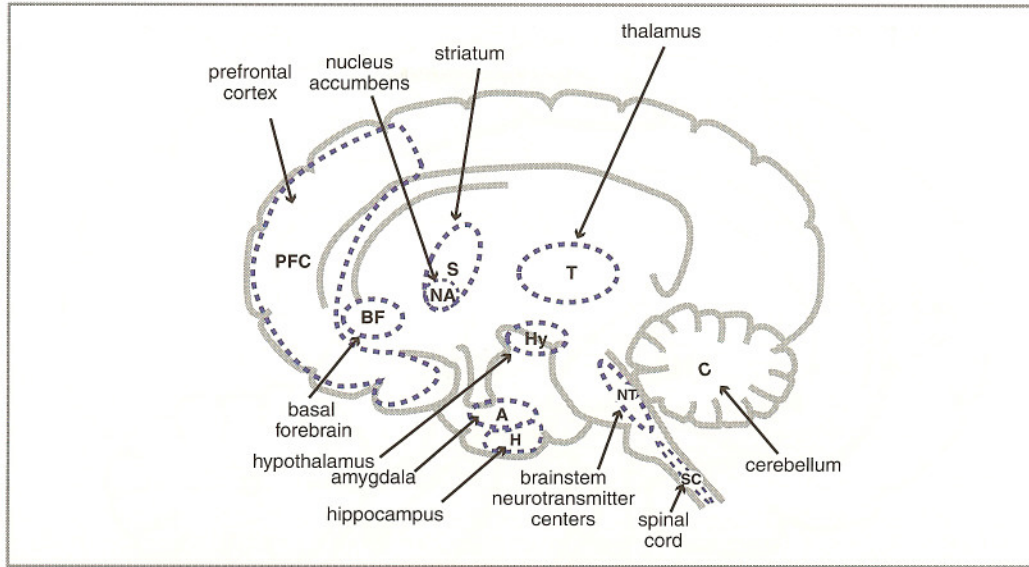


FIGURE 7-6 Key brain regions in two dimensions. A two-dimensional depiction of the brain (medial view) is provided here. The general locations and names of eleven brain regions are indicated. These eleven areas are connected by many different neurotransmitter circuits that are relevant to psychiatric disorders and that will be discussed in great detail throughout the rest of this book.

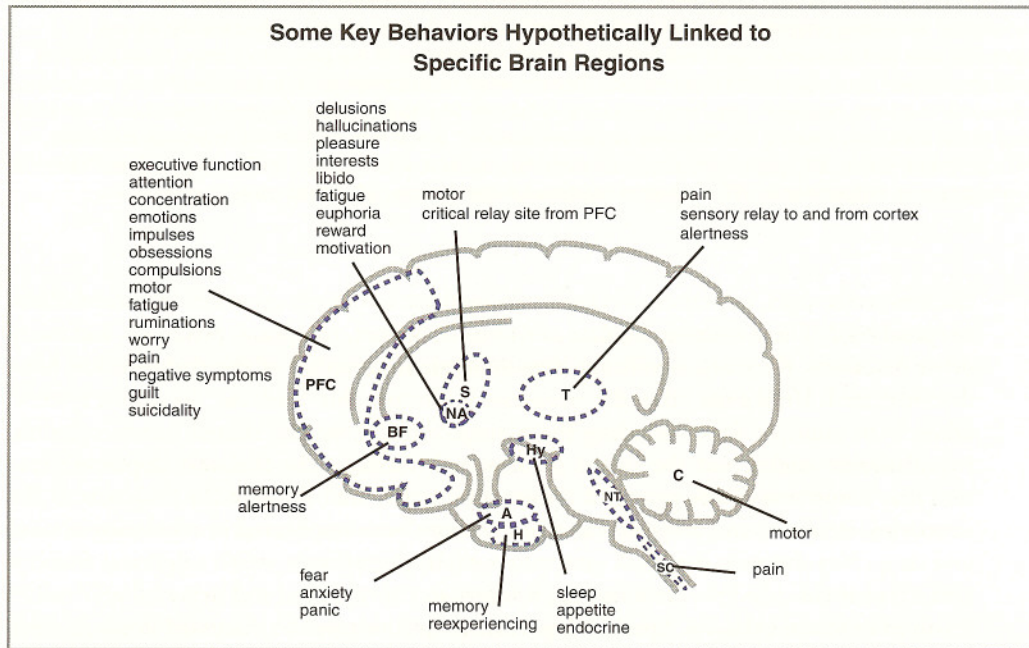


FIGURE 7-7 Behaviors linked to key brain regions. Alterations in neurotransmission within each of the eleven brain regions shown here and in Figure 7-6 can lead to symptoms of psychiatric disorders. Functionality in each brain region may be associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

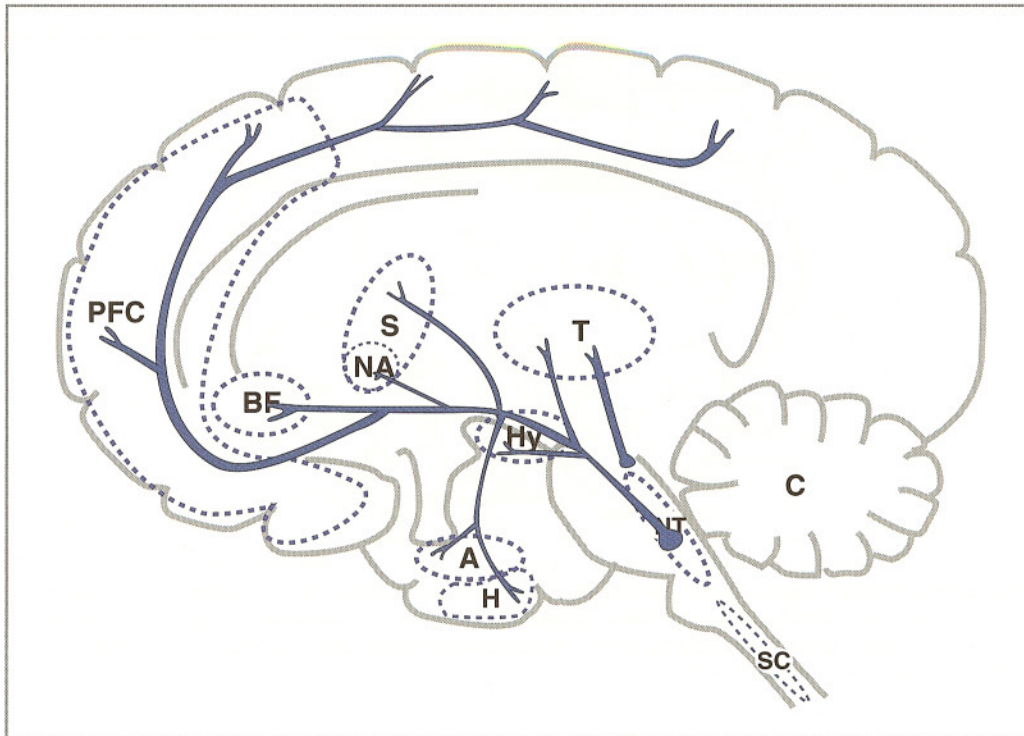


FIGURE 7-8 Major dopamine projections. Major neurotransmitter projections, part 1: dopamine. Dopamine has widespread ascending projections that originate predominantly in the brainstem (particularly the ventral tegmental area and substantia nigra) and extend via the hypothalamus to the prefrontal cortex, basal forebrain, striatum, nucleus accumbens, and other regions. Dopaminergic neurotransmission is associated with movement, pleasure and reward, cognition, psychosis, and other functions. In addition, there are direct projections from other sites to the thalamus, creating the “thalamic dopamine system,” which may be involved in arousal and sleep. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

the substantia nigra, to project to many brain areas but not to any great extent to cerebellum or spinal cord. These neurons regulate movements, reward, cognition, psychosis, and many other functions. Recently, significant dopaminergic innervation of the thalamus has been demonstrated. Unlike the other dopaminergic pathways, this “thalamic dopamine system” arises from multiple sites, including the periaqueductal gray, the ventral mesencephalon, hypothalamic nuclei, and the lateral parabrachial nucleus. The thalamic dopamine system may contribute to the gating of information transferred through the thalamus to the neocortex, striatum, and amygdala and has recently been implicated in regulating arousal and sleep. Not shown is the small incertohypothalamic pathway, which originates from an area of the brain called the zona incerta; it innervates amygdaloid and hypothalamic nuclei involved in sexual behavior. Specific dopamine projections will be discussed in much more detail in the clinical chapters dealing with specific psychiatric disorders.

Norepinephrine

The major norepinephrine projections are shown in Figure 7-9; they arise largely from the brainstem neurotransmitter center known as the locus coeruleus, although some also

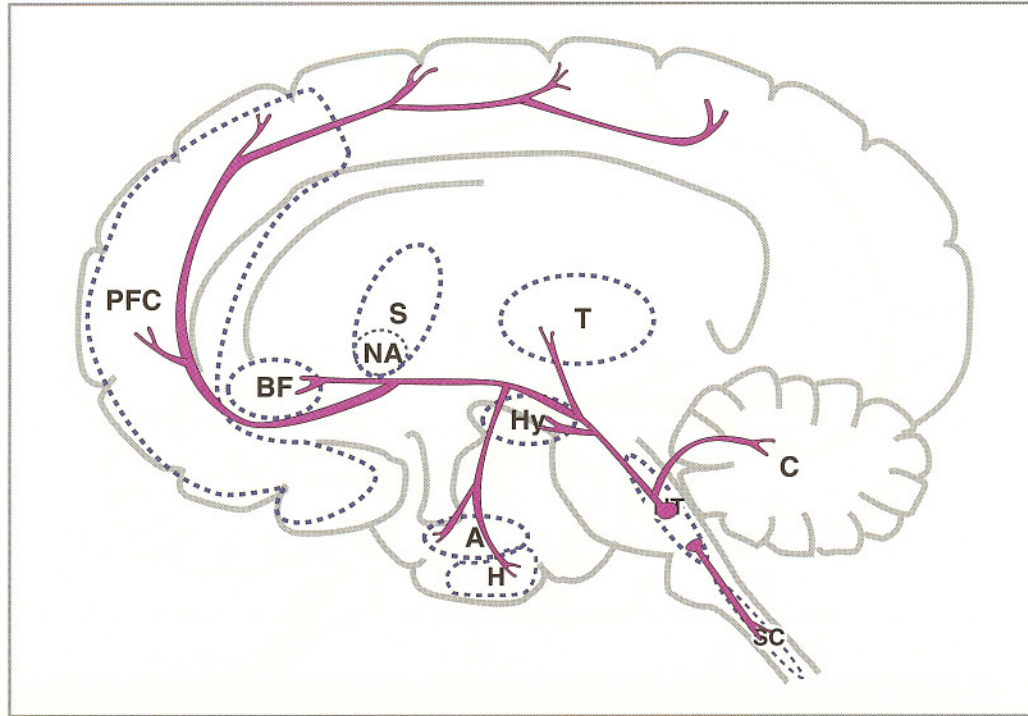


FIGURE 7-9 Major norepinephrine projections. Major neurotransmitter projections, part 2: norepinephrine. Norepinephrine has both ascending and descending projections. Ascending noradrenergic projections originate mainly in the locus coeruleus of the brainstem; they extend to multiple brain regions, as shown here, and regulate mood, arousal, cognition, and other functions. Descending noradrenergic projections extend down the spinal cord and regulate pain pathways. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

arise from the lateral tegmental norepinephrine cell system also in the brainstem. They regulate mood, arousal, cognition, and many other functions. Spinal projections arise from noradrenergic cell bodies in the lower (caudal) parts of the brainstem neurotransmitter center and regulate pain pathways. Ascending noradrenergic pathways arise along the middle and top (rostral) end of the brainstem centers and find their projections terminating diffusely throughout the brain, including most of the same places where serotonin pathways terminate; however, there are few noradrenergic projections to the striatum/nucleus accumbens (compare to Figure 7-10).

Serotonin

The major serotonin projections are shown in Figure 7-10; they arise from several clusters of discrete brainstem nuclei in the brainstem neurotransmitter center. The upper (rostral) nuclei include the dorsal and medial raphe as well as the nucleus linearis and the raphe pontis. These diffusely innervate most of the brain areas indicated, including the cerebellum, and regulate a wide range of functions from mood, to anxiety, to sleep, and many others. The lower (or caudal) serotonin nuclei comprise the raphe magnus, raphe pallidus, and raphe obscurus and have more limited projections to the cerebellum, brainstem, and spinal cord, where they may regulate the pain pathways.

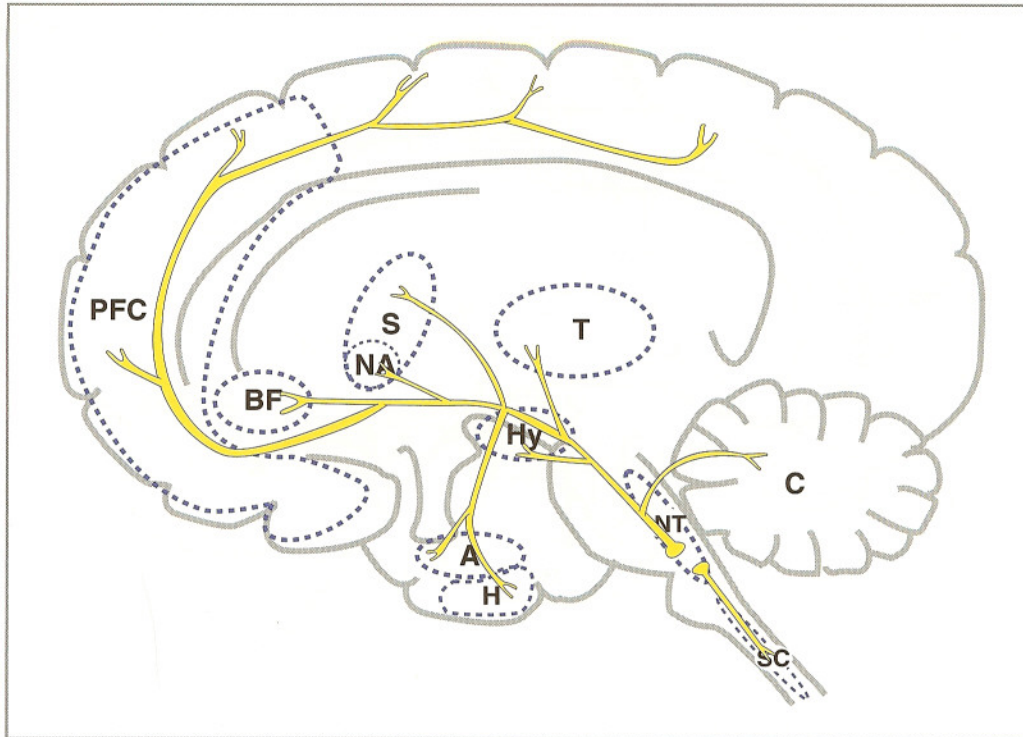


FIGURE 7-10 Major serotonin projections. Major neurotransmitter projections, part 3: serotonin. Like norepinephrine, serotonin has both ascending and descending projections. Ascending serotonergic projections originate in the brainstem and extend to many of the same regions as noradrenergic projections, with additional projections to the striatum and nucleus accumbens. These ascending projections may regulate mood, anxiety, sleep, and other functions. Descending serotonergic projections extend down the brainstem and through the spinal cord; they may regulate pain. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

Acetylcholine

Two sets of acetylcholine projections are shown in Figure 7-11, where they arise from the brainstem neurotransmitter center, and in Figure 7-12, where they arise from the basal forebrain. Some of the cell bodies for acetylcholine are not shown, including those in the striatum and some of those in the brainstem that innervate oculomotor and preganglionic autonomic neurons. Those cholinergic neurons arising from the brainstem neurotransmitter center that travel along with the monoaminergic neurons (Figures 7-8, 7-9, and 7-10) to innervate many brain areas are shown in Figure 7-11; they may regulate arousal, cognition, and many other functions. Four small nuclei in the brainstem supply this ascending cholinergic innervation.

A second and perhaps more prominent site of cholinergic cell bodies innervating the brain arise in a complex of nuclei in the basal forebrain (Figure 7-12). This includes an area called the basal nucleus, or sometimes the nucleus basalis (of Meynert), as well as the medial septal nucleus and the diagonal band (all indicated as BF, for basal forebrain, in Figure 7-12). These cholinergic fibers are thought to have a prominent role in memory.

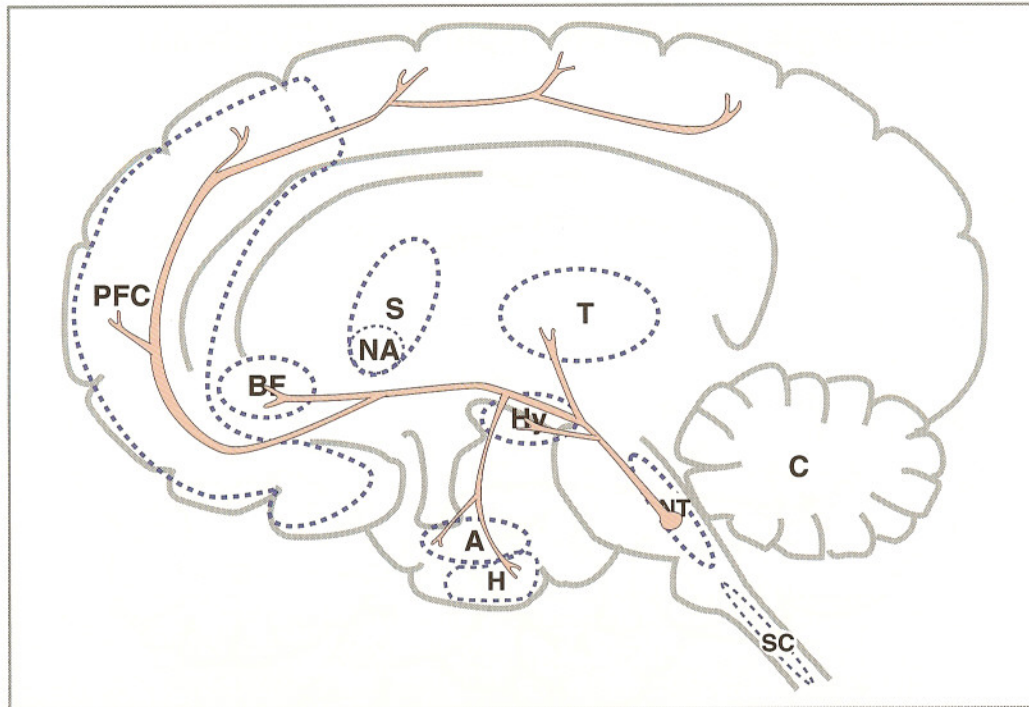


FIGURE 7-11 Major acetylcholine projections via brainstem. Major neurotransmitter projections, part 4: acetylcholine via brainstem. Acetylcholine projections originating in the brainstem extend to many brain regions, including the prefrontal cortex, basal forebrain, thalamus, hypothalamus, amygdala, and hippocampus. These projections may regulate arousal, cognition, and other functions. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

Histamine

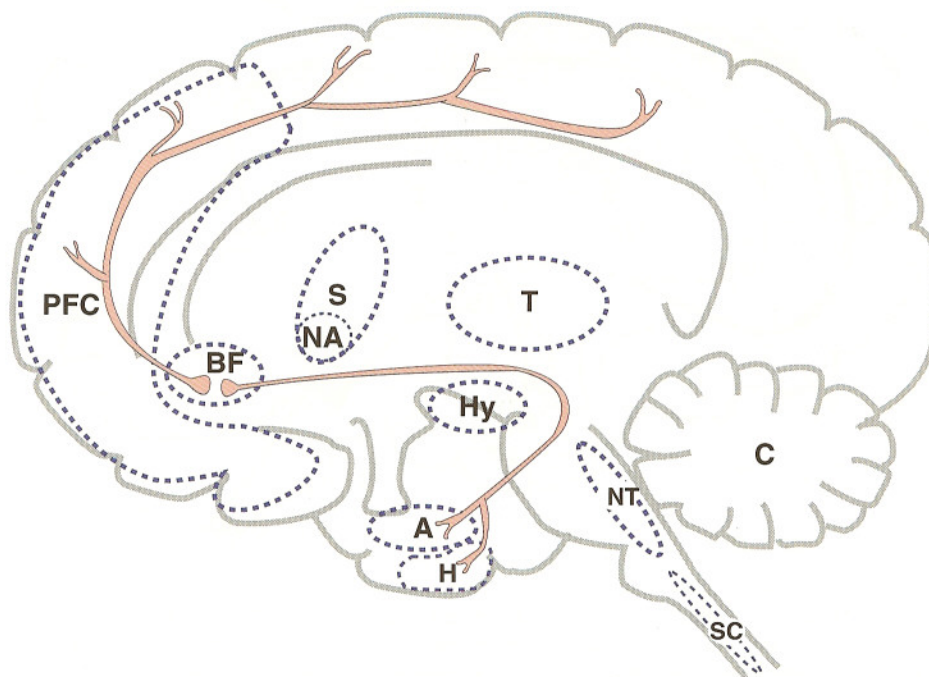
The final set of neurotransmitter pathways illustrated here are those for histamine (Figure 7-13). This interesting neurotransmitter arises from a single small area of the hypothalamus known as the tuberomammillary nucleus (TMN), which is also part of the “sleep-wake switch” and thus plays an important part in arousal, wakefulness, and sleep. The TMN is a small bilateral nucleus that provides histaminergic input to most brain regions and to the spinal cord.

Linking it all together into functional loops

Corticocortical circuits

As we have stated above, cortical circuits provide the engine for the brain’s behavioral and functional outputs. Circuits process information and then act on that information by linking neurons together into functional loops. One type of functional loop is a cortex-to-cortex circuit, where one part of the cortex talks to another, a so-called corticocortical interaction (Figure 7-14A). For example, pyramidal cells in one part of the prefrontal cortex link to pyramidal cells in another part of the prefrontal cortex. These connections utilize glutamate output from one pyramidal cell’s axon directly onto the dendritic tree of another pyramidal cell.

Cholinergic Projections from Basal Forebrain



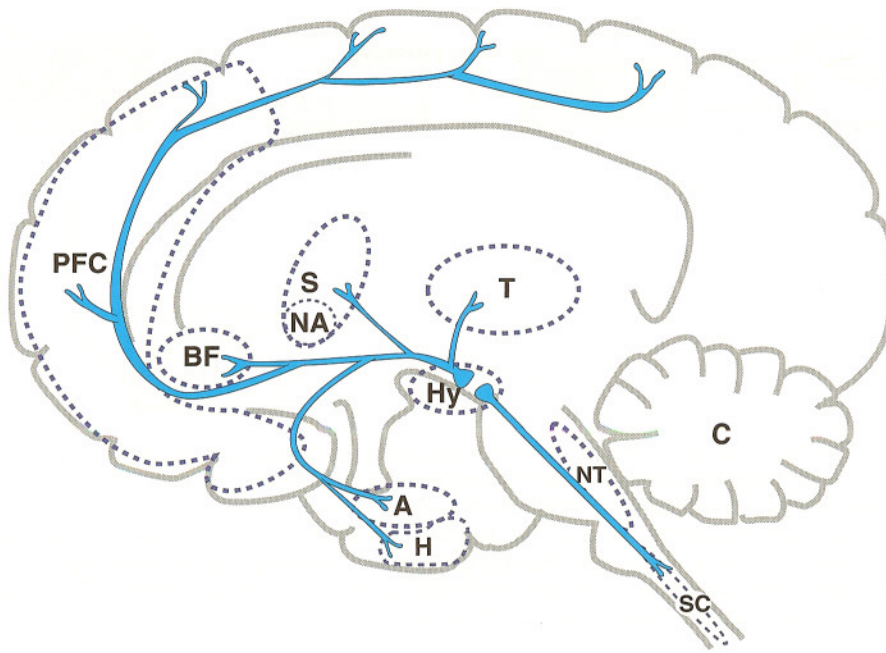
Important cholinergic neurons in the basal forebrain project to the cortex, hippocampus, and amygdala.

FIGURE 7-12 Major acetylcholine projections via basal forebrain. Major neurotransmitter projections, part 5: acetylcholine via basal forebrain. Cholinergic neurons originating in the basal forebrain project to the prefrontal cortex, hippocampus, and amygdala; they are believed to be involved in memory. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

Both cortical areas can be “tuned” by input from below: namely, neurotransmitter input arriving from neurotransmitter centers to innervate these very same pyramidal cells (Figure 7-14B). This is an example of how circuits allow a neurotransmitter not only to directly influence a neuron but also – by virtue of neuronal connections within a circuit – to affect a third neuron through an intermediary. That is, blue dopamine input to prefrontal cortex (PFC) area 1 in Figure 7-14B not only directly influences PFC area 1, symbolically turning it blue, but also has an indirect impact on PFC area 2 through the connections of PFC area 1 with PFC area 2. Likewise, pink acetylcholine input directly influences PFC area 2, symbolically turning it pink, yet this indirectly influences PFC area 1 as well.

Some of the more important corticocortical circuits and connections involving the prefrontal cortex are shown in Figure 7-15. Not all areas have robust, bilateral interactions with each other. For example, DLPFC has relatively sparse direct connections with limbic

Histaminergic Projections from the Hypothalamus



The histamine center is in the hypothalamus (TMN, tuberomammillary nucleus), which provides input to most brain regions and the spinal cord.

FIGURE 7-13 Major histamine projections. Major neurotransmitter projections, part 6: histamine. Histamine neurons arise from the tuberomammillary nucleus of the hypothalamus and project widely throughout the brain and to the spinal cord. Histamine is predominantly involved in sleep and wakefulness. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

structures such as amygdala and hippocampus. Thus, some brain areas must go through a second area in order to influence a third area. These corticocortical interactions are discussed in relation to specific psychiatric symptoms – ranging from fear to attention, memory, problem solving, impulses, and emotions – in chapters dealing with specific psychiatric disorders.

Cortico-striatal-thalamic-cortical circuits

Another important cortical circuit is called the “CSTC loop” – the cortico-striatal-thalamic-cortical loop. This circuit allows information to be sent “downstream” and out of the cortex, yet the cortex gets feedback on how that information was processed (Figure 7-16A). Prefrontal cortex projects to the striatal complex and then to the thalamus. Both the

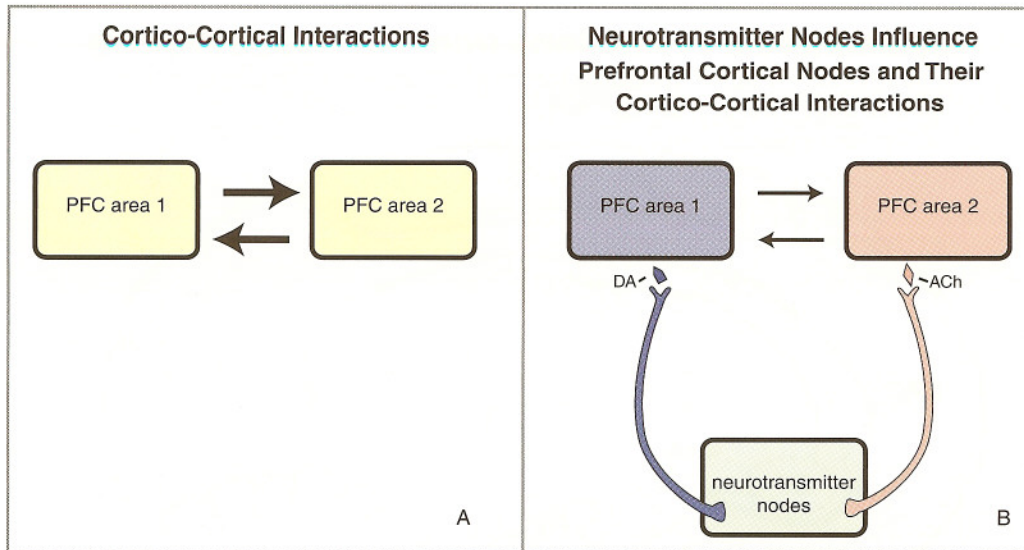


FIGURE 7-14 Cortico-cortical interactions. Information from different brain regions is processed and communicated via neuronal interconnections that form functional loops, or circuits. One type of functional loop is a cortex-to-cortex circuit, or corticocortical interaction (A). Corticocortical interactions can also be mediated by input from neurotransmitter nodes (B). As shown in panel B, dopaminergic projections directly modulate activity in prefrontal cortex (PFC) area 1 – depicted as this area turning blue – while indirectly modulating activity in PFC area 2 via its interaction with PFC area 1. Similarly, cholinergic projections directly modulate PFC area 2 – shown as this area turning pink – while indirectly modulating PFC area 1.

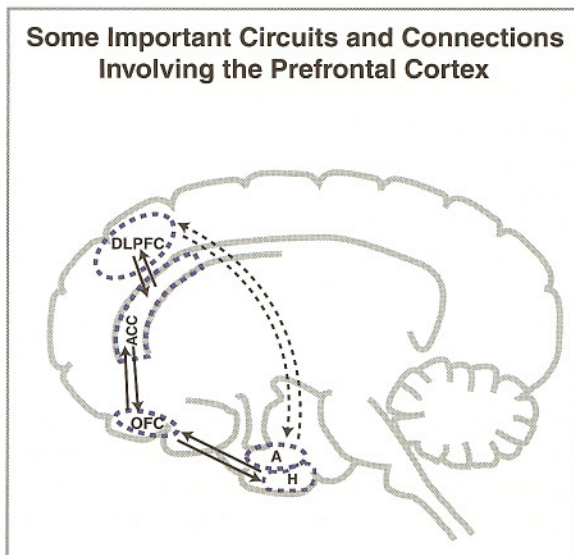


FIGURE 7-15 Key cortico-cortical circuits. Several important prefrontal corticocortical circuits are shown here. The anterior cingulate cortex (ACC) has corticocortical interactions with the dorsolateral prefrontal cortex (DLPFC) and the orbital frontal cortex (OFC). The OFC, in turn, has corticocortical interactions with the hippocampus. The DLPFC has only sparse direct connections with the amygdala and hippocampus.

striatum and the thalamus are topographically organized to interact only with specific areas of the cortex. The loop through the striatum may have a synapse through another part of the striatal complex before it leaves to go to the thalamus. The thalamus relays back to the original area of prefrontal cortex, sometimes right back to the original pyramidal cell.

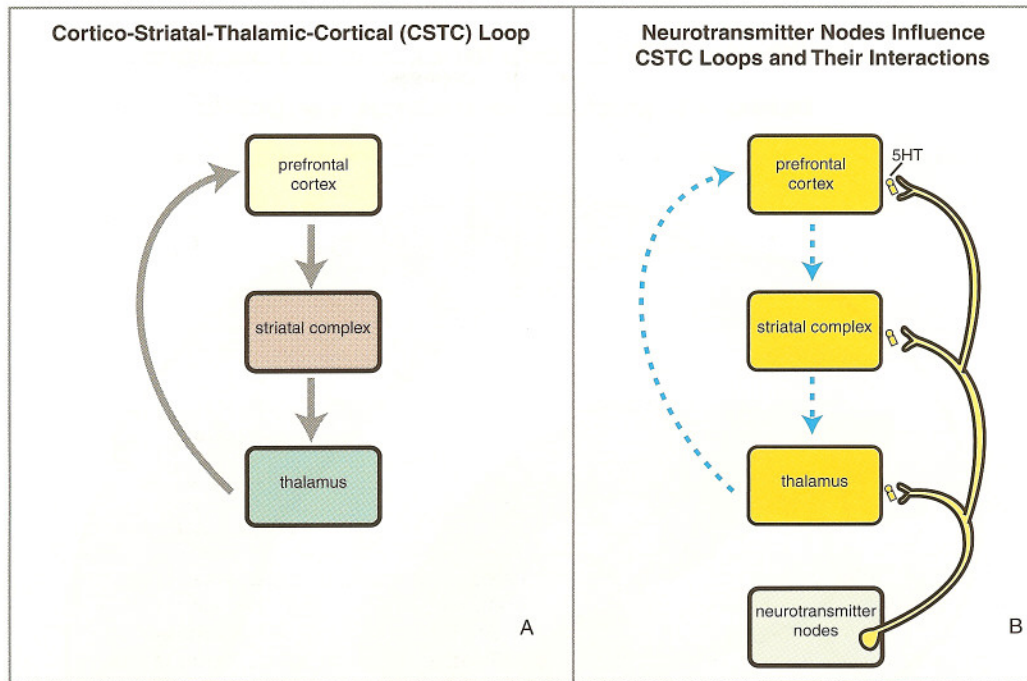


FIGURE 7-16 Cortico-striatal-thalamic-cortical loop. An important circuit is the cortico-striatal-thalamic-cortical (CSTC) loop. The prefrontal cortex projects to the striatal complex, which projects to the thalamus, which feeds back to the prefrontal cortex (**A**). The CSTC loop can be modulated by neurotransmitter nodes that project to the cortex, striatum, or thalamus (**B**). In panel B, serotonin projects to all three regions (depicted as the three regions turning yellow) and inhibits output (indicated by dotted lines connecting the regions).

Neurotransmitters have three chances to influence CTSC loops, since many neurotransmitters innervate all three levels of a CSTC loop (Figure 7-16B). Shown here is an example of serotonin projections arising from their brainstem neurotransmitter nodes and innervating the thalamus, striatal complex, and prefrontal cortex. Releasing serotonin within the CSTC loop symbolically turns all three areas yellow, with inhibition of output at all levels indicated by dotted lines connecting the CSTC loop in Figure 7-16B. This is contrasted with no yellow serotonin influence on these brain areas and fully functioning outputs within the CSTC loop in Figure 7-16A.

A look at how CSTC loops might appear in a three-dimensional brain where you can see through the cortex is shown in Figures 7-17 through 7-21. Each of these serves as an example of the principle of topographical representation of function. Thus, in Figure 7-17, the cortical engine is in the *dorsolateral prefrontal cortex* (DLPFC), projecting to the top (rostral) part of the caudate within the striatal complex, then to the thalamus, and right back to DLPFC. Loops like this are thought to regulate executive functions, problem solving, and cognitive tasks such as representing and maintaining goals and allocating attentional resources to various tasks.

However, the very same type of loop arising out of the *dorsal anterior cingulate gyrus* (ACC) modulates a very specific cognitive function – namely, selective attention. The dorsal ACC evaluates functions such as self-monitoring of performance. In this case, a pyramidal cell now in dorsal ACC projects to a different part of the striatal complex, near the bottom

Hypothetical CSTC Loop for Executive Functions

DLPFC → Striatum → Thalamus → DLPFC

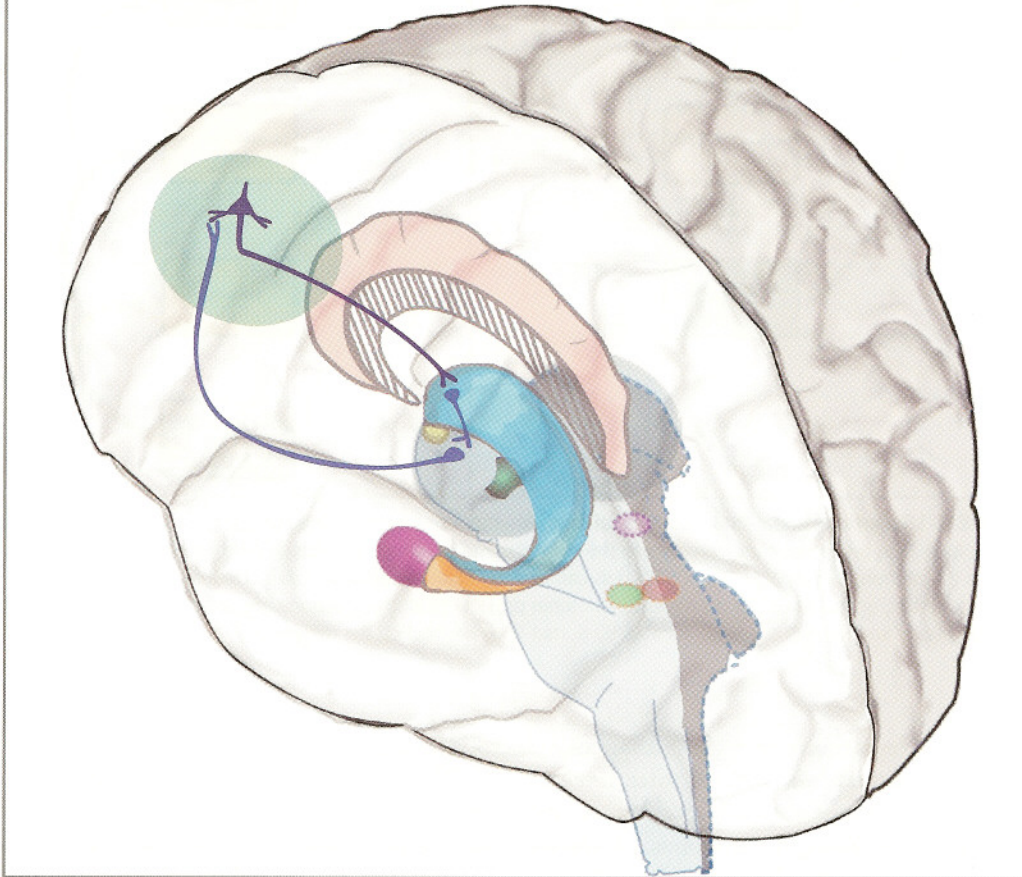


FIGURE 7-17 Cortico-striatal-thalamic-cortical loop: executive function. There are many cortico-striatal-thalamic-cortical (CSTC) loops, depending on which prefrontal region is involved as well as where in the striatum and thalamus the neurons project. This figure depicts the hypothetical CSTC loop for executive functions, which involves the dorsolateral prefrontal cortex (DLPFC) and the rostral (top) part of the caudate within the striatal complex.

(or ventral) part of it, then to a different area of thalamus, and back to dorsal ACC (Figure 7-18).

Yet a third CSTC loop is shown in Figure 7-19, with the pyramidal cell engine lying in the *subgenual or ventral part of the ACC* and then projecting to a part of the striatal complex known as the nucleus accumbens; from there it extends to the thalamus and then back to subgenual ACC (Figure 7-19). This loop is thought to regulate emotions, including depression and fear.

A fourth CSTC loop is represented in Figure 7-20, starting with pyramidal output from the *orbital frontal cortex*, to the ventral part of the caudate nucleus in the striatal complex,

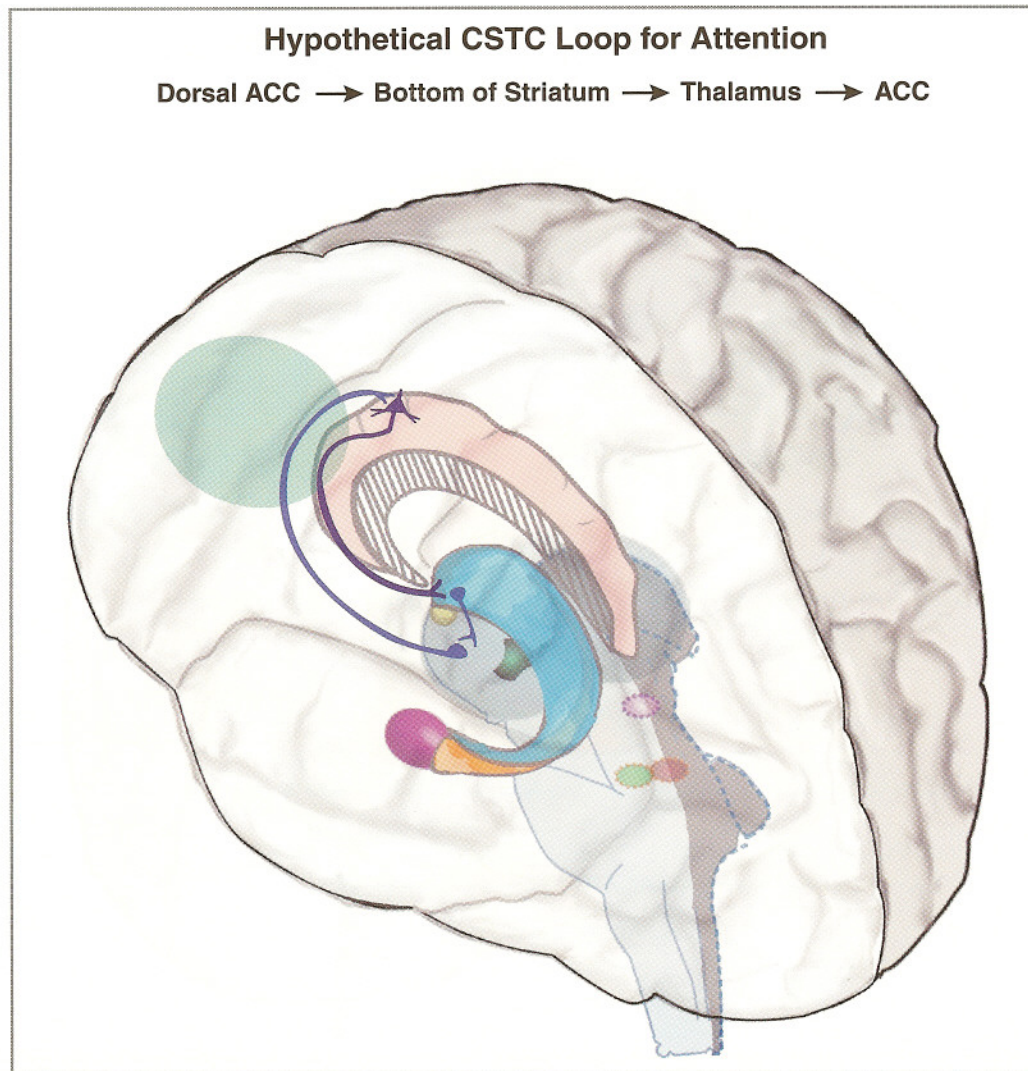


FIGURE 7-18 Cortico-striatal-thalamic-cortical loop: attention. Attention is hypothetically modulated by a cortico-striatal-thalamic-cortical (CSTC) loop arising from the dorsal anterior cingulate cortex (ACC) and projecting to the bottom of the striatum, then the thalamus, and back to the dorsal ACC.

to the thalamus, and back to OFC. Cortical loops from this brain area seem to regulate impulsivity and compulsivity.

Finally, a fifth CSTC loop starts in the *supplemental motor area of prefrontal motor cortex*, projects to the putamen in the lateral part of the striatal complex, then to the thalamus, and back to premotor cortex (Figure 7-21). These loops may modulate motor behavior such as hyperactivity, psychomotor agitation, and psychomotor retardation.

CSTC loops are a very good example of how cortical engines not only drive neuronal structures throughout the brain while receiving feedback from them, but how different functions are regulated by different topographical brain areas. One brain area does not necessarily regulate just one function, and any given function is not necessarily regulated

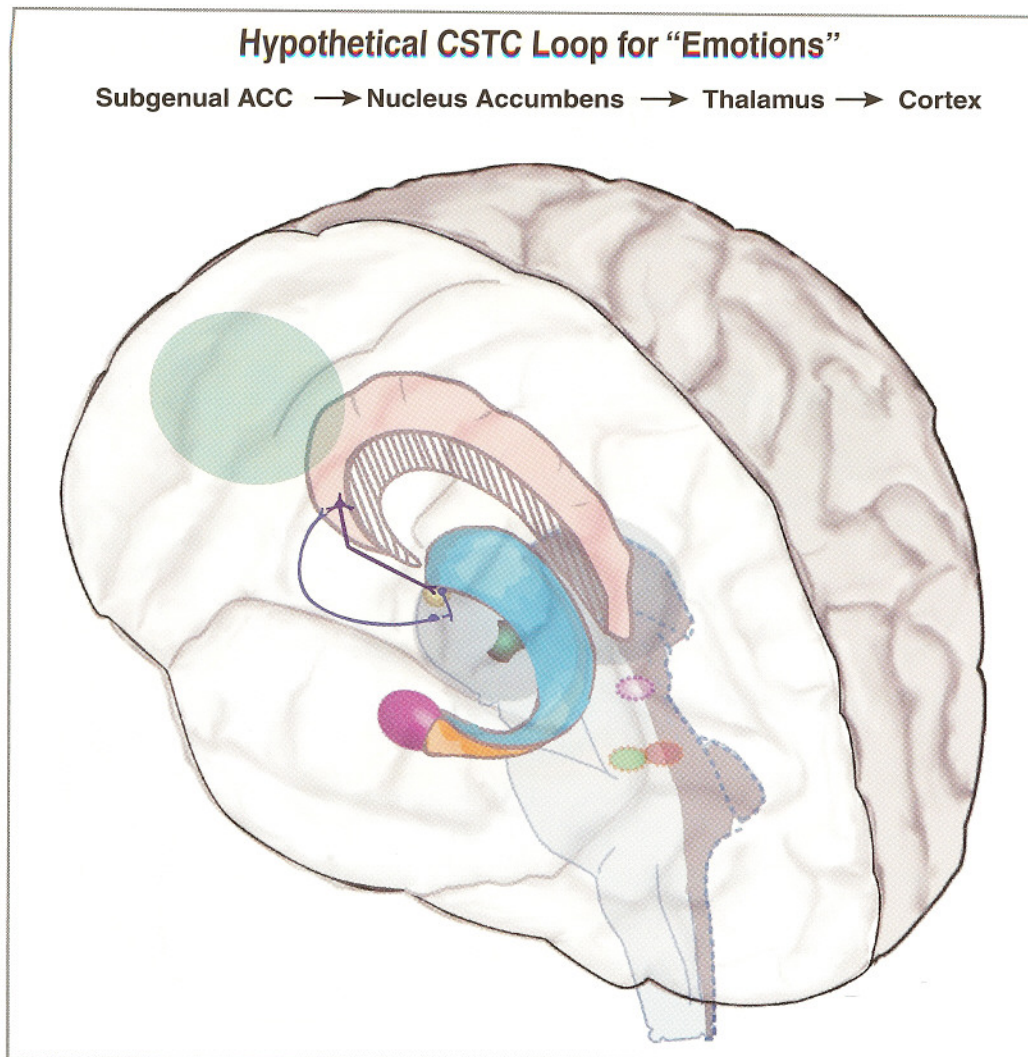


FIGURE 7-19 Cortico-striatal-thalamic-cortical loop: emotion. Emotion is hypothetically modulated by a cortico-striatal-thalamic-cortical (CSTC) loop originating in the ventral, or subgenual, anterior cingulate cortex (ACC) and projecting to the nucleus accumbens, then the thalamus, and back to the subgenual ACC.

by just one dedicated brain area. However, these notions of brain topography are useful to keep in mind when examining functional brain imaging of patients and their specific symptoms.

Pyramidal cells as drivers of cortical circuits

Each of the CSTC loops shown in Figures 7-17 through 7-21 starts and ends with a pyramidal cell in the cortex. Since pyramidal cells drive the engine of cortical circuits, influencing these neurons with drugs that alter neurotransmitter input or output from these cells has a critical role in psychopharmacology. Thus, it is useful to understand a bit about what regulates these interesting and unusual looking cortical neurons.

Hypothetical CSTC Loop for Impulsivity/Compulsivity

OFC → Bottom of Caudate → Thalamus → OFC

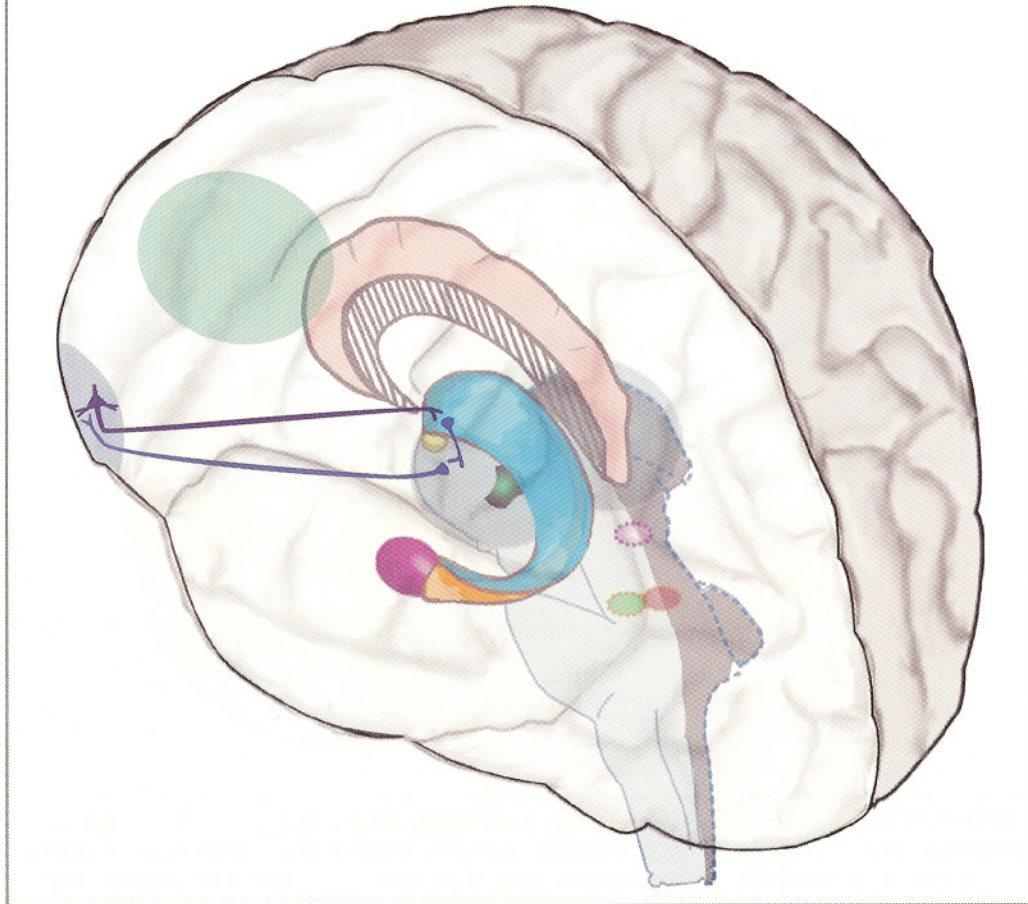


FIGURE 7-20 Cortico-striatal-thalamic-cortical loop: impulsivity. Impulsivity and compulsivity are associated with a cortico-striatal-thalamic-cortical (CSTC) loop that involves the orbital frontal cortex, the bottom of the caudate, and the thalamus.

Pyramidal cell excitatory outputs

Remember that pyramidal cells are discussed in Chapter 1, and are shaped like they are sitting as a triangular pyramid, each having an extensively branched spiny apical dendrite and shorter basal dendrites, as well as a single axon emerging from the basal pole of the cell body (Figure 1-2A, 1-2B, and 1-22 through 1-25).

The cortex is a series of layers or laminae, and pyramidal cells are located in four of the six cortical laminae (Figure 7-22). Where a pyramidal cell sends its output depends upon where it sits in the cortical lamina. Thus, corticocortical outputs come from pyramidal cells residing in lamina 2 or 3 (Figure 7-22). On the other hand, cortical outputs from lamina 5 drive the engine for the CSTC loops to striatum.

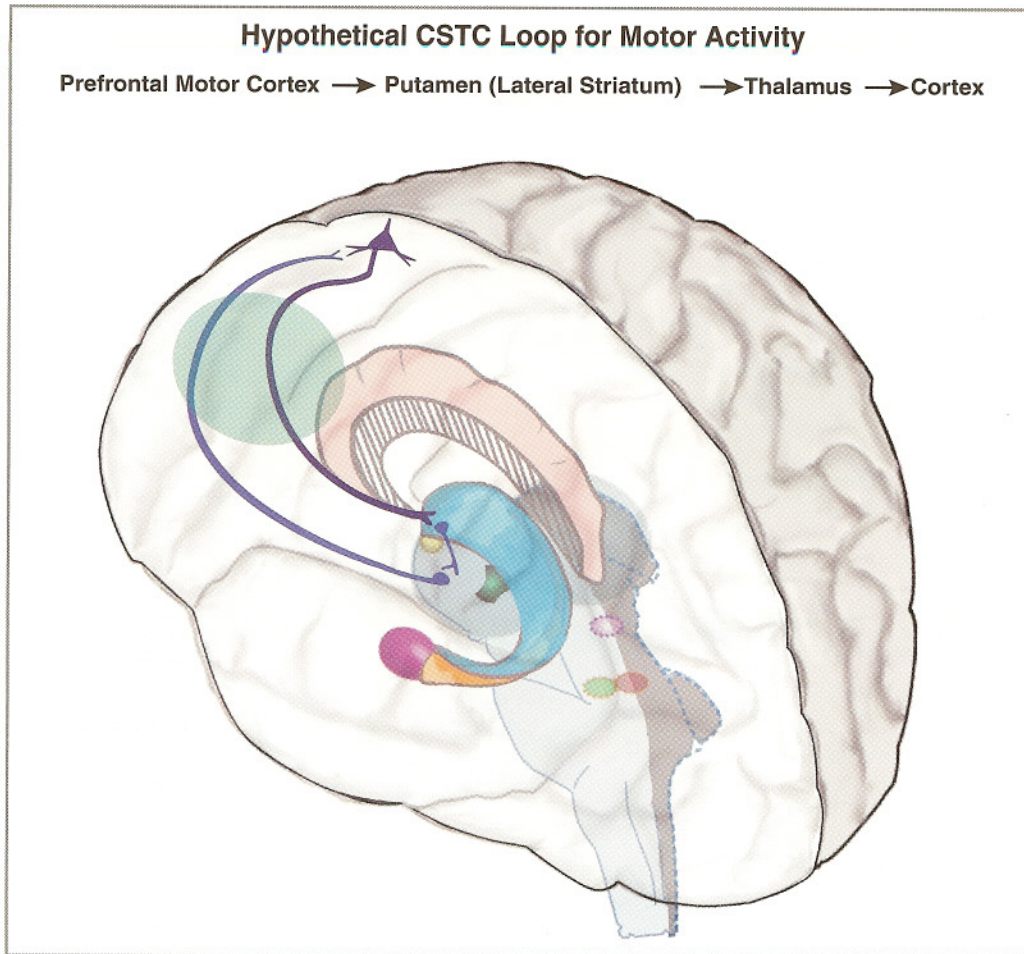


FIGURE 7-21 Cortico-striatal-thalamic-cortical loop: motor activity. Motor activity, such as hyperactivity and psychomotor agitation or retardation, can be modulated by a cortico-striatal-thalamic-cortical (CSTC) loop from the prefrontal motor cortex to the putamen (lateral striatum) to the thalamus and back to the prefrontal motor cortex.

Still other cortical circuits start from pyramidal neurons in lamina 5, which project to the brainstem, or from pyramidal neurons in lamina 6, which project to the thalamus (Figure 7-22). The neurotransmitter output of most pyramidal neurons is glutamate.

Pyramidal cell inhibitory inputs

Pyramidal neurons in the cortex also have many *inputs* from various brain areas. Those from nearby GABAergic inhibitory interneurons are shown in Figure 7-23. The structures of these neurons are also described in Chapter 1 and shown there as basket neurons in Figures 1-3A and 1-3B, as double bouquet neurons in Figures 1-4A and 1-4B, and as chandelier neurons in Figures 1-7A and 1-7B. Now we see these same neurons functioning as GABAergic interneurons in the cortex, innervating cortical pyramidal neurons with their inhibitory input (Figure 7-23). Thus, a red basket neuron is shown in Figure 7-23, on the left, with inhibitory GABA input to the pyramidal neuron's cell body, or soma. At the top of Figure 7-23, a blue double bouquet neuron is shown providing GABAergic inhibitory

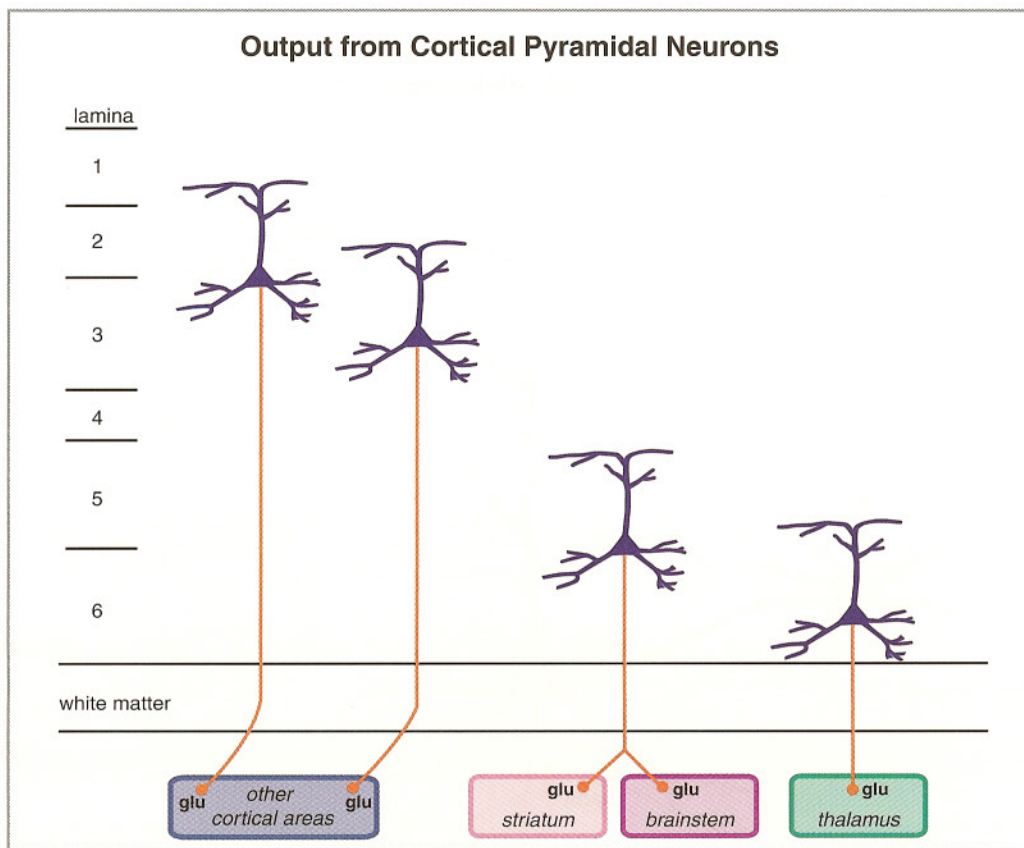


FIGURE 7-22 Output from cortical pyramidal neurons. Cortico-striatal-thalamic-cortical loops begin and end with a pyramidal neuron in the cortex. These pyramidal cells are located in various laminae, or layers, of the cortex, which influences the direction in which they send their output. Cortical pyramidal neurons located in laminae 2 and 3 send output to other cortical areas; those located in lamina 5 send output to the striatum and brainstem; and those in lamina 6 send output to the thalamus. The neurotransmitter output of all cortical pyramidal neurons is glutamate.

input to the end of an apical dendrite on the pyramidal neuron. There is even a second blue double bouquet neuron on the right, inhibiting the double bouquet neuron on the left (Figure 7-23). This arrangement has the net effect of “inhibiting the inhibition,” or “disinhibiting” the pyramidal neuron, with the second double bouquet neuron thus canceling the effect of the inhibitory input of the first. Finally, a green chandelier neuron innervates the initial segment of the axon, also known as the axon hillock of the pyramidal neuron (Figure 7-23). As explained in Chapter 1, this type of inhibitory chandelier GABAergic input to the axon hillock exerts powerful control over the output of that pyramidal cell, possibly even determining whether or not that pyramidal axon will fire an action potential. One can readily see that there are many opportunities to exert inhibitory control on a pyramidal neuron as it ranges throughout the cortex, and that the presence or absence of GABA tone on the pyramidal neuron can have profound influence on the ability of that cortical pyramidal cell to serve as the driver of a cortical engine that delivers the behavioral programs of the brain.

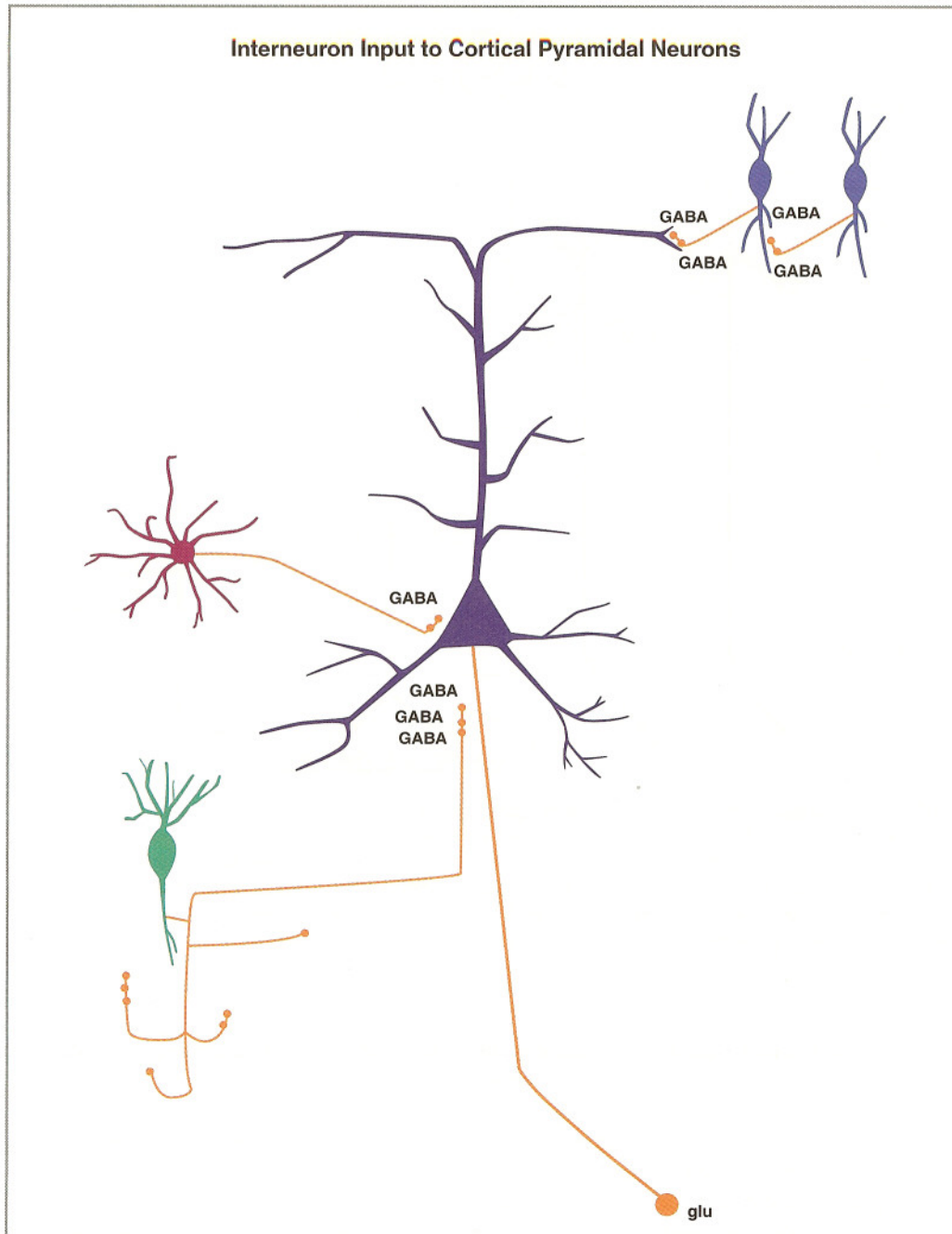


FIGURE 7-23 Interneuron input to cortical pyramidal neurons. Cortical pyramidal neurons receive inputs from many different brain areas. Shown here are different types of GABAergic inhibitory interneurons: a GABAergic basket neuron (red, left), providing inhibitory input to the pyramidal neuron's soma; a GABAergic chandelier neuron (green, bottom), providing inhibitory input to the axon hillock; and two double bouquet neurons (blue, right), providing input to a dendrite of the pyramidal neuron. The left double bouquet neuron provides direct inhibitory input to the pyramidal neuron; however, it itself is inhibited by the right double bouquet neuron, which thus inhibits the inhibition – or disinhibits – the actions of the left double bouquet neuron.

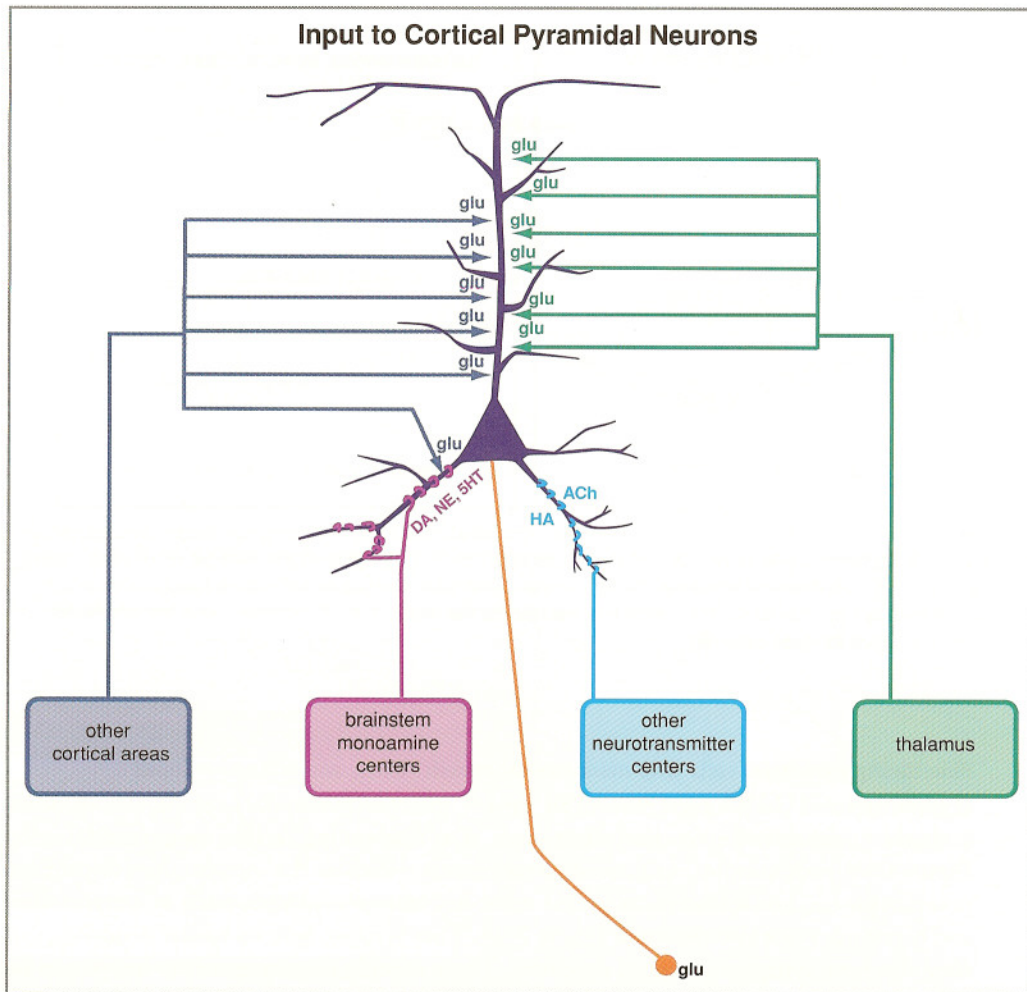


FIGURE 7-24 Input to cortical pyramidal neurons. Shown here are different inputs to cortical pyramidal neurons. Glutamatergic excitatory projections from thalamus and cortical areas synapse with apical dendrites, while monoamines and other neurotransmitters synapse with basilar dendrites (shown) as well as apical dendrites. These neurotransmitter projections can be either inhibitory or excitatory, depending on the neurotransmitter and the receptor involved; however, their actions may be more subtle than those of GABA and glutamate.

Pyramidal cell excitatory inputs

Cortical pyramidal neurons also receive many *excitatory* inputs, coming predominantly to synapse with the apical (top) dendrites and utilizing the excitatory neurotransmitter glutamate (Figure 7-24). These inputs arise from other cortical areas (corticocortical inputs) and from the thalamus (corticothalamic inputs), all utilizing glutamate as neurotransmitter. Thus it is easy to see how the cortical pyramidal neuron can either be excited by these long-distance glutamate inputs, shown in Figure 7-24, or inhibited by short-distance GABA inputs, shown in Figure 7-23.

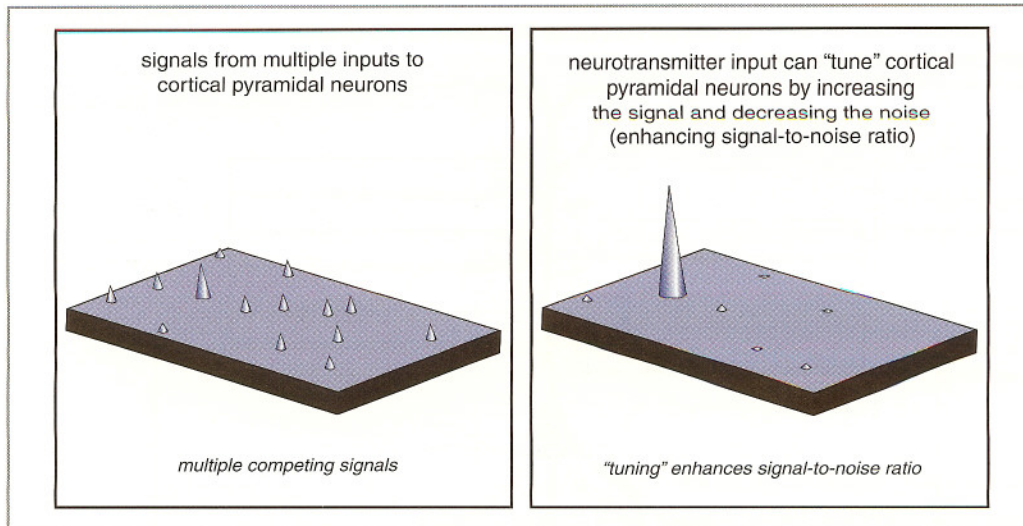


FIGURE 7-25 Signal-to-noise ratio. Cortical pyramidal neurons receive signals from multiple competing inputs, forming “noise” (A). Monoamine input can “tune” cortical pyramidal neurons to enhance a specific signal that should be prioritized by increasing that signal and decreasing the others (i.e., the noise) – in other words, by enhancing the signal-to-noise ratio (B).

Fine tuning pyramidal cells with monoamine, acetylcholine, and histamine input

If glutamate and GABA exert more of an “on-off” effect on pyramidal neurons, monoamines and other neurotransmitters may exert more of a “fine-tuning” action on pyramidal cells. Inputs from various other neurotransmitter centers – such as the monoamines dopamine, norepinephrine, and serotonin as well as other key neurotransmitters such as acetylcholine and histamine – are also shown in Figure 7-24. They synapse here on basilar dendrites, but they also have synapses on apical dendrites. These specific neurotransmitter inputs can be either excitatory or inhibitory, depending on the neurotransmitter and the specific receptor subtype expressed on the pyramidal cell at a given synapse. More often, however, their actions are more subtle than just turning a neuron on or off.

Specifically, monoamines may be particularly helpful in optimizing the output of pyramidal neurons. That is, under many circumstances, the multiple competing outputs all appear at once and can be interpreted as if they are all just “noise” (Figure 7-25A). However, graded degrees of monoamine input can “tune” a pyramidal neuron to a signal that it must prioritize while allowing it to ignore other competing signals (Figure 7-25B). This is sometimes called increasing the signal and decreasing the noise, or enhancing the signal-to-noise ratio.

Just as in tuning a guitar string, more is not always better (Figure 7-26). That is, neurotransmitter input to cause receptor stimulation may optimize pyramidal neuronal functioning, but only to a point. Too much tension on a guitar string can make it sound just as out of tune as too little. The same is apparently true for neurotransmitters such as dopamine, where finding the optimal amount of receptor stimulation is what is needed for optimal tuning of signal-to-noise ratios. Thus, for optimal tuning, some “out of tune” neurons need more neurotransmitters and others need less (Figure 7-26).

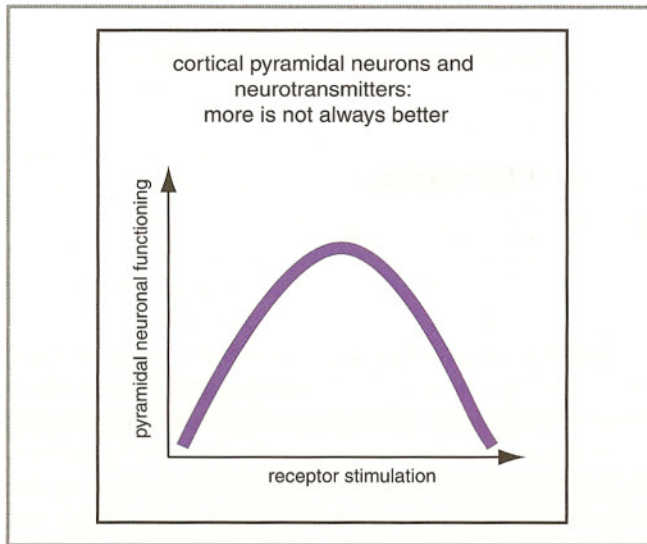


FIGURE 7-26 Pyramidal neuronal function and receptor stimulation. Receptors can be both under- and overstimulated. Finding the optimal amount of receptor stimulation is necessary for optimal tuning of signal-to-noise ratios. This means that in some cases, neurotransmission needs to be increased, but in other cases it may need to be decreased.

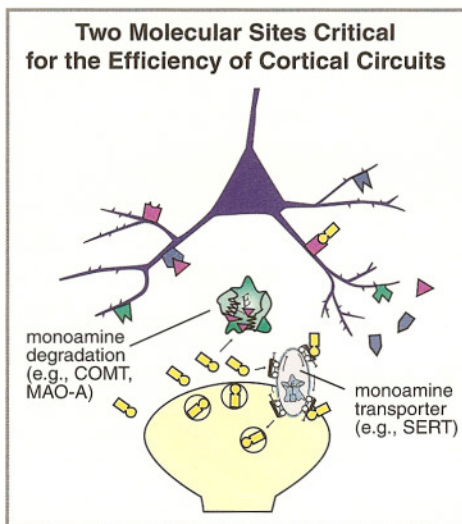


FIGURE 7-27 Molecular sites for regulating monoamines. Two molecular sites important for regulating monoamines and thus for maintaining efficiency of cortical circuits are (1) the enzymes that break down monoamines and (2) monoamine transporters. Examples of enzymes include monoamine oxidase A (MAO-A) and catechol-O-methyl transferase (COMT). Examples of monoamine transporters include the serotonin transporter (SERT).

Regulating the monoamine “tuners”

Two of the key regulators of the monoamines that help to set the tone of a pyramidal neuron are shown in Figure 7-27 – namely, the presynaptic transporters for monoamines and the catabolic enzymes for monoamine degradation. Interestingly, genetic control of these regulators of monoamines also profoundly affects the efficiency of information processing; there are two examples of this that can now be measured in living humans with psychiatric disorders. These are the neuroimaging consequences of variants of the genes for the serotonin transporter (SERT) and for the dopamine metabolizing enzyme COMT (catechol-O-methyl transferase). Both are discussed extensively in various chapters on imaging genetics and different psychiatric disorders.

Summary

Modern psychopharmacology is being transformed by the systematic mapping of psychiatric symptoms to specific brain regions and by the ability to image these regions and their functioning or malfunctioning in patients. Neurons in the cortex are connected to many other neurons, forming cortical circuits that serve as engines for brain functions. Prefrontal cortex is especially important to behaviors, with executive functioning localized to dorsolateral prefrontal cortex, selective attention to dorsal parts of the anterior cingulate, impulsivity to orbital frontal cortex, emotions to ventromedial prefrontal cortex, and motor control to supplementary motor areas. Loops of neurons out of one cortical area and into another (corticocortical circuits) as well as out of cortex to the striatum, thalamus, and back to cortex (cortico-striatal-thalamic-cortical circuits, or CSTCs) are examples of key neuronal networks that have the capacity to transform simple inputs into complex outputs which ultimately mediate brain functions and behaviors. Multiple neurotransmitters influence cortical circuits at every node in the circuit; this provides an opportunity both for genes to influence information processing in circuits by regulating neurotransmitter functioning and for psychopharmacologists to influence symptoms in circuits by administering drugs that alter neurotransmitter actions in specific brain circuits.