

Chapter 4. Enter the Big Three

Major Points

- **The Big Three neurotransmitter systems (ser, nore, and dop)—and drugs that affect them—turn many brain processes on and off.**
- **Ser and nore form a neurochemical yin and yang, and are the principal players in mental illness, with dop having a less important role.**
- **There is a single level of each of the Big Three throughout the brain, and the molecular receptors for ser and nore are ordinarily saturated.**
- **Introduces the concept of a ‘strength’ for each of the Big Three, which means the level of the transmitter plus the sensitivity of the circuitry to that level.**
- **Contrasts mental illness caused by abnormal Big Three strengths and that caused by dysfunctional Big Three systems.**

The current theory is based on the functions of three brain chemicals—serotonin (ser), norepinephrine (nore), and dopamine (dop), which I have referred to as the Big Three—and the circuits they affect. These are not the only chemicals in the brain, but perhaps they are the most relevant to treating mental illness and understanding mental health. Indeed, most psychiatric drugs with known mechanisms of action achieve their effects by altering one or more of these three chemical systems.

The goal of this book is not to describe how the brain works in detail, but rather how the Big Three turn some of its functions on and off. By analogy, while we may not know in detail how a computer works, we definitely know some of the things it can do, including that we can influence some of its inputs and outputs—by typing on the keyboard, clicking the mouse, and turning the power on and off. Doing so affects the internal circuitry of the computer in some manner—and we may speculate as to how—and we can observe some of the corresponding outputs, such as on the video monitor. Likewise, we can adjust the strengths of the Big Three with drugs, and observe the effects on ourselves and on others.

Fundamentals of a Synapse

The Big Three are actually neurotransmitters, or substances that neurons use to communicate with one another across gaps called synapses (see Figure 1). Before we continue, let’s discuss some of the fundamental properties of synapses, where many of these properties are shown in Figure 1. A typical synapse consists of the gap between a so-called presynaptic neuron and a so-called postsynaptic neuron. The presynaptic neuron is sending a message to the postsynaptic neuron, which is receiving the message. The message is carried by the neurotransmitter, which is a simple brain chemical that is stored in little packets called vesicles inside the presynaptic neuron. When an electrical impulse

called an action potential reaches the end of the presynaptic neuron, neurotransmitter is released into the synapse and it floats around, binding to receptors on the outside of the postsynaptic neuron (and even to receptors on the outside of the presynaptic neuron, which are called autoreceptors and can affect the rate at which the transmitter is released) in a key and lock manner. When the neurotransmitter binds to the postsynaptic receptors, this typically starts what I call an intracellular signaling cascade, which is a series of chemical reactions that take place inside the postsynaptic neuron that may help trigger an action potential with which it can communicate with the next neuron. Meanwhile, the neurotransmitter is pumped back inside the presynaptic neuron by molecules called reuptake transporters, thereby terminating the signal. In addition, a molecule called monoamine oxidase (MAO) can break down the transmitter and thereby deactivate it. For each of the Big Three, there are multiple types ('subtypes') of postsynaptic receptors, where each subtype may affect the postsynaptic neuron in a different manner, and may be present in different types of neurons and in different circuits in the brain.

Now let's examine some of the effects that Big Three drugs can have on a synapse. In general, these drugs can either affect the level of the neurotransmitter in the synapse through a variety of means; or instead activate or deactivate the postsynaptic receptors directly, thereby mimicking the effects of the transmitter. Some drugs instead enter the postsynaptic neuron and affect intracellular signaling cascades directly, and I call these intracellular drugs.

Big Three drugs that affect the level of the transmitter in the synapse do so by: increasing or decreasing presynaptic transmitter release by activating (i.e., agonizing) or deactivating (i.e., antagonizing or blocking) presynaptic autoreceptors; increasing or decreasing transmitter reuptake by binding to the reuptake transporter; or decreasing breakdown of the transmitter by binding to monoamine oxidase (MAO). For example, the drug clonidine activates nore presynaptic autoreceptors and thereby decreases the release of nore into the synapse. Prozac deactivates the ser reuptake transporter—hence the name ser reuptake inhibitor (SRI)—and thereby allows more ser to build up in the synapse. The drug Parnate, which was mentioned earlier, decreases the activity of the MAO molecule—hence the name MAO inhibitor—and thereby allows the Big Three to build up in the synapse. Big Three drugs that increase the level of the transmitter in the synapse should strengthen that transmitter system, and drugs that decrease the level should weaken that transmitter system.

Big Three drugs can also mimic the effects of the neurotransmitters themselves by binding directly to postsynaptic receptors, and either activating them (which is what transmitters do), or deactivating them. For example, the drug Zyprexa deactivates two postsynaptic receptors, the dop D2 receptor and the ser 5HT_{2A} receptor, thereby weakening both dop and ser neurotransmission. Big Three drugs that activate postsynaptic receptors should strengthen that transmitter system, and drugs that deactivate postsynaptic receptors should weaken that transmitter system.

Modulatory Neurotransmitters

Most neuroscientists think of the Big Three, especially ser and nore, as *modulatory* neurotransmitters, since they are dispersed throughout many regions of the brain and may have very general effects on brain function, where the simplest form of neural modulation may be activation or inactivation of circuits, like an 'on and off' light

switch or the volume dial on a radio. For each of the Big Three, a relatively small number of neurons located in groups (nuclei) in the brainstem are connected with widespread regions of the brain, and these neurons release the neurotransmitter to modulate the responses of millions of other neurons. (In contrast, other neurotransmitters, such as glutamate and GABA, are released in a very precise, localized manner, usually helping neighboring neurons communicate.) Because of their connections with many regions of the brain, the Big Three are poised to affect a number of brain functions, including mood, emotion, thought, sensation, learning and memory, movement, sleep, drive states, sexuality (sexual drive/orientation), and disease.

The current theory hypothesizes that ser and nore (the Big Two, if you will) are the principal players in mental illness, and that dop has a less important role. As we shall see, ser and nore can be thought of as a neurochemical yin and yang, since many of their effects on the brain are directly opposed. More is known about ser than about nore, partly because of the widespread use of ser strengthening drugs—the serotonin reuptake inhibitors (SRIs), such as Prozac and Zoloft. In this book I repeatedly refer to the ‘strengths’ of the Big Three, by which I mean the extracellular, or outside the brain cell, level of the neurotransmitter in the brain plus the sensitivity of the circuits it affects to that level. (The functioning of the Big Three presynaptic brainstem neurons in releasing these neurotransmitters therefore also plays a critical role in strength.) Based on my research I believe that different people have different genetic strengths of the Big Three, and that these strengths can be affected by drugs and other environmental factors, such as stress. A central point in this book is that the immediate future of psychiatry should involve using drugs to adjust the brain strengths of ser and nore—and in some cases, dop—closer to optimal, mid-range degrees (i.e., The Adjustment). This could improve quality of life, possibly dramatically, both for people with overt mental illness and even for people who are considered normal. In other words, when one of the Big Three is too strong or too weak, the brain is in many ways not functioning in the best possible manner, and this situation worsens when more than one of the Big Three is too strong or too weak.

Single, Systemic Levels

The current theory puts forth the idea that there is a single, systemic level of each of the Big Three, throughout the brain, and for ser and nore, that correlates with the level throughout the rest of the body. For example, in a given person I don’t think there are very different levels of ser in different areas of the brain. And since ser is also found in the gut, I think someone with a high level of ser in the brain will also have a high level of ser in the gut. Likewise, someone with a high level of nore in the brain will also have a high level of nore in the heart.

In support of this single, systemic level hypothesis, I think certain personality traits (see Chapter 7), which may be affected by different Big Three circuits, tend to coexist within a given person. This coexistence is consistent with a particular level of ser, for example, having a consistent effect on these different brain circuits. The single, systemic hypothesis is also consistent with My Case Study, which indicates that the brain level of nore (in making me hypomanic) correlates with the heart level of nore (in simultaneously causing my arrhythmia), and that the brain level of ser (in having an antidepressant effect during my bright light therapy) correlates with the gut level of ser (in simultaneously upsetting my gut). This hypothesis is also consistent with the neural

integrator idea discussed in Chapter 2. However, it does not imply that everyone's circuitry is equally sensitive to the given level, or that the sensitivity of different circuits within a brain must correlate with one another, though I think this latter point tends to be the case as well. For these reasons, knowing the blood or even cerebrospinal fluid (CSF) levels of the Big Three, which researchers have been measuring for years, may not reliably indicate Big Three strengths, since one could have a low level of ser, for example, but with extremely sensitive circuitry to that level, resulting in a strong ser system that couldn't have been predicted from the level alone.

An alternative hypothesis is that there are different levels of the Big Three in different brain areas or circuits, affecting a number of traits in an independent manner. For example, there may be a high level of ser in the prefrontal cortex, affecting thought patterns in particular way, whereas there may be a low level of ser in sensory cortex, affecting sensory perception in a different way. If this alternative hypothesis turns out to be true—and it is widely believed among researchers and psychiatrists, though I am confident that it is not true—it will take a lot longer for us to figure out how the Big Three work. Along these lines, I'm not sure psychiatric researchers want to hypothesize that there are single, systemic Big Three levels because it may be bad for getting grants!

Saturation of Ser and Nore, with a Safety Factor

The ser and nore (and possibly dop) levels seem to build as the day wears on, and are reabsorbed during sleep. This may explain the diurnal (within the day) fluctuation in mood during some cases of major depression, as well as the antidepressant effect of sleep deprivation. This is also consistent with experimental evidence indicating that brainstem ser and nore neurons actively fire action potentials (and thereby release neurotransmitter) while animals are awake, fire less frequently during NREM (non-rapid eye movement) sleep, and don't fire at all during REM sleep.

It also appears that the ser and nore postsynaptic circuitry is ordinarily saturated, or filled to capacity, with these two neurotransmitters, whereas the dop circuitry is not. This means that somewhere in the circuitry raising the level of ser or nore doesn't have any immediate effect, whereas raising the level of dop does have an immediate effect. For example, ser or nore boosting antidepressants generally don't have a noticeable effect for two weeks, whereas dop boosting drugs, such as cocaine and amphetamine, have immediate effects.

The concept of what an engineer might call a 'safety factor' applies here: the level of ser and nore *exceeds* the point of saturation of the receptor population in the postsynaptic circuitry by a certain amount. This means that all of the receptors are bound with transmitter, in a key and lock manner, but there's also some additional transmitter floating around. In other words, if the brain was 'engineered' to operate with saturated postsynaptic receptors, it's not surprising that it also has some extra transmitter floating around as a 'safety' measure, to ensure that the receptors are indeed saturated. The point of saturation plus a safety factor may occur in the receptor population at the first postsynaptic synapse, inside the first postsynaptic neuron (involving signaling cascades inside the neuron), or further along in the circuitry. Ser or nore level boosting antidepressants may upregulate the postsynaptic circuitry by increasing the number or sensitivity of postsynaptic receptors or intracellular signaling cascades after two weeks, while maintaining a safety factor. In other words, the ser or nore circuitry has been

strengthened, and the brain may maintain the safety factor throughout and after this process.

To return to the example of diurnal (within a day) mood fluctuation in some cases of major depression: perhaps stressors (which may deplete the levels of the Big Three) have eliminated the safety factor, while the postsynaptic receptor population has remained the same or diminished somewhat, and therefore mood increases as the day wears on because the unsaturated receptor population is receiving gradually increasing ser or nore input (since, as mentioned earlier in the chapter, ser and nore build as the day wears on). Different ser and nore safety factor levels may make certain people susceptible to mental illness. In other words, the smaller the safety factor the more likely that stressors will trigger mental illness.

Dysfunction and Stress

Some cases of mental illness may not be caused by abnormal strengths of the Big Three at all, but instead by a dysfunctional Big Three system. In other words, the normal functioning of the Big Three circuitry has been disrupted and needs to be reset to a healthy state. It could be that the dysfunction is due to a change in Big Three level without the postsynaptic circuitry adjusting to the change; in other words, a difference between actual level and expected level. For example, depression may in some cases involve a depleted level of one of the Big Three that the brain was not ‘expecting’, resulting in dysfunction in its circuitry. Electroconvulsive therapy (ECT) may reset dysfunctional circuits without altering Big Three levels, since it can be effective both at treating depression and mania, two conditions that may be caused by low or high Big Three levels, respectively. Another way to reset the circuitry may be to adjust Big Three strengths with level altering drugs, such as certain antidepressants.

A few more words about stress and mental illness. Stress may be a precipitating factor in many—but probably not all—cases of overt mental illness. The brainstem ser and nore neurons release these two neurotransmitters in response to certain types of stress, though exactly which types of stimuli cause these neurons to respond is an area of active research. If certain types of stressors cause massive release of ser or nore, then soon afterward there may be depleted release and diminished synaptic levels of these neurotransmitters, a phenomenon that a neuroscientist would call postexcitatory depression. The brain may ‘think’ that it still has the old level of the transmitter, and therefore there is dysfunction: a difference between the expected level and the actual level. In addition, there can be long-term activation of the body’s stress coping machinery—including activation of the hypothalamic-pituitary-adrenal (HPA) group of brain areas and release of the stress hormone cortisol—during major depression and perhaps other types of mental illness.

Continua Versus Thresholds

Now that we’ve discussed some of the properties of the Big Three, let’s briefly examine the issue of ‘continua’ versus ‘thresholds’ in mental illness. Recall that continua are things that exist as a smooth range, such as the temperature of the air, whereas thresholds are things that have an abrupt yes/no answer. Both phenomena definitely exist in the brain, and I think both can exist in cases of mental illness. My Case Study, for

example, even contains examples of continua *with* thresholds: I responded to different doses of the drugs desipramine and Zyprexa in a continuous manner, with smoothly increasing responses to increases in dose, but when Zyprexa was increased beyond a threshold dose it caused the brain freeze. Just because the levels of the Big Three and their postsynaptic receptor populations are probably at least coarsely continuous within the population of all people, doesn't mean that during mental illness the brain can't exhibit thresholds. For example, consider these apparent thresholds: people with bipolar disorder may either exhibit mood cycling or not, and people with major depression may either exhibit early morning awakenings or not. Ser or nore circuitry dysfunction may also represent a threshold. In contrast, one study has shown that attention deficit hyperactivity disorder (ADHD), or at least hyperactivity among children, is a continuum, in which essentially *everyone* becomes less physically active when given ADHD stimulant drugs. In other words, there may not be a rigid threshold that distinguishes people with ADHD from those without ADHD. And as I'll discuss in Chapter 11, mood, or more generally expanded dysthymia, may be a continuum in which essentially everyone can be made better off or at least changed by Big Three altering drugs, as in The Adjustment. Finally, the current manner of diagnosing mental illness represents a threshold: one is said to either have or not have an illness.