

## Chapter 5. Big Three Strength Interactions: The Triangle

### Major Points

- **The Big Three interact by affecting one another's strengths, illustrated by a simple diagram called 'The Triangle', where ser and nore form the base and dop forms the apex.**
- **The most important interaction is that ser and nore each strengthen dop, illustrating why certain antidepressants induce mania in people with bipolar disorder.**
- **Any drug that affects one of the Big Three is 'dirty' in that it also affects the other two.**

Based on all the research to date, I believe that ser and nore (and possibly dop) interact by affecting the same circuitry. The Big Three may also interact in another way, by affecting each other's strengths directly, and this is of practical importance to treating mental illness. These strength interactions may take place in the brainstem (where the Big Three presynaptic neurons reside), or in the cerebral cortex (where the outputs of the Big Three presynaptic neurons are received by postsynaptic neurons), and may not involve the levels of the transmitters. There is growing evidence, particularly from studies of the rodent brain, that the Big Three affect each other's strengths, but the exact nature of these interactions is not clear and neither is their importance.

I refer to the Big Three strength interactions as 'The Triangle' (see Figure 2), which is based on long-term interactions that take place over weeks or months (such as the effects of antidepressants) rather than short-term effects which take place over minutes, hours, or a few days, and have typically been observed in drug studies with animals. I do not mean to imply that the Big Three don't also interact with other neurotransmitter systems, but that The Triangle represents the principal strength interactions these three brain chemical systems have with each other.

Ser and nore form the base of The Triangle, partly because these two neurotransmitters are more similar in their brain distribution and function to one another than either is to dop. As we shall see, ser and nore appear to form a 'push-pull' pairing, since their effects on a number of characteristics and traits are directly opposed. Dop forms the apex of The Triangle. Here's the most important reason why: for individuals who suffer from bipolar disorder (manic-depressive illness), drugs that strengthen ser and drugs that strengthen nore both trigger mania. Mania is a condition in which an individual exhibits elevated mood, faster thinking, wildly ambitious (grandiose) ideas, hyperactivity, and often agitation. Since an increase in strength of either ser or nore can induce mania in a given bipolar individual, there seems to be some common factor that both of these neurotransmitters strengthen. That common factor is probably dop. Why's that? Firstly, the street drug cocaine, which strengthens dop, produces a 'high' that mimics mania, with the classic symptoms of incredible energy and feeling 'on top of the world'. Other drugs that strengthen dop, such as amphetamine and Ritalin, are capable of producing a similar

high. Secondly, dop is distributed densely in the prefrontal region of the brain, which is thought to be involved in thinking, and therefore stronger dop may speed up thinking and possibly result in more grandiose thinking.

So dop appears to be capable of being strengthened by ser and nore in bipolar individuals. In addition, depressed individuals often report that their thoughts have slowed down, and instead of having grandiose ideas they tend to have very negative ideas. Administration of ser strengthening antidepressants and nore strengthening antidepressants often reverses these thought patterns, which is consistent with dop strengthening. And even in normal individuals, administration of an antidepressant such as Prozac, which strengthens ser, can speed up thought processes and boost self-esteem—both phenomena are described in *Listening to Prozac*—and there is evidence that Prozac strengthens dop in the rodent prefrontal cortex. The new attention deficit hyperactivity disorder (ADHD) drug, Strattera, which strengthens nore, has been shown to increase prefrontal levels of dop in rodents, and this has also been shown for reboxetine, an antidepressant that strengthens nore.

These lines of evidence indicate that, in the human brain, dop is indeed strengthened when ser or nore is strengthened. In the basic diagram of The Triangle (see Figure 2), *thick plus arrows* pointing from ser and nore to dop describe this strong strengthening phenomenon. The *thin minus arrows* in the diagram indicate the opposite effect in all of the other interactions between the Big Three, weakening the neurotransmitters through what we'll call 'feedback inhibition'. This means that dop weakens both ser and nore, and that ser and nore weaken each other. As we shall see, feedback inhibition may explain several psychiatric phenomena, such as weak ser causing psychosis in some cases of schizophrenia and mania. In schizophrenia, typical antipsychotics such as Haldol and Thorazine may actually *strengthen* ser, and thereby terminate psychosis, through their known direct effect of weakening dop, since in The Triangle weakening dop strengthens ser because the feedback inhibition is diminished. Likewise, in most cases of mania, nore may have become super strong and thereby weakened ser, triggering psychosis. We will discuss schizophrenia and mania in more detail in Chapter 10.

The topic of Big Three strength interactions is related to the issue of how the brain maintains the strengths of each of the Big Three neurotransmitter systems in the first place, where I believe these systems are, for most people, quite constant throughout life. For example, when one of the Big Three is affected by an environmental factor such as a stressor and reaches a threshold strength, does the brain have a feedback mechanism that brings the neurotransmitter back to its normal strength? The brain does have presynaptic autoreceptors (see Figure 1) that sense the synaptic level of the transmitter and can then change the amount of transmitter that is released, but these mechanisms apparently aren't powerful enough to stop drugs from working—in the long term at least—or mental illness from developing. So the fact that psychiatric drugs usually work suggests that the brain does not have extremely robust long-term regulation of the Big Three strengths, and the fact that mental illnesses exist is consistent with this conclusion.

The current theory hypothesizes that the natural ser and nore systems (which are determined by genetics and past experiences) strengthen dop, as does strengthening ser and nore with drugs. Just because ser or nore strengthening drugs strengthen dop doesn't mean that the natural ser and nore systems must also strengthen dop, but this is an

important assumption that has implications throughout this book. So under this premise and as described in The Triangle, the natural strength of dop should correlate with the sum of the natural ser and nore strengths. In other words, the stronger ser and nore are in a given person, the stronger her dop will also be.

If ser and nore really do strengthen dop, then most antidepressants are ‘dirty’ drugs in that their effects aren’t restricted to a single neurotransmitter system. And if there are even more Big Three interactions as described in The Triangle, then any drug that affects one of the Big Three—and perhaps even a drug that affects only a single subtype of Big Three external receptors—is dirty. (Note: by ‘external receptors’ I mean receptors on the outer surface of the neuron; also known as ‘extracellular receptors’.) Moreover, perhaps depressions really are always specific to one of the Big Three, but The Triangle explains why people may still respond to an antidepressant that changes the strength of any one of the Big Three.