

“...And the loud laugh that spoke the vacant mind...”

“*The deserted village,*” Oliver Goldsmith (1728-1774)

7. DOPAMINE DISTRIBUTION

THE TIME FRAMES AND THE ROLES OF DOPAMINE

Our growing success in calculating how the body would respond to drug change over the long term, whether increasing or reducing the drugs, was due to a model in which neurons for various functions have distinct reset rates.

Various brain regions have distinct dopamine properties

When we started this project, we were conforming to the standard ideas about dopamine circa late-1980's. All neurotransmitters (NTs) were assumed to work in the same fashion: one NT storage tank per receptive nerve; and in approximately the same time frames: all nerve/neurotransmitter relationships were quick. Neurotransmitters attached on quickly, were plucked off quickly, and then, if desired, could be used quickly again.

What our patients experienced did not conform to this model. It appeared as if specific drug withdrawal symptoms, those related to motor function, mental function, or fear, each of which is known to occur in a specific brain region, each occurred at different response rates.

Our charts indicated quick motor responses to dosage change, as expected, showing surges and terminations of dopamine-related motor activity over a period of up to six hours, which could be attributed to specific doses. But other symptoms that occurred in response to drug doses and dose changes, such as permanent adoption of On-Offs, worsening of freezing, loss of self-confidence, fear, hypersensitivity, or nausea, seemed to occur during twelve-hour, twenty four-hour, ten-day or ten-week periods of increased or decreased dosage. These longer periods were far too long to correspond to any given dose, even if we were figuring a much longer half-life than the manufacturers.

The short-term rates, up to twelve hours, appeared to be primarily affecting motor function. The longer periods (ten-day and ten-week patterns) appeared to have more of an influence on the symptoms of hypersensitivity, insomnia, and raw emotion. However, once the emotional and gut level (long-term) symptoms went out of control, the motor function also seemed to go haywire, but in a different manner: several weeks after a drug decrease, panicked pacing and violent, whole-body ticcing and shaking might appear, and even increase in intensity for two months before subsiding.

To make sense of what we were seeing, we had to hypothesize a radical departure from conventional understanding in which all brain cells operated at the same tempo, with each having its own private cellular stock of dopamine. Only then did our patients' symptoms begin to make sense. We worked with this hypothesis regardless of lack of evidence from western researchers.

We nervously hypothesized that nerves might have drastically different reset rates, ranging from nanoseconds to *weeks*, a spread much greater than the mild range being suggested at the time. Based on empirical evidence, we proposed that, subsequent to

stimulation from dopamine, each kind of nerve would refresh (be ready to fire off again) at a rate specific to that nerve type or brain area.

We were comforted, as you can imagine, when we started perusing the large amount of information suggesting an eight to twelve-week period of adjustment for drugs ranging from cocaine to Prozac. However, there was still no hard proof of a reset mechanism for that unheard of span.

Imagine our gratification when, just two years into our study, it was discovered that dopamine receptors, in response to the dopamine agonist nicotine, actually have a delayed refresh mechanism that lasts for an astonishing twelve hours!¹ Once the receptors had been filled with nicotine and the one brief nerve response was completed, the receptors would not accept another nicotine for twelve hours. This was a far cry from the quick on, quick off, quick on again scenario that had been assumed for all brain nerves, based on nothing in particular, ever since the discovery of acetylcholine.

Three more hypotheses

Buoyed by this finding, and suspecting that the other delayed refresh rates will also be discovered, we created a hypothetical model for dopamine in which:

Dopamine allocation is prioritized by brain zones: over the long term, limbic function is the highest priority, motor is the last.

Different brain zones process (attach and detach) dopamine at different tempos: motor is very quick, frontal lobe function is quick, and limbic can be very slow.

Limbic dopamine can accumulate, but motor area dopamine does not.

In a healthy person, motor function employs the tip of the limbic's iceberg of accumulated dopamine. When dopamine levels are temporarily altered by a flush of dopamine-altering drugs, the motor area may respond to the temporary drug surge, regardless of limbic levels. The long-term prioritizing of dopamine (abbreviated DA) will result in DA being shunted to the limbic area for accumulation. The allocation of dopamine to the various brain zones may superficially (visibly) appear to favor the motor area, but in fact, the prioritizing system will eventually direct all excess dopamine into the limbic zone.

The many hats of dopamine

Health

Dopamine is more than just a movement inducer. Dopamine is involved in the brain circuitry of pleasure, of paying attention, and of processing sight and sound. Dopamine levels influence the immune system, the perception of time, and body temperature regulation. Dopamine is involved in movement initiation and falling asleep. Dopamine's work assignment depends on what part of the brain it finds itself in, and the brain is able to shift dopamine around as needed.

¹ Nicotine, a dopamine agonist, was long considered to be a neurotransmitter that attached to acetylcholine receptors only. As recently as 1990, all of nicotine's effects were deemed cholinergic. Now, in 2003, the focus of nicotine research is on nicotine's dopaminergic properties, its effect on dopamine receptors.

Sickness

An imbalance of dopamine is related to many diseases, not just Parkinson's disease. For example, schizophrenia is caused by an excess of dopamine in the deepest, central part of the brain, paired with decreased activity in the decision-making, frontal part of the brain. It will come as no surprise to the PDers who suffer hallucinations because of their dopamine-enhancing medication that the voices and visions suffered by schizophrenics are set in motion by elevated dopamine levels.¹ Going the opposite way, Thorazine, a dopamine-suppressing drug used for treating schizophrenia in the latter half of the twentieth century, often caused a tremor and a shuffling gait just like the shuffle of Parkinson's disease. Dopamine excess and deficiency are suspected in the manic and depressive phases, respectively, of bipolar disorder.

Next, since what dopamine does depends on what part of the brain it's in, we need to learn a little bit about three main subdivisions of the think box.

OUR FRIEND, THE BRAIN

In this section you will be learning a bit about three main aspects of brain function and the role of dopamine in each part. Most of the material here conforms to the current (2003) understanding and is subject to change. Our hypotheses about the various rates of reset and dopamine processing and the prioritization of dopamine allotments based on our new model will be included at the end of each section on the specific brain function/region being discussed.

This will be an oversimplified lesson in brain topography. All of you would-be brain surgeons reading this, remember: this is extremely oversimplified. How oversimplified? To start, just because it is much easier to think of different neurons residing in departments, I am going to speak of the movement, frontal lobe, and limbic functions as if they each emanate from distinct, compartmentalized areas. You brain specialists know that all the brain functions are integrated, and even frontal, parietal (side), and rear zones of the brain have contact with cells in the core. However, throughout this workup, motor, frontal, and limbic brain functions will be described as if they lived in separate zones. And then, even though there are dozens of brain zones with very specialized tasks, I am going to reduce the whole grey mass into three major areas, with three basic functions, and propose the approximate refresh rate for each area.²

The rate of reset is pure hypothesis, based merely on the experiences of hundreds of patients and tens of thousands of hours that we logged, compared, and analyzed. But at least it's based on something. What we started with – the standard information at the time

¹ "The Chemistry of Mental Chaos," *Newsweek*, March 11, 2002, Newsweek, Inc., New York, p. 48.

² I will not describe all the in-between chemicals in each area that act as transporters or triggering molecules for dopamine, or the locations of dopamine storage bins and receptors, or those molecules that break up the very neurotransmitters that the brain has gone to great time and expense to put together. I am just going to talk about what dopamine does in each of the three areas, and the rate at which it comes and goes. We are going to **ignore** all those other details! Is this a great anatomy class or what?

Instead of these micro details, we will focus our attention on how dopamine processing in each area compares with dopamine processing in the other areas in general. And don't memorize too much – most of these details are just "facts." Like most scientific facts, they are likely to change again in the next few years. (See Appendix 5 and 6.)

– was based not on anything physical whatsoever, but on the idea that, since nerves were all made of nerve tissue, they should all behave in the same way. We like to think that our hypothesis, though young, at least corresponds to observations and is worthy of consideration.

Now let's pick up a scalpel and divide the oversimplified brain into three sections: the core, the front, and the sides.

The core

The central part of the brain is also called the limbic system, and is sometimes nicknamed the reptile brain, or lizard brain.¹ This is where the raw, non-thinking nerve² activities take place. The limbic system controls purely visceral responses, non-analyzed emotions such as rage, fear, and hunger. It controls processes like breathing and the movement of the digestive tract. It regulates critical, life-preserving processes that occur with no modifications from the logical, artistic, or will power parts of the brain. A command from this limbic center can override will power, reason, and habit. Think of raw animal passion, the shark that smells blood, or the mother protecting her child. “Act now, think later!” That's the motto of the limbic area.

The front

The frontal lobe, located in the forehead, governs mood, decision-making, and will power. This part of the brain also regulates ego and mental focus.³ “I think, therefore I am,” is the creed of the frontal lobe.

The sides/motor area

The sides of the brain have various functions: motor (movement), memory, speech, logic, vision, coordination⁴ and more. In this discussion of dopamine, I will refer

¹ OK, if you are a brain specialist, you are possibly grabbing your pencil to start one of those scorches beginning with, “Dear madam, are you aware that there are many parts to the limbic system, and the so-called reptile brain is actually only one part, etc.” Right. I am writing this for people who do not need to fine tune. This is for readers who may well consider that the brain is an undifferentiated mass of grey matter, and that it functions as a telephone switchboard – the old 1950's understanding of the brain. Read on; you will find that the point I am making holds up, even though I don't break the limbic portion down into its dozens of parts.

² As noted earlier, nerves, neurons, axons, dendrites and the rest are going to be called nerves. Those of you who have learned that the brain has neurons and not nerves, pat yourself on the back.

³ And a lot more. See the two preceding footnotes.

⁴ Obviously, for you folks at the front of the classroom who have some background in brain study, I am including in the “sides” some functions that occur in the cerebellum, the site of learned coordinations. For you non-biology readers who are curious as to what I mean, here are examples of a learned, coordinated cerebellar activity: playing a memorized piece on the piano or driving a car. These activities require a steady motor flow with no noticeable thinking. In Parkinson's disease, this type of fluid coordination is lost. Dopamine is needed in this back part of the brain for these learned/coordinated activities.

In this chapter, since some cerebellar functions can be considered extensions of motor function and not a completely separate function, I am including this back-brain activity in with the general idea of

to this section as the motor area, and will ignore most of the other functions of the side brain. Motor function is the process most visibly affected in Parkinson's disease.

Actually, motor function has elements in the center and in the front of the brain, as well as on the sides. For example, the thought process involved in initiating reasoned movement might come from the front of the brain. Mood (also coming from the frontal lobe) affects the manner in which we move. For that matter, the substantia nigra's dopamine, which transforms movement thoughts into movement function, is located deep in the core. But for our purposes, namely, understanding how dopamine behaves differently in different brain areas, I will say that the motor area is located in the sides. You cagey readers will recognize that some non-motor problems of unmedicated PD, such as difficulty in recalling nouns when speaking and difficulty in daydreaming, items not strictly considered motor functions, are also governed by the sides of the brain, the part that we are calling the motor area.¹

Most PDers who use DEDs (dopamine-enhancing drugs) are only concerned about the short-term assist to the motor area. They like to think that this is the main area targeted by these drugs. They are wrong. The motor area works at its best when the slowly changing limbic area is saturated. Furthermore, PDers in our program who decreased their DEDs too quickly experienced the exact symptoms that will be described in the scenario below when the limbic system, *not* the motor system, becomes stripped of dopamine.

sides-of-the-brain motor area. The principles that we're working towards with regard to dopamine still apply.

Now, for those who are truly up on their brain chemistry, I will admit that the oversimplification ignores the relationship of the midbrain and the motor area. I just lump everything together into one of three areas. I am not writing this as a technical book on brain function. I am describing a bare minimum of brain generalities so as to get across the idea that dopamine hooks up and releases at various rates in the brain sections that do various jobs. These variances are the key to the seemingly chaotic side effects of dopamine drugs. So please forgive the broad brush with which I paint the brain parts. Many in my audience have no background in medicine, even in science. My goal is to make a book that will enable people to negotiate the difficult path of drug understanding. Everything else, including nomenclature of obscure brain chemistries and anatomies, is secondary.

¹While this oversimplification may be disdained by modern students of neurology, there is increasing evidence that a macro overview of the brain may actually be more accurate than the currently popular micro view. Although scientists in the early 20th century assumed that isolating individual molecules and labeling various brain components would lead to a complete understanding of the grey matter, it appears more and more as if the entire brain must be regarded as a unified construct in which molecules change shape and function and various brain areas interrelate and even change function, as needed. The role of mood in regulating the immune system, and the role of left-right hemisphere integration in mastering tasks as diverse as spelling, wrestling, and singing are starting to diminish our idea that we can compartmentalize and categorize the brain. It may someday be discovered that the brain is a microcosm of the universe, a mass of swirling changes that can only be understood and predicted by knowing its point of origin. This theory, that predictability is only possible if the origin is known, is gaining acceptance in physics, but it is not yet employed by biologists.

If history is an indication, however, sometime in the future we will be arrogantly mocking the biologists who are still trying to figure out the chemicals of the brain as if they were cogs in a clock. Of course, human nature being what it is, those mockers will, in turn, be mocked somewhere further down the road.

Dopamine roles in the three brain parts: a suppressor, precursor, and stimulant

How does dopamine relate to these three brain areas according to the current scientific thinking? According to the latest scientific model, in the limbic area, dopamine is a *suppressor* molecule. Dopamine stops signals from getting through. In the frontal lobe, dopamine is a *precursor* molecule for norepinephrine, a NT that does most of the frontal lobe work. Dopamine doesn't do much actual work in the frontal lobe, it is presumed, but is transformed into the mood/thinking NT norepinephrine, as needed. In the motor area, dopamine is a *stimulant*. Dopamine is thought to be a trigger in this zone, initiating actions in motor nerves.

Quite a change from dopamine's historical role as a mere muscle relaxant, the opposite of acetylcholine! No wonder dopamine-elevating drugs can cause such a wide range of responses, from euphoria to spasming. The specific brain response to any given dopamine-enhancing drug depends on exactly which brain sub zones are targeted by that drug. It also depends on the brain half-life of the dopamine-enhancing drugs (DEDs) and their dosage level. There are many sub zones, and, even within some of the small brain areas, there are varying dopamine responses.

For example, in the motor area, one group of dopamine receptors (the D2's) will accept only the dopamine agonists Permax and bromochryptine. In the very same brain area, there are other dopamine receptors (D3's) that can hook up only with Mirapex and Requip. This difference in dopamine receptors, even within the narrow confines of a specific region, such as the motor area, contributes to the different actions of DEDs; even within specific areas, each of the dopamine-enhancing drugs will behave slightly differently. And yet, in the big brain picture, all the DEDs have much in common.

DOPAMINE IN THE THREE BRAIN PARTS

Limbic Land – dopamine as suppressor

In the limbic area, dopamine acts as a suppressor molecule, or Off switch. Hundreds of nerve impulses constantly swarm towards the limbic area of the brain from the skin, muscles, gut, and sensory organs. (Let's ignore the nerves flowing out of this area.) The incoming nerve signals want to tell your brain what is going on in the world and report on the happenings inside your own body. The flood of incoming nerve signals is selectively screened: most nerve signals do not get past the gate; they never make it into the limbic area.

Dopamine serves as the screen that protects limbic land. Molecules of dopamine attach to the nerves of this area. The presence of dopamine suppresses and sedates the nerves. When there is adequate dopamine bathing the nerve surface, the nerve is content. The saturated nerve will not respond to incoming messages. When an incoming nerve signal is stymied by a dopamine-drenched nerve, it is as if the incoming nerve signal never happened. The incoming signal is said to be "inhibited," or suppressed.

When, because of some trauma, the dopamine in this area is dislodged, the exposed nerves spring to life, and nerve signals can zip through the holes where dopamine was displaced, flooding the limbic zone with nerve telegrams. In times of ease, most of the incoming nerve signals are stopped by the dopamine doorman. The presence of dopamine shushes the midbrain nerves and lulls them into complacency. Only if the

incoming nerve impulse is unfamiliar, unusually large, or coming from a particularly crucial body part, will it be able to get past the dopamine defense and into the limbic area. Once the incoming message arrives in limbic land, the impulse may be responded to, as needed.

Most responses in the limbic system are automatic. You do not have a choice about how you will respond. This is why it is crucial that most nerve impulses never even penetrate into this area. The limbic area is far too primitive for decision-making. Most responses to a nerve impulse getting into the limbic area are either Go or Not Go. Of course, if the decision is “Go,” then the limbic area may or may not react on an animal (non-thinking) level.

The reaction of the limbic area depends on the quantity of signals coming through, as well as the source of the signals. If the electrical signal is small, with only a few nerve impulses slipping past the dopamine screen, the signal may be relayed to the frontal lobe for analysis. If the signal is alarming, the adrenaline switch may be flipped on and steps taken accordingly. If the signal is dire (as indicated by a large quantity of signals coming through), there may be an utterly unreasoned response: pure rage, or pure terror.

The higher the level of dopamine in the limbic area, the greater the likelihood that incoming responses will be ignored. And oppositely, when dopamine levels are low, incoming responses can pass into the limbic area more easily, implying great danger.

Anything and everything that stimulates any nerve of the body sends a neural impulse to the limbic area. If it weren't for the dopamine deadening of most of the incoming impulses, the brain would be constantly flooded, receiving more information than it could possibly handle. For example, the optic stimulation from a dewdrop and the feeling of your flannel shirt on your arm both send a nerve message to the limbic address. Without the dopamine barrier in place, both of those signals might constitute an emergency:

“Help!” screams the visual impulse in response to the dewdrop, “I’m blinded by the dewdrop!” And the skin sensor, detecting a flannel shirt warns, “Red alert! A shirt is hurting my arm!” Thanks to the screening of all but the largest, the unfamiliar, and the most critical impulses, these neural messages rarely get through to the brain. If you are healthy and have sufficient dopamine, your brain won't receive these mundane, non-critical nerve reports. But if dopamine levels have been stripped, as occurs during drug withdrawal, this hypersensitivity can result.

The dopamine in the limbic area suppresses most of the incoming impulses, nearly all of which are alarms, very few of which are pleasant. Most pleasant nerve impulses are actually only pleasant because we have time to think about them and make good associations. Aside from the sensation of a full stomach, there are very few impulses that are pleasant in and of themselves. In general, all incoming information is a red alert, a danger signal. Without dopamine in this area, you would be subject to too much stimulation, swamped with false alarms.

Therefore, we say that dopamine acts as an Off switch in this “reptilian” part of the brain.

Insufficient dopamine in Limbic land

If there is not enough dopamine in the limbic area, one is jumpy, edgy, raging, overwhelmed with sensory signals, and, most likely of all, fearful. *The extent to which*

you do or do not feel fear every moment corresponds to the amount of dopamine you have in your limbic system.

More dopamine means *less* fear, less awareness of aches, pains, and bothersome distractions. With more dopamine in the limbic area, there is less hunger, less panic. When the limbic area is filled with dopamine at just the right level, one can focus on higher thinking, pondering the meaning of life, or enjoying the company of friends.

The opposite happens when there is a decrease in dopamine: *less* dopamine means *less* ability to maintain equipoise. Less dopamine means less self-control. If there is not enough dopamine in this area, one might scream with pain, lash out in fear, fly into a rage at the drop of a hat, raven with hunger, or quiver with nausea and fear of eating.

If I'm being painfully redundant, here's why: most PDers imagine that their dopamine-enhancing drugs are simply movement enhancers. They have no idea of the real power of dopamine. They do not suspect that while their dopamine drugs appear to be stimulating the motor area, they are doing so in a large part by manipulating the limbic area, the fear center. The antiparkinson's drugs work primarily in the crucial Live or Die center of the brain. And unless a person absolutely understands the multiple faces of dopamine, he will not be able to make heads or tails out of the bizarre responses that eventually develop from the antiparkinson's medications. So, remember: dopamine is a suppressor molecule in the primitive brain. It suppresses information about the outside world and your relationship to it. More dopamine leads to calmness. Less dopamine creates dread and unreasoned response.

Slow motion dopamine changes

The healthy limbic system is partially saturated with dopamine at all times, assuring that most incoming signals will not get through.

We hypothesize that changes in dopamine levels occur very slowly in the limbic system. It may take up to ten weeks for a change in overall brain dopamine levels to come to equilibrium in the limbic area. It can take days for even a slight modification of dopamine increase or decrease to come to equilibrium in the limbic zone.

This hypothesis is not based merely on what happened with our patients. We've all seen examples of this slow-motion change in response. For example, when we get a new pair of shoes that fits differently from our old shoes, the foot sends a "new sensation!" warning to the brain. The dopamine-saturated nerve for foot pain lifts an eyebrow, but doesn't get overly excited. Possibly a small amount of dopamine is displaced by the new sensation. The brain notices this tiny change in the incoming nerve impulse. After several days, during which the incoming signals do not increase, the brain decides to move this signal into the "familiar, not a problem" category. Dopamine is allowed to settle back in around the foot pain nerve, and we never notice the sensation of the shoe anymore. This dopamine change was subtle and slow. It can take several days, maybe even a week or two, to become familiar with something new. It is good that this panic center of the brain responds slowly to change.

In an emergency, however, dopamine is stripped away more quickly. For example – as I write this from California, "earthquake country" – imagine the sight and sound of an earthquake toppling your house, shattering your windows and opening a rift in your front lawn as you sit, stunned, in the living room. These large, unfamiliar sensations flood your limbic brain with unusually powerful impulses. These signals, breaking past the

dopamine barrier, will cause lots of chemical changes in your brain. Adrenaline, the emergency neurotransmitter, also known as the Fight or Flight chemical, will start roaring through your body and brain. It seems that this combination of adrenaline and the sheer quantity of the incoming impulses will dislodge the dopamine that had been shepherding the drowsy limbic area. The dopamine in your limbic zone might scatter like chaff in a hurricane. The adrenaline will allow you to make lightening fast actions and turn off all pain-awareness nerves. The stripped limbic zone will allow you heightened awareness of the sights and sounds around you. The sheer quantity of nerve signals coming in will make you feel that you are experiencing more life-per-minute than usual, giving the illusion that time is slowing down. Your perception of time will alter so that seconds will seem like minutes, and you will have the power and impulse to act now and ask questions later. The emergency actions that you make will be powered by adrenaline. The limbic area, suddenly stripped of its dopamine, provides the fantastically heightened awareness.

After a few days, when the adrenaline level has climbed down and you've caught your breath, the wholesale displacement of the dopamine from the limbic area will start to be noticeable. For weeks afterward, you will be shaky and agitated, starting at small noises and lashing out at your mother-in-law while the limbic system remains out of sorts, until the dopamine that was scattered all through your brain during the emergency settles back down into its usual amount and location. It can take ten days before the dopamine in the limbic area even *begins* to resettle itself. It takes approximately ten weeks (and in some cases even longer, such as in cases of lasting emotional trauma) before the dopamine in the limbic area is restored to equilibrium after a shocking event.

We propose that there are short-term (a few hours) and long-term (ten weeks) reset buttons on the dopamine receptors in the limbic area. These delays, we suspect, are the reason why the limbic area cannot be restored quickly to its former state, even if there is plenty of dopamine present.

This time-lag delay in dopamine reattachment and dispersal in the limbic area provides a major clue in unraveling the mysteries of the DEDs. This concept is probably the single most important thing to remember for any person who is trying to make sense of drug increase or drug reduction symptoms.

Following are some examples of ways in which the pharmaceutical industry, though offering no neural mechanism, acknowledges this limbic delay. Directions for Prozac (an antidepressant) say, "Full antidepressant effect may be delayed until 4 weeks of treatment or longer."¹

Instructions for Xanax (an anti-anxiety drug) note, "Wean patient with high doses gradually...to prevent withdrawal symptoms. A 2- to 3-month withdrawal may be necessary."²

L-dopa manufacturers explain in the drug insert, "Maximum effectiveness of medication may not occur for several weeks or months after therapy begins." They also state, on the same page under "information for the patient," "Therapeutic response may not occur for up to 6 months," and also, "Because of risk of precipitating a neuroleptic malignant syndrome, observe patient closely if levodopa is reduced abruptly or stopped."³

¹ *Physician's Drug Handbook*, 9th edition, Springhouse Corporation, Pennsylvania, 2001. p. 449.

² *Ibid.* p. 23.

³ *Ibid.* p. 595.

The full benefits of Mirapex, an antiparkinson's dopamine agonist, may not appear for up to six months, and the manufacturer's insert on the drug warns, "Neuroleptic malignant syndrome (elevated temperature, muscular rigidity, altered consciousness, and autonomic instability) without obvious cause has occurred with rapid dose reduction or withdrawal."¹

The extended period (up to ten weeks) that is needed to adjust up or down in response to limbic dopamine change and the trauma to this brain area that might occur if dopamine levels are abruptly altered make "approximately ten weeks" the single most important time frame to keep in mind when taking, increasing, or reducing any Dopamine-Enhancing Drug (DED).

The PD pioneers found this ten-week pattern coming up repeatedly in their charts. When we combed the drug company warnings and pharmacology books about drug chemistry, we discovered that this ten-week pattern for dopamine readjustment is known to those researchers and doctors who specialize in drug addiction. Regrettably, and in spite of the drug manufacturers' warnings and suggestions, not one of the pioneers' neurologists had any idea whatsoever about the ten week requirement for dopamine accommodation; all of them were hostile to the very idea of anything longer than a three-day adjustment period.

Variations on "slow" limbic change

The ten-week period is not the only time frame that operates in the limbic area. There is a range of time frames, as seen with this cigarette example: there is a short-term (twelve hour) dopamine receptor reset switch that causes the first puff of the day (or the first puff in twelve hours) to be more pleasurable than subsequent smokes, a ten week reset switch that determines the time boundaries of the worst symptoms of nicotine withdrawal, and then there are permanent brain changes and brain associations that are formed, so that decades after quitting smoking, a certain memory or trauma can trigger desire for a cigarette.

A small dopamine displacement, such as the one triggered by a new pair of shoes or a broken bone, can be accommodated fairly quickly, in a matter of days or weeks. After a large dopamine shift, such as occurs during an earthquake, physical or emotional trauma, or a drug regimen change, it might take at least ten weeks before the dust settles. Despite the wide variations, the rate of dopamine change is slow in the limbic area when compared to the fleeting neurotransmitter attachments and detachments found in most other brain domains.

This slowness of dopamine attachment and detachment from the dopamine receptors in the limbic area is a good thing – it prevents us from bounding back and forth between rage, fear, and bliss. Except for horrific emergencies (during which time adrenaline steps in and keeps us on an even emotional keel), the dopamine levels in the limbic area are adjusted gradually, over weeks and months. A healthy brain is usually able to process physical, emotional, and psychological inputs logically and according to habit without ever disturbing the barely-fluctuating dopamine levels of the crude, reactionary limbic system.

¹ *Physician's Drug Handbook*, 9th edition, Springhouse Corporation, Pennsylvania, 2001.p. 850.

This plodding rate of change is the reason that it takes several days of vacation before the stress of work begins to recede, and why a drug addict can often stop taking his drugs for several days before withdrawal symptoms begin to appear. In the former case, a vacationer, in the absence of stress, will slowly accumulate more dopamine in the limbic area and gradually blossom with an inner peace. In the latter case, during drug withdrawal, dopamine levels slowly drop and the limbic area gradually becomes over-stimulated, exposing the drug addict to free-floating fear and pain.

Even in the case of abrupt drug withdrawal, it may take two to ten days (depending on the drug and dosage level) before the dopamine free-fall even *begins* to be obvious. After dopamine levels descend down to the basement, it may be ten weeks before the limbic brain starts restoring dopamine (with native dopamine) to high enough levels to move the system back into something approaching a comfort zone. During the ten weeks while the dopamine levels are too low, the brain may be assaulted by sound, light, and pain. A person in this dopamine deficient condition may have shaking heebie-jeebies, paranoias, and no way to stem the flood of nerve input to this reptilian brain that acts before it thinks. But, although tortuous, this agony of withdrawal is not the most life-threatening situation that limbic area dopamine can produce...

The gravest danger: dopamine excess

The most dangerous neurotransmitter situation for a human is this: dopamine excess in the limbic area. An excess of limbic dopamine creates bliss at the most primal level. In this unreasoned state, there is no capacity for fear, pain, rage, or hunger. A person whose limbic area is over-flooded with dopamine may be utterly without capacity or desire for self-protection. While 21st century addiction researchers refer to dopamine as the neurotransmitter that regulates pleasure, a more accurate label would be “the NT that removes fear.”

Walking off a cliff, self-immolation, or striding through a glass window can all appear as charming, even amusing, experiences, if there is no capacity for fear.¹ Death and mortality are not a concern if the limbic area is oversaturated with dopamine. For this reason, excess dopamine in the limbic system can be instantly deadly. Excess dopamine in the brain is the most dangerous neurotransmitter situation possible; it can kill faster than any other neurotransmitter imbalance.

Therefore, the body has built-in safeguards to ensure that there are *never* excessive levels of dopamine.² **If dopamine levels are ever, however briefly, elevated beyond**

¹ These are all activities that people have cheerfully performed under the influence of powerful DEDs such as speed (methamphetamine), an illegal street drug related to Eldepryl, an antiparkinson’s drug.

² In Traditional Chinese Medicine, dopamine excess is the dreaded Kidney Yang Excess. Some schools of thought hold that there is no such thing as Kidney Yang Excess – there cannot be too much of such a good thing. However, that is pure semantics. What these people mean is that, by design, the body can never *naturally* exceed the Safety Limit. They also are making the point that a goal of life is to maximize Kidney Yang (the joy of pure Life Force).

When Kidney Yang is increased through meditation and focused prayer, there is no danger, and the sky is proverbially the limit. But when short-term increases in Kidney Yang are imposed on the body by chemicals such as heroin, cocaine, or other dopamine-enhancing drugs, this most precious aspect of mind-body is perverted into a dangerous brief caricature of wisdom and joy: the dreaded and “impossible” Kidney Yang Excess.

what the body deems a safe point, the body has stern and unforgiving ways of assuring that dopamine levels will never, ever, be too high again.

These ways are referred to as addiction if the source of the dopamine is illegal. These ways are referred to as “accommodation” or “tolerance” if the drugs are produced by the pharmaceutical industry. By any name, the processes are the same. These processes involve short-term and long-term changes in brain chemistry. Because of the grave dangers associated with excessive levels of dopamine, a brain that has experienced excess dopamine, even for a brief time, will chemically alter itself. The genetic expression of the brain cells is altered, thus altering the performance of those brain cells for a long, long time – maybe forever. These alterations are designed to lower the baseline dopamine levels so that an excess level of dopamine will never, ever, happen again.

The supreme danger inherent in dopamine excess is the reason why the brain has so many mechanisms for reducing dopamine levels. Killing the cells that produce dopamine, increasing the enzymes that break up or detach dopamine, and shutting down the nerves that receive dopamine are just a few of the measures the brain can take if the dopamine level is, even for a moment, excessive. The brain can also immediately reduce dangerous dopamine levels for the short term by setting in motion uncontrolled, even frantic, muscle activity or mental activity (including hallucinations and delusions), thus burning up some of the excess dopamine. By having the arms, legs, face, diaphragm, and heart muscles spasm and thrash about, dopamine may get used up more quickly and subside all the sooner to safer levels.

Dopamine allocation

Prioritizing

How is dopamine doled out amongst the various brain parts? It used to be assumed that any nerve that needed dopamine had a nearby private supply (vesicle), which was dedicated to a single nerve. When the storage bin got the “Open sesame” signal, dopamine could flow from the vesicle onto the nerve, do its job, and then immediately be carted back to the nerve’s private reservoir. However, this model is of no help in figuring out how brain nerves access the floods of dopamine that surge indiscriminately into the brain in the wake of dopamine-enhancing drugs. This model may not even be correct.

The issue of dopamine distribution is a crucial one for the PDer. What happens in the brain when dopamine floats through the brain at random, as it does when a person takes certain dopamine-enhancing drugs? How does the brain decide which brain lobe gets to use the goodies? What is the mechanism for dopamine distribution, some method for deciding which brain area gets how much and at what rate?

Actually, the distribution of dopamine is not just an issue for drug-using PDers. Even in healthy people who supposedly have plenty of dopamine, it appears that when mood and external events alter dopamine levels in one part of the brain, it affects the entire brain. This is seen, for example, in the case when overall brain dopamine increases from elevated mood or even good weather. Good weather can decrease the amount of dopamine that is needed for temperature regulation. The subsequent increase in available dopamine can be employed in other areas of the brain. Movement, mood, and pleasure perception may all elevate slightly when the weather changes for the good after a long

period of poor weather. On the other hand, when the weather is cold, and more dopamine is needed in temperature regulation, we move more slowly, mood drops and the immune system is slightly suppressed. (The immune system is closely tied to norepinephrine (NE) levels – and dopamine is an NE precursor.)

Feeling sick or under the weather can affect our rate of movement initiation, and DED (dopamine-enhancing drug) withdrawal affects mood. All dopamine functions appear to be intertwined. A drain on dopamine in one part of the brain will affect other parts of the brain. There is a limited amount to go around, and the various brain parts share from a common pot. Dopamine distribution is in constant flux, and *all* brain parts benefit or suffer from healthy or incorrect dopamine levels, respectively.

In that case, how long does it take for dopamine to sort itself into various brain zones and, if there is a dopamine deficiency, which brain area gets the short end of the stick in the long run?

In our model, each of the various brain areas responds to overall dopamine change based on its rate of dopamine uptake and its refresh rate. For example, the limbic area can only change slowly to reflect an excess or shortfall in overall dopamine, and therefore it cannot take advantage of excess supplies as rapidly as the motor area, which uses dopamine quickly. This might lead us to think that the motor area, which responds in a flash to free-floating dopamine, would accumulate dopamine faster than the limbic area. And yet, this accumulation does not seem to occur.

Despite the faster rate at which dopamine can be processed in the motor area, over the long term it is the limbic area, even though slower to grab the dopamine, that seems to get more of the dopamine stashed away. Whether this is actually due to a prioritizing system or due to the limbic area's superior capacity for dopamine storage or both, we can only guess. But the net result is that dopamine can get stockpiled in the limbic area over time, whereas the motor area does not seem able to build up a supply.

Based on our patients' responses to their DEDs, we hypothesize the following: when there is excess dopamine floating around in the brain, the limbic area gets first whack at it. However, because the dopamine attachments form slowly in this area, the limbic area doesn't necessarily get to take full advantage of being number one on the priority list. The motor area, quick to respond, *appears* more affected by DEDs in the short term.

On the other hand, if there is a general shortage of dopamine, the brain will redistribute the supply so that, eventually, over weeks, the needs of the limbic area are satisfied. The motor area has to take a back seat; motor area dopamine needs may even be denied.

An example of this would be the sequence of the appearance of those Parkinson's symptoms that are related to dopamine deficiency. In PD, the entire system is low on dopamine, and yet the limbic area is able to function somewhat normally for years after the motor area begins to fade: it may be hard to get up from the sofa, but the lungs and heart keep working just fine. Susceptibility to anxiety may not occur until years after PD has been diagnosed. Temperature regulation, on the other hand, may be poor even before the motor problems become apparent. In other words, the overall dopamine levels are dropping, but the various systems that use dopamine do not decline uniformly – there is some system at work that prioritizes which area gets first grab at the dwindling

dopamine. We hypothesize that the limbic area is higher ranking than the motor area and gets first pick.

Limbic Review

1) Dopamine is a suppressor in the limbic area.

2) Dopamine attaches and detaches to limbic area receptors very slowly, except in cases of emergency, when it is displaced by adrenaline, or in cases of DED (dopamine-enhancing drug) decrease, when the accustomed supply simply disappears.

3) When dopamine in the limbic area is drastically decreased, it may cause fear, rage, shaking, tremor, nausea, oversensitivity to sound, light, touch, smell, and taste, tightening of the muscles (as if hypothermic [overly cold]), slowness of movement, insomnia, paranoia, and inability to think clearly, to name a few responses.

4) When dopamine in the limbic area is excessive, the opposite may occur: absence of fear, joyful illogic, insensitivity to pain, heat, or cold, and, very often, excessive motor or mental function.

THE FRONTAL LOBE – DOPAMINE AS PRECURSOR

In the front of the brain, dopamine plays an undercover part in the regulation of mood and will. The neurotransmitters that control most frontal lobe activities are (are?...were? Brain theory changes so fast these days...) thought to be serotonin and norepinephrine. So where does the dopamine come in? Dopamine is the precursor molecule for norepinephrine (NE). Dopamine levels help determine how much NE will be manufactured. For some time, researchers have known that most mood-altering drugs, such as the antidepressants and anti-anxiety drugs, which are designed to specifically increase serotonin or norepinephrine, have addictive properties that correspond to dopamine excess. Only recently have researchers realized that serotonin-boosting (SSRIs) and tricyclic mood drugs do cause a concomitant change in dopamine levels.¹

Why should a serotonin-increasing drug cause an increase or decrease in dopamine? It may be that when serotonin levels are artificially boosted, as they are in the case of serotonin reuptake inhibitor drugs, dopamine that was allocated to turning into a frontal lobe neurotransmitter becomes surplus. This dopamine is freed up from its normal assignment and it becomes part of the dopamine reserves again, whence it causes excess levels of dopamine.²

¹J. Glenmullen, MD, *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives*, Simon & Schuster, NY.

²The delayed response in the serotonin and norepinephrine enhancers may actually be due to the fact that their effectiveness is not due to serotonin or norepinephrine – it may be due to the way that these two NTs alter dopamine levels. Certainly, the authorities in the field admit that they don't really know how these drugs are working. The current model cannot explain the way these drugs work. Our hypothesis, on the other hand, not only describes what we've seen over the very long term with DEDs, it makes sense of some of these other drug mysteries as well. In the "definitive guide" to psychoactive drugs, Dr. Julien writes, "Although reasonable correlations have been found between drug-induced increases in the levels of norepinephrine and serotonin and positive, mood-elevating effects in people who are depressed, several limitations and inconsistencies in this pattern have also been seen.

"One major difficulty is that the time course of action is vastly different for the biochemical effect and the clinical response. Although neurotransmission of norepinephrine and serotonin is augmented soon

Where does extra brain dopamine go, in most cases? It is prioritized into the limbic system. Thus, in the presence of drugs that amplify frontal lobe function, drugs that ostensibly increase only serotonin (abbreviated 5-HT) and norepinephrine (NE), the levels of free-floating dopamine are increased. Subsequently, fear, rage, and hunger, the domain of the limbic area, are also decreased. One might even propose, despite the appearance that frontal lobe enhancing drugs are boosting 5-HT and NE, that it is the simultaneous boost to limbic dopamine that actually causes the improvement in mood.

Picking up the pace

The frontal lobe's chemistry changes faster than the limbic system's. Once the dopamine levels are at equilibrium, mood and focus, both governed by the frontal lobe, can last for a few days or a few minutes. This is the healthy pace with which logical minds respond to the rapidly changing, complex vagaries of life.

How long does it take for mood to change? Your mood can change quickly when, for example, you receive a thoughtless remark such as, "What happened to your hair?" or, "You look just awful!" As soon as you hear a negative statement, you can feel your mood start to change.

Going the opposite way, you can be sulking along, nursing a grudge, when suddenly an old song on the radio reminds you of happier times. By the time you start singing along, your mood has lightened.

It is possible to have a sustained focus in this area of the brain lasting for days, but for the most part, this is a product of training and habit. The actual chemistry of the area can change every few minutes.

Self-conscious awareness, another feature of this brain lobe, comes and goes quickly, with sleep and waking. The change from sleep to awareness usually takes just a few seconds, or at most, a minute or two; we propose that dopamine processes in the frontal lobe must be fairly quick.

Dopamine prioritizing in the frontal lobe

When there is extra dopamine floating around in the attic, it appears that the frontal lobe gets second whack at it, after the limbic area. If the frontal lobe had been feeling a bit low, and it gets a chance to grab some dopamine and convert it into NE, it can do so quickly. Eventually, of course, as the brain drifts towards equilibrium, the limbic area might take precedence, but because the limbic hook-ups change slowly, the frontal lobe might be able to use the extra dopamine in the meantime. This might explain the fairly rapid mood changes that can occur in response to strong DEDs. The short-term mood enhancement brought about by DEDs usually only lasts as long as the improved motor function. In fact, very often, a drug-using PDer can receive warning that his motor function is about to wear off – he senses the change in his mood that can precede the end of a dose.

after the drug is taken, the clinical antidepressant effect may not appear for three to six weeks." This quote is from the 2001 edition of *A Primer of Drug Action*, R. M. Julien, MD, PhD., W.H. Freeman and Co., New York, NY, 1999, p. 126.

If it is in fact the DA that uplifts the mood, then the slowness of dopamine accumulation could account for the delayed effect of these drugs – drugs that supposedly act only on one NT. Realistically however, in a system as interrelated as brain NTs, there is no such thing as a drug that acts only on one NT.

It may actually turn out that DEDs improve movement primarily through the alterations that they make in the frontal lobe, not the motor area. This might explain, in part, why recovering PDErs have such different motor responses to their first glimmers of native dopamine than they do to their drugs. This subject is discussed later in chapter 21.

Our hypothesis also states that if there is insufficient dopamine, the limbic area will eventually take what little there is, and the frontal lobe will be deficient. For example, when a body is shaking with fear or pain (limbic dopamine deficiency) and reacting out of pure primal instinct, it does not have the opportunity to indulge in moods, nor does it perform logically. This may be because the frontal lobe can't have a full complement of chemistry until the dragon in the limbic area is contented.

Of course, one can picture an exception to this rule: a person in great pain may be able to be temporarily lulled into a fleeting good mood by a pleasing distraction, even though underlying pain and limbic deficiency are present. When the distraction is gone, however, the pain will step forward again. This short-term quick fix, the redirecting of dopamine for frontal lobe usage, allows a shut-in, for example, to temporarily override pain, when a good friend comes to visit.¹

Frontal Lobe Review

- 1) Dopamine in the frontal lobe is a precursor NT; it is converted, as needed, into norepinephrine. Based on the changes to DA levels after the use of serotonin-enhancing drugs, we propose that serotonin is also related to DA levels.²
- 2) Dopamine attaches and releases fairly quickly in the frontal lobe. We propose that the time frame may range from seconds to minutes.
- 3) Deficient dopamine can cause deficiency in the neurotransmitters of the frontal lobe (NE and 5-HT), leading to depression, moodiness, inability to think clearly, and lack of focus and will.

¹ In such an instance, when a person can temporarily override the limbic area with a quick snatch of dopamine to the frontal lobe, the person is often accused of having pretended to be in pain, simply looking for sympathy. This is not true – that moment of good mood may come at real cost. Subsequent to the burst of good mood, this person may have depleted some of the dopamine stock so that, soon enough, the limbic area will be suffering even more. On the other hand, if the spirits are lifted significantly, such as occurs in response to either a spiritual uplift or a placebo effect, the input can actually generate more dopamine, truly improving the situation.

² The relationship between serotonin and dopamine is not at all understood. It has been theorized that they are “opposites” because a drug-induced increase in serotonin will lead to a reduction in native dopamine levels. However, knowing as we do that dopamine is highly self-regulatory, and a reduction in native dopamine is the common side effect of any increase in pharmaceutical dopamine, it would almost seem as if serotonin is a dopamine-like compound, as far as the brain is concerned. That would explain why an increase in serotonin from pills leads to a paired increase in dopamine, but over the long-term, a decrease in dopamine.

Certainly, the side effects of serotonin-enhancing drugs, especially when taken at high levels, have many points in common with the side effects of dopamine-enhancing drugs, including ataxia (inability to coordinate muscle movements), tremor, myoclonus (twitching or spasms), confusion, agitation, diarrhea, cardiac irregularities and tremor. I suspect that these two compounds have a relationship that is much more complex than simply being “opposite:” most likely, they are two sides of a very similar coin. It may be that serotonin performs many dopamine-like roles. Also, one has to wonder wryly– does the idea that serotonin is the “opposite” of dopamine refer to dopamine’s historical role as a muscle relaxant or to dopamine’s modern role in providing pleasure? Certainly, serotonin, the major antidepressant NT, is more like a cohort, and not an opponent of dopamine, recently renamed the Pleasure NT.

- 4) Excessive dopamine can cause excess neurotransmitters in the frontal lobe, thus leading to dangerously elevated mood and motor function (mania), intensity of thought and focus, delusions of physical prowess, and possibly even feelings of omniscience and psychic power.

THE MOTOR AREA - DOPAMINE AS STIMULANT

Lastly, we come to the motor area of the brain. It is now recognized by dopamine researchers that, in the motor area, dopamine is a stimulator. Isn't that fantastic? Dopamine is a suppressor in the core/limbic zone, a precursor in the front, and a stimulant in the motor area.¹ Dopamine is an NT multitasker!

Dopamine stimulates the nerves of the motor area. Its presence on a nerve receptor can initiate movement, stimulate speech, memory and laughter. It stimulates coordinated activity and integrates the logical and artistic sides of the brain.

Presto!

Dopamine molecules have a very brief active life in this area. Upon its release from the vesicle, dopamine is rapidly hooked up to its position on a nerve. Moments after the dopamine is hooked up, as soon as the nerve has had its chance at firing off, another chemical (called a reuptake enzyme) grabs onto the dopamine and detaches it from its nerve, scuttling it back to the storage sac. Depending on whether the nerve is for a slow moving or a fast moving muscle (a calf muscle compared to an eye-blinking muscle), the nerve will reset itself quickly or very quickly and be ready to fire off again as soon as the muscle is back into position. How fast can dopamine function in this area? It can function as fast as the blink of an eye. Literally. The mind decides it wants to blink. Dopamine is the NT that triggers the nerve that makes the thought, "blink!" Dopamine is the NT that converts the thought into action. As soon as this blink thought has finished, the dopamine molecules are ripped off the nerve cells where they set the blink in motion. They are carted back to their storage sac, where they are stored until another motor, memory, or musing thought is triggered.²

Dopamine works quickly in this motor area. How fast? It can work as fast as a twitch, as quickly as a thought. When we talk, dopamine initiates the speech centers, both the ability to speak and the choice of words. Those processes occur nearly as quickly as the thought behind the words – sometimes faster. When we fall asleep, dopamine levels in this part of the brain drop off sharply and quickly. When we wake up, it takes a moment for the full dopamine load to get moving again, but once it does, it is up on its toes, ready to go.

¹ To all you neurosurgeons out there who are steaming at this level of oversimplification, please, get your frontal lobe under control. This is a book for the general public. And to the general public, who may suspect that there is more to it than this, you are correct. There are dozens of special areas in the brain, not three. Still, for our purposes, you will find that these basic ideas about dopamine are sound – as sound as any science can be in this changing world.

² Acetylcholine is a part of this chain of events, it being the NT that actually trips the switch on the muscle activating nerve, but without the dopamine, the process won't even initiate.

A shortage of dopamine in the motor areas causes slowness of movement, slowness of the reflexes, slowness of speech, and slowness in processing sounds and ideas.

When there is an excess of dopamine in the motor area, there can be excessive movement and hyper-fast movement. An example of excessive movement is the twitching and grimacing that occurs in DED overdose. Another example is echolalia, when a person hears a word and then repeats that word dozens, if not hundreds of times, unable to stop. Excess dopamine in this area can create the fantastically quick movements that are recorded in the movies of the L-dopa experiments, in which the subjects pump their limbs literally faster than the eye can see. Excess dopamine in the motor area allows the extremely powerful and physically impossible movements, such as picking up a truck, that methamphetamine users have been known to perform while under the influence. An excess of dopamine in this area can cause muscular and mental activities that are literally impossible for a normal human to perform.¹

Prioritizing

The motor area is the last area to get dopamine out of the native supply reserves. Until the limbic area and the frontal areas have enough dopamine, the motor area vesicles will have to struggle along with what little they can scrounge. However, if a sudden surge of dopamine washes over the brain (such as occurs with pharmaceutical or illegal dopamine-enhancers), the fast-acting motor area might be the first area to take advantage of it, snagging some dopamine for itself in the short term.

Motor area review

- 1) Dopamine in the motor area is a stimulant; it triggers nerve responses.
- 2) Dopamine can attach and disengage very quickly in the motor area.
- 3) A shortage of dopamine in this area prevents or slows movement, reflexes, and integrated thinking.
- 4) An excess of dopamine in the motor area can cause excessive, overly fast and/or random movement and speech.

¹ These activities, in which human bodies and brains perform in ways for which they were never designed, can cause irreparable damage to the body or brain. For example, one danger of the street drug Ecstasy (a dopamine enhancer) is fatal dehydration, which can occur after a full day and night of tireless dancing with no awareness of fatigue or thirst. But at the time of the “impossible” activity, the doer feels no pain and has no sense that anything fantastic is occurring. Also, the accompanying excess stimulation of the thinking areas can create hallucinations and delusions of heightened power. Ecstasy also creates permanent lesions in the brain. Not surprisingly, some PDers have discovered that this DED temporarily alleviates PD symptoms. In England, some PDers petitioned (in 2002) to have this highly dangerous drug made legal for PDers because it can “treat” Parkinson’s.

COMBINING INFORMATION ABOUT ALL THREE BRAIN AREAS

The motor area only works if the frontal lobe is already up and running. The frontal lobe only works well if the limbic area is content. Here's a quiz: which brain area slows down first when we go to sleep, the mind or the movement zone? Answer: the motor area moves slow down first. As we fall asleep, first our physical body grows calm (motor area), and then our self-awareness ebbs (frontal lobe). After dopamine is withdrawn from these two areas, and they are both operating at very low levels, sleep occurs. The body is maintained in sleep by the limbic area, which keeps the heart beating and the lungs pumping. The limbic area is also able to order up subconscious movement, such as the slow, mindless turning that we do in our sleep. When it's time to wake up, the frontal lobe awakens first, and we feel a stirring of consciousness. We remember who we are, where we are, and what lies ahead on the day's agenda. After that, the motor area kicks in; we start to yawn and stretch, and then open our eyes.

It would be terrible if this logical sequence were not followed: if the motor area stayed alert after the frontal area fell asleep, we might dance and sing while snoozing. If the frontal lobe was able to process thoughts while the limbic area was in a state of emergency, we could be trapped in useless indecision while the emergency roared around us. If the motor area could function at highest capacity while the limbic area was under stress, we might easily kill someone because we were feeling edgy.

Now, all of the above events do occur: people walk in their sleep, people become caught up in indecision while watching a child burn to death, and sometimes people act out their whims in a passionate manner with seemingly no override from the frontal lobe. However, these are all pathologies, dysfunctions. The basic program, the standard for brain function, is that the limbic area is the first one that must be pacified, then the frontal lobe can activate, and finally, the motor area can start to rock and roll.

Because the motor area can respond quickly to a surge of dopamine flooding through the brain, it may appear as if the motor area receives first priority – shuddering into action as the first flush of dopamine hits the brain – but over the long run the brain will insist that dopamine be accumulated first into the limbic area and then into the frontal lobe, while the motor area is not allowed to accumulate much at all.

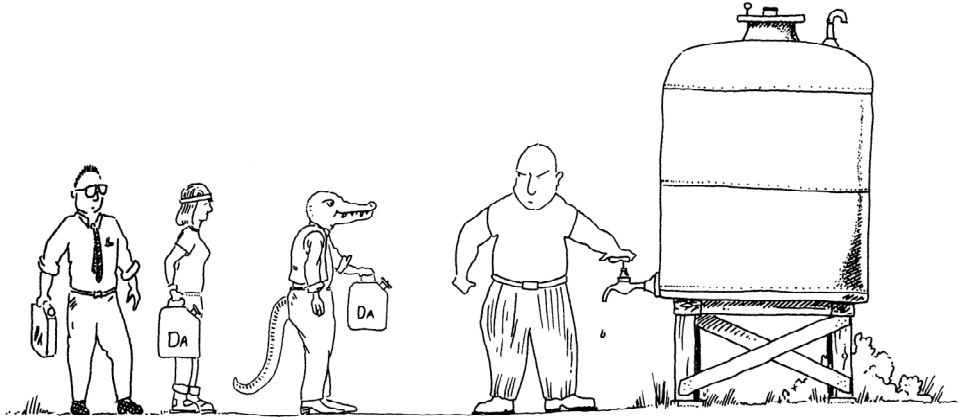


fig. 7.1

This drawing whimsically suggests that, in the presence of dopamine (DA)-enhancing drugs, the motor area – a lowest priority area – makes a swift move towards the front of the line, cutting in front of the frontal lobe and possibly getting ready to shove aside the limbic zone, thus disrupting the normal order of dopamine prioritization.

DOPAMINE MECHANISMS

This short section will discuss some of the more technical aspects of dopamine processes: the dopamine thresholds and windows. These must be somewhat understood in order to make sense of the graphs and charts that will follow in later chapters. Following that, there will be a brief proposal of how brain protection processes may cause PD drugs to appear ineffective, or alter the normal prioritizing of dopamine.

Thresholds

Dopamine, like many other neurotransmitters, works on the threshold basis. This means that there must be a certain minimum, a threshold level, of dopamine present on a nerve before any dopamine-related activity can result. Most people assume that a little dopamine gives a small result, a little bit more gives a little bigger result, and so on. This is wrong; until the level of dopamine rises up to the threshold level, no dopamine

business can result. As soon as dopamine supply goes over the threshold level, full functionality appears.¹

Here is an example using pretend numbers: let's say that a single nerve has 200 dopamine receptor sites and a threshold of 100. If 99 of the receptor sites are filled, the nerve will not activate. If 100 receptors are filled, the nerve will fire off exactly once. If 150 receptors are filled up, the nerve will still fire off exactly once. That is how a threshold works – it gives an all or nothing response.

Dopamine evidently has some excess thresholds as well. For example, using the numbers in the above example, the nerve will fire off once if there are between 100 and 150 dopamines attached to the nerve. But, since excess dopamine is addictive, we can guess that there is a danger signal if and when too many of the receptors are filled. In this case, let's suppose that the danger signal occurs when 151 receptors are filled. In the presence of 151 dopamines, the nerve will go off exactly once, just as it would have if there had been 100 or 150 dopamines attached, *and* the nerve will send a signal to Safety Central to start reducing dopamine production. If there is far, far too much dopamine, the body may promptly institute visible methods for getting rid of some of the dopamine, methods such as dyskinesia. It may also activate invisible methods such as disabling the dopamine receptors or transporters.

Windows

The distance between the threshold and the danger signal, or Safety Limit, is called, in PD drug parlance, the “window.” The effectiveness window is a dopamine level that is high enough to get a response but low enough so that side effects are not triggered. Keeping dopamine levels within the window is the goal of good medication management. The problem with this goal is that it is based on visible trauma and ignores the invisible brain damage.

¹ You PDers in the audience may say that this is not the case, that sometimes you can move slowly, and other times you move normally, thus disproving the threshold theory. In fact, you are using your waning adrenaline when your dopamine drops below the threshold at those times when you are moving more slowly. In the decades while your PD was developing invisibly, you were losing many motor functions and dopamine levels were dropping. You took up the slack with adrenaline. It is when you are finally too tired to care, or so shocked or frightened or sick that the body's adrenaline levels drop very low, that your Parkinson's disease becomes apparent and your dopamine deficiency becomes exposed. This usage of two neurotransmitters to do the job of one helps explain the partial movement that PDers can have.

During recovery from Parkinson's, the adrenaline levels drop to zero, and an unmedicated ex-PDer then finds that he or she does alternate between absolutely normal movement and no movement at all. The profound relaxation that occurs during recovery allows the adrenal glands to finally get some much-needed rest. The resultant dopamine flow is therefore very easy to observe; it is either above the threshold or below, with almost nothing in between. The abrupt cessation and resumption of motor function can resemble the On-Off of drug function, except that it only takes a few restorative minutes, or sometimes a nap, for abrupt resumption of full motor function. Another significant difference is that these no-dopamine periods decrease over many months.

LESS-KNOWN DOPAMINE ROLES TWEAK DRUG RELIABILITY

Other roles for dopamine

Dopamine plays other parts in the body drama. Dopamine is not just a suppressor, precursor, and stimulant. It also regulates body temperature, helps to ameliorate social stresses, and is depleted by infectious disease. People with Parkinson's are familiar with some of these situations; they notice that they cannot move as well in extremes of temperature, when under social stress, or if sick. What they may not realize is that dopamine plays a key role in regulating these body stressors.

It is important to bear in mind all of the influences that can be affecting dopamine levels if one is trying to maintain the best possible body function with the lowest possible level of drugs. For example, very often a PDer will think that he needs to increase his medication because he perceives that he feels stiffer or his drugs are not working as quickly as they were. He may assume the drug dosages are no longer adequate. However, it may be that the real problem, the reason he is moving more stiffly, is because autumn has arrived, bringing with it colder weather. The PDer may unwittingly be using more dopamine in temperature regulation, and so his drugs may not seem as effective. He may only need to turn up the heater or wear an extra layer of clothing rather than increase his medications. He may have been unable to detect that the temperature was growing colder – his DED medications were increasing his limbic dopamine so that he did not feel chilled. But the cold weather was forcing his body to use extra dopamine to keep the body temperature stabilized. Extreme heat also upsets the dopamine balance and can lead to worsened motor function.

It is worth noting that people are most often diagnosed with PD in the fall and winter, or after a surgery or illness.¹ Very often, they note that their symptoms ebb during spring and summer, or during vacations. This is due to the many roles played by dopamine. Simply observing one's physical movement is not an accurate indicator of the progression of Parkinson's disease, nor is it a way to determine appropriate drug levels. Many other factors must be considered as well in determining the cause of seemingly low or high dopamine levels on any given day.

To add to the complexity, consider this: dopamine is a precursor for norepinephrine, and norepinephrine, in turn, stimulates adrenaline receptors, including extra cerebral adrenaline receptors. It is conceivable, following this chain reaction, that L-dopa pills might create not just a dopamine response, but also a norepinephrine and adrenaline response. The fantastic array of side effects that can be set in motion by L-dopa or DEDs may be related to this branching, far-reaching set of dopamine derivatives.²

¹Although most PDers are cold all the time, about ten percent of our patients went the other way, and were always uncomfortably hot. Curiously, several members of the "hot group" were first diagnosed with PD in the late summer, during the hottest days of the year.

²It is possible that within another year or two all of this information will be either found out to be wrong or found to be merely the tip of the iceberg. Candace Pert, in her *Molecules of Emotion*, presents a brilliant, well-supported hypothesis that extra-cerebral and cerebral neurotransmitters communicate across the entire body map. Not only that, but also the shape and function of these compounds, once thought to be fixed and static, may be tremendously flexible, so that various chemicals can do different jobs at different times. Stay tuned!

In conclusion, to wisely determine dosage levels, a person using DEDs must be aware of all of the influences that can deplete dopamine, the ways in which the brain prioritizes available dopamine, and how various brain parts manifest excess and insufficient dopamine.

Due to the mind-clouding traits of the DEDs, a person taking DEDs might be able to best gauge his medication needs by having a close friend or spouse carefully observing his external circumstances and physiological, emotional, mental, and physical settings. Otherwise, he may increase his drugs when putting on a sweater or eating a hot lunch might have met the case. Also, one must be aware that the medication simply cannot hope to mimic “normal” brain function.

Dopamine enhancing drugs alter the natural order

What happens when DEDs are introduced into the brain? The normal order of brain area dominance/prioritizing can be altered. It is these alterations in normal brain regulation that create some of the disturbing, baffling side effects of antiparkinson’s medications. When DEDs come surging into the body, they do not follow the normal release pattern of prioritizing dopamine towards the limbic area first, the frontal lobe next, and the motor area last of all. Instead, the brain may act in unpredictable ways.

For example, the quick-acting motor area, which can take advantage of dopamine quickly if the upstairs is flooded with DEDs, may grab the dopamine before the limbic area does. In a case like this, a person who takes DEDs may thrash violently in his sleep or even sleepwalk. This response is not unusual with people taking too-high levels of DEDs, or in those who take their anti-PD drugs at night.

In another example, such a person might also have writhing, spasming dyskinesia from too much dopamine in the motor area, but not be able to tell that he is moving in an unusual way because his frontal lobe, also flooded, can’t accurately assess the erratic movements and interprets them wrongly as signs of brilliance. This inability to recognize inappropriate physical, social, and even sexual behavior is often exhibited in PDers who are overmedicated.¹

¹ Many of my medicated PD patients have acted out in socially unacceptable manners, including inappropriate sexual advances to strangers and friends, while under the influence of their PD drugs. While the spouses are usually furious or deeply grieved by these behaviors, they should bear in mind that anyone taking more than minimal – or possibly any amount – of PD drugs is not thinking clearly, and may even be stoned out of his mind. While he may appear to be superficially “normal,” he may have no access to the parts of his brain where social inhibitions are stored. He may also not remember having done anything untoward ten minutes after the perpetration, or if he does, may try to justify it as being “divinely guided” or his “real self” expressing itself. Such behaviors can be a clue that the dopamine levels are grossly excessive.

Summary

This has been a long chapter, with lots of physiology and details about dopamine. But if you can keep these principles in mind, you or your loved ones may be able to judge more clearly whether or not you are overmedicated, undermedicated, or just right. Your MD may not be able to help you because he will see you once or twice a year for fifteen minutes and he can't possibly know how you are behaving most of the day. Furthermore, he may incorrectly think that hallucinations and spasming are normal symptoms of Parkinson's disease. Try to keep this in mind: in a healthy person's brain, in order to maintain the correct sequence of brain area stimulation and to ensure that dopamine is in the correct levels at all times in each of the correct brain areas, the tiny cells of the brain work with exquisite calibrations.

The allocation, engagement, and reuptake of dopamine are parts of an exact, precise mechanism. There is no room for error. Error in dopamine release causes pathological behaviors, everything from hallucinations to heart-stopping arrhythmias (heart spasms and irregularities).

Errors in the brain's dopamine regulation cause many movement, mental, and emotional disorders, not just Parkinson's. Schizophrenia, depression, and many other psychopathologies are caused by dopamine imbalance.

In distinct contrast to the elegant precision of healthy dopamine regulation, the dopamine-enhancing drugs deliver a dump truck of dopamine over the entire brain, bathing it in a random wash of dopamine. Although some of the DEDs direct their actions towards one brain area more than another, they can never hope to attain the level of discrete cellular fine-tuning that is required for healthy brain function. Instead, the massive surges of dopamine that are created with dopamine agonists, MAO inhibitors, alcohol, cocaine, opiates, methamphetamine, L-dopa, nicotine, Ecstasy and dozens of other legal and illegal chemical compounds inundate the brain with a flash flood of dopamine that cannot possibly be distributed correctly. The overloaded brain, flush with that most dangerous of neurotransmitters, **dopamine**, can act out in pathological ways.

Confronted with dopamine excess or deficiency, each brain area has its own ways of acting out. And you must remember an important linguistic distinction: in the case of people who are behaving strangely due to their PD drugs, these wrong behaviors arising from dopamine excess or deficiency are casually referred to as "side effects of antiparkinson's medications." In people who are taking illegal drugs, these same ways of acting out are condemned as "dangerous pathologies."