

Appendix 7

THE ALPHA PRIMATE/COCAINE STUDY

In the first chapter of this book a reference was made to a published research project that studied cocaine addiction in primates.¹ This appendix gives more details on that study. This 2002 study helps support our findings about addiction in PDers before and after recovery. There are two parts of the alpha primate cocaine study that are particularly significant: first, the subjects who became alphas still used cocaine but no longer needed an ever-increasing dosage of cocaine to maintain their response, and secondly, SPECT scans showed a difference in dopamine receptor activity after a primate changed from isolation status to alpha status. This appendix will explore the results of this study in two parts.

PART I

The study and its cocaine related findings

In the study, male primates were first kept in isolation cages for months and had free access to cocaine. They were allowed to self-dose. It was observed that *all* the animals were equally addictable: they all used ever-increasing amounts of cocaine. The increase in need was assumed to be due to addiction. Following this study, the animals spent several months with no cocaine to get the cocaine out of their system.

A subsequent study determined that when the same animals were caged together in four-member, all-male social groups, the primates that became the alpha male of their group (the dominant male at the top of the pecking order) still used cocaine but they never needed to increase their daily doses beyond their starting levels. The social groups' lowest ranking members, the omega males, were *more* subject to addiction than before: their cocaine dosing increased more rapidly and soared to a higher level than when all the subjects had lived in isolation.

A key feature of addiction as it is currently defined is the need for ever-increasing amounts of the addictive substance to attain an effect. Because all primates needed ever-increasing amounts of cocaine in the first part of the study, the conclusion was formed that all the participants were subject to addiction. After the housing change that led to social formations, the now alpha males did continue to use cocaine, but did not need to increase their doses over time. It appeared as if these primates, when alphas, were not susceptible to addiction.

¹ *Nature Neuroscience* 5(2): 169-174, 2002, Mike Nader.

More details

This research was exploring a possible link between social standing and addiction. The brilliant and very helpful researcher, Mike Nader, implied that there is such a link: elevation of social standing might have caused a decrease in susceptibility to addiction.

Happy, carefree alphas

The author of this study hypothesized that the dominant primate had more of the good things in life, and therefore had less need for cocaine. He proposed that the alphas had a higher dopamine level (possibly due to all the fun they were having as alphas) and therefore did not need as much cocaine. Since less cocaine was being ingested, the addiction rate, both pace and quantity, was lower. The chimps at the bottom of the totem pole were assumed to be less happy, and therefore craved cocaine to help make themselves happy despite their dire circumstances.

The assumption being made is that alpha males are happy, or at least contented, males. This assumption is, I propose, in error.

Wary alphas

I hypothesize the opposite: alpha males are more alert, less able to let their guard down. Upon attaining alpha status, the dominant subject must rely more on adrenaline than on dopamine. The dopamine/adrenaline relationship must shift towards the adrenaline end, away from the dopamine end. This adrenaline shift would be necessary to maintain safety, as well as maintaining alpha status: a dominant primate must be continually alert. He is the subject of relentless scrutiny by all other males. The other males behave with subservience, but they are also always watching him to see if he shows signs of weakening. The alpha is the one for whom any show of weakness would be dangerous, even fatal.

The top monkey is always looking over his shoulder. He needs constant vigilance against predators and the constant threats of bodily harm from challengers. He needs to show constant readiness to defend females, infants, and children from any and all threats. He needs the ability to, from a lonely distance, oversee the harmony in the group of females and children. He must behave fearlessly, even pretending to be unhurt when injured.

The pack of challengers will quickly mount a potentially deadly group challenge if any sign of weakness is shown. Although his superior fighting tactics and focus helped him to attain the honored alpha seat from which he can contribute his superior DNA to the harem's gene pool, he must suffer his "honor" in loneliness and constant wariness.

Research review

One wag from *The Economist*, reviewing Mike Nader's conclusion, even went so far as say that it seemed unjust: alphas had all the sex, all the fun, and everyone kowtowing to them, plus they didn't get addicted. He noted that the losers, the ones with no sex and therefore no fun, also had the greatest propensity for addiction. The *Economist* chappy felt that this just wasn't fair – the animals having the least fun also were most prone to be drug addicts!

I wonder if it ever occurred to this reviewer that the life of an alpha male in a cage with three jealous challengers, no privacy, and no females or children would be about as

far away from “fun” as any lifestyle I can imagine. The constant edginess of maintaining his dominance in a close setting with three smirking subordinates, all of whom were just waiting, waiting for the alpha to make a slip so that they could kill him in a group attack, does not seem especially jolly.

A PD parallel with alphas

Many people with Parkinson's disease, whose dopamine levels coincidentally are very low, can relate to this feeling of constant alertness, a high level of self-control, and refusal to show any sign of weakness. They are often very successful in life, very intelligent, and may, in work and play, maintain a more self-controlled persona than their colleagues.

Famous PDers who have exhibited this personality include Adolph Hitler, Chairman Mao Tse Tung, General Douglas MacArthur, Yasir Arafat, Pope John Paul II, and many others. It has been proposed that Napoleon Bonaparte kept his hand in his shirt front to control a tremor – certainly his famous sleep pattern was consistent with that of many unmedicated PDers. As for the Great Emperor who unified China in 221 BC, it seems likely, based on his “premature aging” and early death from what sounds like aspiration pneumonia, that he too was an alpha male with Parkinson’s disease.

The intensity of activity and purpose and high level of emotional self-control of PDers is well recognized. The underlying fear that drives them is described as “emotional harm avoidance,” and is a recognized part of the Parkinson’s personality.

Many PDers are not obviously “dominant:” some PDers choose to use their adrenaline to maintain an unshakeable equipoise. This stability is not based on inner serenity, however. For the most part, those PDers who behave with undisturbable balance are doing so because they dread any sort of tension. A pathological fear of emotional, and in some cases physical, harm or conflict of any sort may lead them to use their terrific powers of intelligence and alertness to behave as if subordinate, even though they are actually running the show to their own specifications. This form of manipulative behavior is much more subtle than passive-aggressive; this behavior is actively harmonizing, and, in the case of PDers, is based on a pathological level of fear.

“Harm avoidance” may well be a dominant factor in the behavior of an alpha male. It may well be that alpha males, like PDers, are adrenaline-dominant, dopamine-subordinate. If this is the case, this primate research may help support our own observation, made during our four years of research, that PDers appear to be fairly resistant to addiction. It may also help explain why, upon beginning to recover, PDers become normally, or even abnormally, susceptible to addiction.

Addictability is variable

Regardless of whether or not the changes occurred due to more fun or heightened vigilance, the most exciting thing about this study was its conclusive proof that addictability was variable. External (non-genetic) change in social standing could alter addictability. This is a very new concept.

The abrupt changes seen in our patients who began recovering from Parkinson’s disease while still taking antiparkinson’s medications defied anything we had read in our medical texts. If, in fact, susceptibility to addiction could change quickly, and in response to something so “superficial” as a change in emotional condition or social status, as was

suggested by this primate study, then possibly our findings were no longer quite so much of a bizarre aberration. As one colleague said to me with regard to this timely primate study, “You never would have thought of doing this study; they did your research for you!”

PART II

The study and its findings with regard to SPECT scan changes in alpha males

SPECT scans employed in the study measured the level of activity at the subjects’ brain dopamine receptors. These scans use a radioactive “tag,” or “tracer,” a molecule that is attracted specifically to dopamine receptors, and to which a radioactive bit has been added. The subject is given the tags intravenously, and the scanning machine then measures the amounts of radioactivity that moves into the various brain areas.¹ The researchers in this study were wondering if monkeys with different social ranking would have different levels of activity in their brains’ dopamine centers.

As an aside, the relationship between social standing and addictive drug and alcohol use has been pondered for millennia. Because addicts sometimes lose their social skills, to say nothing of jobs and relationships, when their brains become preoccupied with drugs, the apparent relationship between drugs and social standing is this: low social standing is sometimes related to drug addiction. On the other hand, one might say that it is low social standing that causes one to reach for a mind-altering drug in the first place. Sociologists argue strongly back and forth as to whether or not the poor social standing preceded the drug addiction, or if the drug addiction led to the poor social standing. The study with primates was looking for brain differences between individuals prior to drug use and again after the socialization changes in hopes of finding a clue about these ancient questions.

Alpha males have more dopamine receptor activity

The before-socialization and after-socialization SPECT scans of the animals’ brains indicated that primates living alone in separate housing all had similar responses to the tags; their dopamine receptors’ activity levels were all comparable.

Subsequent to the group housing, the levels of dopamine receptor activity changed. This change corresponded to the social ranking of the primates; the radioactive dopamine-like tracer showed up as greater receptor-area activity in the alpha male and decreased receptor-area activity in the omega male.

Conclusion of the researcher: increased activity means increased dopamine levels

The researcher who assessed the results of this study guessed that alpha males’ increased tracer activity at dopamine receptor sites probably equaled higher levels of native dopamine activity. He further concluded that this elevated dopamine level was the reason the alphas did not need ever-increasing doses of cocaine. Because cocaine’s

¹ For a fun aside, one of the first researchers to use this technology became infamous. In the USA the laws prevented him using humans for his research, so he went to China in 1999 and used the machines there. He used himself as a subject and used a radioactive cocaine analog, measuring his own brain’s response. He published his work and was hailed as both a brave hero (by his own university) and a villain (by competing universities, who insisted that he should somehow be punished).

pleasure enhancement comes from its ability to elevate dopamine, the researcher assumed that the underlying dopamine increase, as suggested by increased receptor activity, eliminated the need for more dopamine enhancement.

This logic may be completely wrong. To show how this assumption may be 180° backwards, let's look at the findings of SPECT scans on the brains of PDers and consider the assumptions. Hopefully, as you read this, you are recalling the preceding appendix on fallacies in science, and how wrong assumptions lead to convoluted proofs further downstream.

What SPECT scans show and what they do not show: still anybody's guess

I want to consider the possibility that the radioactive tags that *purportedly* measure dopamine receptor activity and thus imply a certain level of dopamine activity, may not actually measure these things. They may do only this one, much smaller thing: they may show how many empty dopamine receptors are available.

Let us assume that a radioactive tag that is designed to fit in a dopamine receptor succeeds in getting into the brain. The extent to which the brain absorbs these tracers and lodges them into the receptors might depend to a large degree on how many receptors are sitting by idly. It may be that, in a situation where the receptors are already saturated with dopamine, the injected tags will not be able to find a resting spot – it may even be that they will have increased difficulty in crossing the blood-brain barrier.

On the other hand, if a person has a dopamine deficiency, the tracers may find dopamine receptors open armed and waiting for a hookup. In this latter case, an increase in SPECT scan radioactivity in the area of the dopamine receptors will indicate that the subject has an excess of *unused* receptors; these receptors may be unused due to an underlying *shortage* of dopamine – just the opposite of the conclusions given in this study.

SPECT scans in PDers: an aside

SPECT scans in PDers usually show reduced receptor activity. This finding, coupled with the long-held (fifty years) assumption that PDers sole problem was a lack of dopamine, inexplicably was used to “prove” that low dopamine levels were connected with low receptor activity as seen in SPECT scans.

Logically speaking, one would have thought that low receptor activity would indicate low receptor activity, and nothing else. If anything, a deep thinker should have proposed that PDers, having insufficient dopamine, would also have lots of empty dopamine receptors. These empty receptors would have been sitting ducks for the radioactive tags. This would then mean that decreased dopamine availability, as seen in PD, should lead, theoretically, to *increased* receptor activity in the presence of the radioactive tags, increased compared to a normal brain that supposedly has a full complement of dopamine. This would have been logical.

Since the opposite result was found in PDers, namely that PDers have both lowered receptor activity compared to normal and are also traditionally purported to have lowered dopamine levels, one might hope that some researcher might have considered the possibility that our overly simplistic view of Parkinson's might be wrong. This hope, of course, is far-fetched. Logic scarcely entered into the thing, and the idea that the preexisting ideas about Parkinson's were wrong was never entertained. It was announced,

shortly after SPECT scans were first employed in PDers, that low receptor activity must naturally be an indicator of low dopamine levels! The reverse was then dutifully noted: high receptor response to the radioactive tags meant that the subject must have high levels of dopamine.

No one has ever actually tested this theory by performing SPECT scans on rat brains and then assaying the results to see whether or not a high tracer level at the receptors corresponds to a high level of dopamine. Instead, a sort of backwards thinking, based on assumptions about Parkinson's disease, has led to the current mode of interpreting these new scans – a mode that may be completely wrong.

While one might still use the tests to decide whether or not a PDer's dopamine receptor activity level is consistent with the scans of others who have also received a diagnosis of Parkinson's, the expanded conclusion that high receptor activity indicates high dopamine levels may be completely wrong.

Logic: the road not taken

It might be that not only dopamine itself, but all parts of the dopamine system, including dopamine transporters, dopamine reuptake enzymes, dopamine-producing cells and dopamine receptors are all slowly, over the years, decreased in a person with Parkinson's disease. This would explain the low dopamine receptor response in PDers' SPECT scans.

This more logical assumption might lead to a better understanding of Parkinson's disease, a disease in which the body has turned off the dopamine *system* altogether, or at least turned it down very, very far for a very long time. This would explain why PDers have both a decrease in dopamine and, eventually, a decrease in dopamine receptors. Let's look at the thing from this angle. After that, we can go back to the primate study and consider a conclusion quite different from the one made by the paradigm-weighted researcher who imagined that his happy, contented alphas were refraining from cocaine because increased dopamine receptor activity – and therefore high levels of dopamine – were keeping them content.

PDer SPECT scans: let's suppose

SPECT scans of people with Parkinson's disease show decreased receptor activity: the radioactive tracer drugs simply find fewer resting spots in the brain of people whose various dopamine structures have decreased or been dismantled over decades of unuse. During their decades of subclinical PD, their dopamine-producing structures, dopamine receptors, dopamine transporters, and other dopamine-related enzymes have been decreasing.

Were this not the case, and if all the dopamine receptors were still in place along with all the rest of the dopamine-related chemistry, and the only thing missing from a PDer was the dopamine itself, the infusion of tagged, dopamine receptor-seeking drugs should swarm onto the receptors, the tagged drugs filling in the otherwise vacant receptors.

This is NOT what we see in a SPECT scan of a person with Parkinson's. Even though a PDer is given an adequate quantity of tagged drugs, the scan still shows a lower receptor activity than a normal brain. This may mean that not only dopamine levels, but *receptor* levels (the number of receptors) are eventually decreased in Parkinson's disease.

Or possibly receptor responsiveness is decreased. Or for that matter, maybe the amount of tracer pulled inside the blood-brain barrier is the commodity that decreases in a person with Parkinson's disease. Or the correct answer may be "D," all of the above. No one knows.

While these low-receptor SPECT scan tests are beginning to be used to confirm a diagnosis of Parkinson's disease, they might be better used to confirm that Parkinson's disease is not caused by mere dopamine deficiency, but by some alteration in the entire dopamine processing system over time, an alteration that prevents radioactive tracers from collecting on PDers' receptors in quantities as large as they can on healthy people's receptors.

Primates vs. PDers: where we are going with all this

Following their change in social status, primates in the cocaine study underwent rapid changes in their response to cocaine and their SPECT scans also showed a quick change from the previous scans. The alpha males were *no longer addictable* to cocaine, and their SPECT scans showed an *increase* in dopamine receptor activity.

People with Parkinson's also have a *low level of susceptibility to addiction*, **but** their SPECT scans show a *low* level of dopamine receptor activity.

If there is any relationship between the lack of addictability and the level of dopamine receptor activity, why do these two groups have such opposite SPECT scans?

Short-term neurotransmitter change as compared with long-term neurotransmitter change

The primates in the study were only observed over a period of months. During this brief period, the alphas may well have changed their adrenaline/dopamine ratio so that their adrenaline was higher and their dopamine was lower. This would make them less subject to addiction. Their healthy brains would still have a full complement of dopamine-related chemistry and structures, but they would be temporarily not in use. Radioactive tags, if inserted into the bloodstream, might easily find their way into the system and cluster onto the unused dopamine receptors, thus making a large showing at the receptor sites, a showing that would indicate much activity in these areas on the scans.

In sharp contrast to this temporary drop in dopamine manifesting in the alpha males, a PDer has brain changes that have been taking place over decades. Is it possible that the brain change of Parkinson's that stifles the entire dopamine system might lead to a gradual decrease in dopamine, dopamine-producing cells, dopamine-related enzymes, and dopamine receptors? By the time the PD is diagnosable, decades later, there might be a substantial decrease in all structures or functionality of structures that relate to the dopamine system. If this is possible, then it only makes sense that a SPECT scan of a PDer will show less activity in receptors: he may have fewer receptors, period!

If so, then we have the answer to the puzzling difference between PDers whose dopamine systems have been shut down for decades and primates whose dopamine systems have been recently put on hold while they perform as alphas. A SPECT scan of the PDer's brain will show a decrease in receptor activity, particularly on the damaged side of the brain, the side that has not been receiving a healthy electrical signal to its dopamine system. A SPECT scan of a recently promoted primate may show a significant

number of vacancies in the dopamine receptors, as manifested in larger than usual numbers of the tag molecules being picked up.

Hypothesis

The long-term changes in PDers may not be analogous to the quick alteration in primate brains that occurs in response to a change in social status. Comparing these situations and trying to make a connection between diminished SPECT activity in the former and increased SPECT activity in the latter may not be as worthwhile as previously imagined. It may be that the fast time frame of neurotransmitter release, and the slow, concomitant structural changes that occur over time make it inappropriate to form conclusions about a primate's *short-term* change based on previous data gathered from observing PDers' *long-term* change; the historical basis for concluding that low receptor activity is related to low dopamine stems in part from SPECT scans of PDers, plus lots of conjecture. The researchers, trying to impose interpretations of PDer SPECT scans onto the SPECT scans of primates, may have been comparing dried apples and fresh oranges.

Further proof: uncooperative brain cells

Recent research suggests that even in PD brains that are supplied with adequate dopamine levels via levodopa, some dopamine receptors, especially those that have had long term exposure to dopamine-enhancing drugs, increasingly refuse to use the dopamine that is thrust upon them.

This reluctance on the part of PDer receptors to accept dopamine may also contribute to the lower tracer levels seen in PDer SPECT scans. PDers' SPECT scans may register low receptor activity levels even when dopamine is present! In other words, the results of a SPECT scan do not actually reflect dopamine levels or the quantity of receptors. They merely indicate how many tracers are being used by receptors – nothing more, nothing less.

What SPECT scans really show

The deeper meaning of these SPECT scans is still cloaked in mystery. Like Plato's cave dwelling fellows making conjectures about the real sizes, shapes, and colors of objects which the fellows – remaining in their caves – only perceive as inconstant shadows¹, the people who employ SPECT scans are only guessing as to the meaning of the black and white images generated by the radioactive tracers deep in the brains of their subjects.

Looking ahead

What we really need here are SPECT scans of people who have just made the transition from normal to pre-parkinson's. When their foot injury occurs and they switch into ferocious denial of the injury, that would be the time to get a SPECT scan of these latent PDers. It may well be that they too would show increased activity of tracers in that first flush of powerful denial and self-control, when adrenaline surges through the body and dopamine receptors are lying around empty.

¹ See Plato's *The Republic*.

This is all very much fun to ponder, and it doesn't need to be further addressed in this book about medication. But this little foray into the meaning of SPECT scans might, if nothing else, help the reader to remember that science, with all its reproducible data, does not provide Truth. The real value of this appendix's musing on SPECT scans is pointing out that it is naively assumed that increased tracer activity means increased dopamine when, in fact, increased receptor activity in response to tracers may mean less native dopamine.

It used to be assumed, because the sun rose every morning, that the sun went around the earth. It turns out the best assumption to be made from the fact that the sun rises every morning is simply this: the sun *appears* to rise every morning. Every other possible theory that derives from that observation is only a guess. Science is not about Truth. Science is about converting observations into guesses. The guesses necessarily reflect our desires and prejudices.

The extreme value of this study

The most valuable aspect of the primate study, from the perspective of Parkinson's research, is that it suggests that a model for Parkinson's can actually be found in an animal setting. Until now, the only way to get an animal cell model that even remotely resembled the dormant dopamine-producing cells of PD was to destroy cells via toxins. There was no known way to induce a long-standing adrenaline/dopamine imbalance in an animal, that I knew of.¹

Because animals in nature do not have the emotional constraints and personality/ego perversions that are the necessary basis for denial of injury, I had presumed that there would never be an opportunity to observe an animal model of Parkinson's disease. However, I had never considered the sad situation of the alpha male.

The alpha male, friendless, extremely responsible, even selfless, always on alert, looking over his shoulder for potential attacks or betrayal from his boyhood playmates, living *for* society but not *of* it, is a beautiful, natural example of several aspects of the Parkinson's personality. That these noble, selfless animals – after the heavy burden of alpha-hood is won – should also be, like PDers, unaddictable to dopamine-enhancing drugs, may be another indication of their brotherhood with the unaddictable PDer.

Most medicated PDers have pooh-poohed the idea that their vaunted will power will be affected when their Parkinson's-inducing fear pattern is altered; they often refuse to believe that such a change is possible – often with disastrous results. The rapid change in alpha primates provides proof that such a change is possible: the measured, rapid change in primate addictability seen in this study in response to a change in social setting presents a new way to think about addiction.

If high or low resistance to addiction can be understood primarily to have a physiological basis rather than the will power basis with which most PDers credit themselves, possibly they will better comprehend the dangers that confront them if they begin to recover from Parkinson's disease while taking supremely addictive medication.

¹ While I believe much of the animal testing in labs today constitutes unnecessary abuse, animals in the wild do provide a valuable window into natural phenomena, a window uncluttered with the "civilized" emotional twistings and sociologically induced illness that humans are heir to. Animals in the wild make a valuable contribution to our observances of natural history.

Summary

The abrupt reduction of addictability in alpha males when they are under stress may be related to the decreased susceptibility to addiction that is seen in people with Parkinson's. Also, SPECT scans, while they may not offer the proof of high or low *dopamine* levels per se, may be valuable in this regard: alpha primates show a change in their dopamine receptor areas when their social status changes. This indicates an objective basis for noting that brain neurotransmitter levels may be influenced powerfully by sociological (external, also known as "environmental") factors.

Also, there may or may not be a relationship between the decreased addictability of alpha males – a presumably dopamine-related phenomenon – and the objective, concomitant finding of altered SPECT scans in the dopamine receptor area of these animals.