Two

One Second Before

Various muscles have moved, and a behavior has happened. Perhaps it is a good act: you've empathically touched the arm of a suffering person. Perhaps it is a foul act: you've pulled a trigger, targeting an innocent person. Perhaps it is a good act: you've pulled a trigger, drawing fire to save others. Perhaps it is a foul act: you've touched the arm of someone, starting a chain of libidinal events that betray a loved one. Acts that, as emphasized, are definable only by context.

Thus, to ask the question that will begin this and the next eight chapters, why did that behavior occur?

As this book's starting point, we know that different disciplines produce different answers—because of some hormone; because of evolution; because of childhood experiences or genes or culture—and as the book's central premise, these are utterly intertwined answers, none standing alone. But on the most proximal level, in this chapter we ask: What happened one second before the behavior that caused it to occur? This puts us in the realm of neurobiology, of understanding the brain that commanded those muscles.

This chapter is one of the book's anchors. The brain is the final common pathway, the conduit that mediates the influences of all the distal factors to be covered in the chapters to come. What happened an hour, a decade, a million years earlier? What happened were factors that impacted the brain and the behavior it produced.

This chapter has two major challenges. The first is its god-awful length. Apologies; I've tried to be succinct and nontechnical, but this is foundational material that needs to be covered. Second, regardless of how nontechnical I've

tried to be, the material can overwhelm someone with no background in neuroscience. To help with that, please wade through appendix 1 around now.

Now we ask: What crucial things happened in the second before that pro- or antisocial behavior occurred? Or, translated into neurobiology: What was going on with action potentials, neurotransmitters, and neural circuits in particular brain regions during that second?

THREE METAPHORICAL (BUT NOT LITERAL) LAYERS

We start by considering the brain's macroorganization, using a model proposed in the 1960s by the neuroscientist Paul MacLean.[1] His "triune brain" model conceptualizes the brain as having three functional domains:

Layer 1: An ancient part of the brain, at its base, found in species from humans to geckos. This layer mediates automatic, regulatory functions. If body temperature drops, this brain region senses it and commands muscles to shiver. If blood glucose levels plummet, that's sensed here, generating hunger. If an injury occurs, a different loop initiates a stress response.

Layer 2: A more recently evolved region that has expanded in mammals. MacLean conceptualized this layer as being about emotions, somewhat of a mammalian invention. If you see something gruesome and terrifying, this layer sends commands down to ancient layer 1, making you shiver with emotion. If you're feeling sadly unloved, regions here prompt layer 1 to generate a craving for comfort food. If you're a rodent and smell a cat, neurons here cause layer 1 to initiate a stress response.

Layer 3: The recently evolved layer of neocortex sitting on the upper surface of the brain. Proportionately, primates devote more of their brain to this layer than do other species. Cognition, memory storage, sensory processing, abstractions, philosophy, navel contemplation. Read a scary passage of a book, and layer 3 signals layer 2 to make you feel frightened, prompting layer 1 to initiate shivering. See an ad for Oreos and feel a craving—layer 3 influences layers 2 and 1. Contemplate the fact that loved ones won't live forever, or kids in refugee camps, or how the Na'vis' home tree was destroyed by those jerk humans in *Avatar* (despite the fact that, wait, *Na'vi aren't real!*), and layer 3 pulls layers 2 and 1 into the picture, and you feel sad and have the same sort of stress response that you'd have if you were fleeing a lion.

Thus we've got the brain divided into three functional buckets, with the usual advantages and disadvantages of categorizing a continuum. The biggest disadvantage is how simplistic this is. For example:

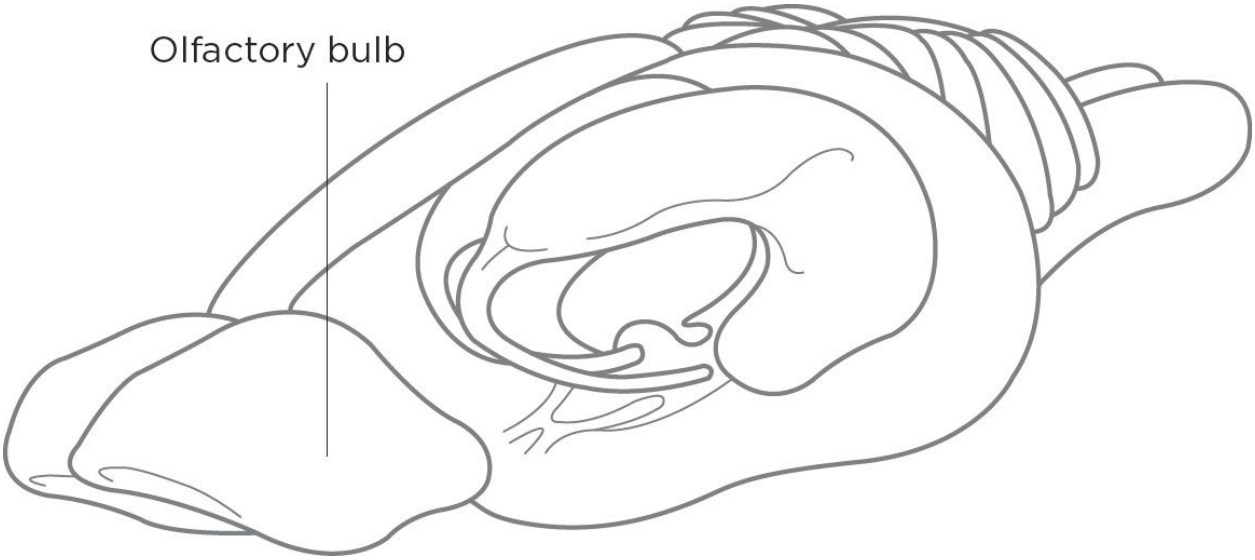
a. Anatomically there is considerable overlap among the three layers (for example, one part of the cortex can best be thought of as part of layer 2; stay tuned).
b. The flow of information and commands is not just top down, from layer 3 to 2 to 1. A weird, great example explored in chapter 15: if someone is holding a cold drink (temperature is processed in layer 1), they're more likely to judge someone they meet as having a cold personality (layer 3).
c. Automatic aspects of behavior (simplistically, the purview of layer 1), emotion (layer 2), and thought (layer 3) are not separable.
d. The triune model leads one, erroneously, to think that evolution in effect slapped on each new layer without any changes occurring in the one(s) already there.

Despite these drawbacks, which MacLean himself emphasized, this model will be a good organizing metaphor for us.

THE LIMBIC SYSTEM

To make sense of our best and worst behaviors, automaticity, emotion, and cognition must all be considered; I arbitrarily start with layer 2 and its emphasis on emotion.

Early-twentieth-century neuroscientists thought it obvious what layer 2 did. Take your standard-issue lab animal, a rat, and examine its brain. Right at the front would be these two gigantic lobes, the "olfactory bulbs" (one for each nostril), the primary receptive area for odors.



Neuroscientists at the time asked what parts of the brain these gigantic rodent olfactory bulbs talked to (i.e., where they sent their axonal projections). Which brain regions were only a single synapse away from receiving olfactory information, which were two synapses, three, and so on?

And it was layer 2 structures that received the first communiqués. Ah, everyone concluded, this part of the brain must process odors, and so it was termed the rhinencephalon—the nose brain.

Meanwhile, in the thirties and forties, neuroscientists such as the young MacLean, James Papez, Paul Bucy, and Heinrich Klüver were starting to figure out what the layer 2 structures did. For example, if you lesion (i.e., destroy) layer 2 structures, this produces "Klüver-Bucy syndrome," featuring abnormalities in sociality, especially in sexual and aggressive behaviors. They concluded that

these structures, soon termed the “limbic system” (for obscure reasons), were about emotion.

Rhinencephalon or limbic system? Olfaction or emotion? Pitched street battles ensued until someone pointed out the obvious—for a rat, emotion and olfaction are nearly synonymous, since nearly all the environmental stimuli that elicit emotions in a rodent are olfactory. Peace in our time. In a rodent, olfactory inputs are what the limbic system most depends on for emotional news of the world. In contrast, the primate limbic system is more informed by visual inputs.

Limbic function is now recognized as central to the emotions that fuel our best and worst behaviors, and extensive research has uncovered the functions of its structures (e.g., the amygdala, hippocampus, septum, habenula, and mammillary bodies).

There really aren’t “centers” in the brain “for” particular behaviors. This is particularly the case with the limbic system and emotion. There is indeed a sub-subregion of the motor cortex that approximates being the “center” for making your left pinkie bend; other regions have “center”-ish roles in regulating breathing or body temperature. But there sure aren’t centers for feeling pissy or horny, for feeling bittersweet nostalgia or warm protectiveness tinged with contempt, or for that what-is-that-thing-called-love feeling. No surprise, then, that the circuitry connecting various limbic structures is immensely complex.

The Autonomic Nervous System and the Ancient Core Regions of the Brain

The limbic system’s regions form complex circuits of excitation and inhibition. It’s easier to understand this by appreciating the deeply held desire of every limbic structure—to influence what the hypothalamus does.

Why? Because of its importance. The hypothalamus, a limbic structure, is the interface between layers 1 and 2, between core regulatory and emotional parts of the brain.

Consistent with that, the hypothalamus gets massive inputs from limbic layer 2 structures but disproportionately sends projections to layer 1 regions. These are the evolutionarily ancient midbrain and brain stem, which regulate automatic reactions throughout the body.

For a reptile such automatic regulation is straightforward. If muscles are working hard, this is sensed by neurons throughout the body that send signals up

the spine to layer 1 regions, resulting in signals back down the spine that increase heart rate and blood pressure; the result is more oxygen and glucose for the muscles. Gorge on food, and stomach walls distend; neurons embedded there sense this and pass on the news, and soon blood vessels in the gut dilate, increasing blood flow and facilitating digestion. Too warm? Blood is sent to the body's surface to dissipate heat.

All of this is automatic, or "autonomic." And thus the midbrain and brain-stem regions, along with their projections down the spine and out to the body, are collectively termed the "autonomic nervous system."*

And where does the hypothalamus come in? It's the means by which the limbic system influences autonomic function, how layer 2 talks to layer 1. Have a full bladder with its muscle walls distended, and midbrain/brain-stem circuitry votes for urinating. Be exposed to something sufficiently terrifying, and limbic structures, via the hypothalamus, persuade the midbrain and brain stem to do the same. This is how emotions change bodily functions, why limbic roads eventually lead to the hypothalamus.*

The autonomic nervous system has two parts—the sympathetic and parasympathetic nervous systems, with fairly opposite functions.

The sympathetic nervous system (SNS) mediates the body's response to arousing circumstances, for example, producing the famed "fight or flight" stress response. To use the feeble joke told to first-year medical students, the SNS mediates the "four *F*s—fear, fight, flight, and sex." Particular midbrain/brain-stem nuclei send long SNS projections down the spine and on to outposts throughout the body, where the axon terminals release the neurotransmitter norepinephrine. There's one exception that makes the SNS more familiar. In the adrenal gland, instead of norepinephrine (aka noradrenaline) being released, it's epinephrine (aka the famous adrenaline).*

Meanwhile, the parasympathetic nervous system (PNS) arises from different midbrain/brain-stem nuclei that project down the spine to the body. In contrast to the SNS and the four *F*s, the PNS is about calm, vegetative states. The SNS speeds up the heart; the PNS slows it down. The PNS promotes digestion; the SNS inhibits it (which makes sense—if you're running for your life, avoiding being someone's lunch, don't waste energy digesting breakfast).* And as we will see chapter 14, if seeing someone in pain activates your SNS, you're likely to be preoccupied with your own distress instead of helping; turn on the PNS, and it's

the opposite. Given that the SNS and PNS do opposite things, the PNS is obviously going to be releasing a different neurotransmitter from its axon terminals—acetylcholine.*

There is a second, equally important way in which emotion influences the body. Specifically, the hypothalamus also regulates the release of many hormones; this is covered in chapter 4.

So the limbic system indirectly regulates autonomic function and hormone release. What does this have to do with behavior? Plenty—because the autonomic and hormonal states of the body feed back to the brain, influencing behavior (typically unconsciously).* Stay tuned for more in chapters 3 and 4.

The Interface Between the Limbic System and the Cortex

Time to add the cortex. As noted, this is the brain's upper surface (its name comes from the Latin *cortic*, meaning "tree bark") and is the newest part of the brain.

The cortex is the gleaming, logical, analytical crown jewel of layer 3. Most sensory information flows there to be decoded. It's where muscles are commanded to move, where language is comprehended and produced, where memories are stored, where spatial and mathematical skills reside, where executive decisions are made. It floats above the limbic system, supporting philosophers since at least Descartes who have emphasized the dichotomy between thought and emotion.

Of course, that's all wrong, as shown by the temperature of a cup—something processed in the hypothalamus—altering assessment of the coldness of someone's personality. Emotions filter the nature and accuracy of what is remembered. Stroke damage to certain cortical regions blocks the ability to speak; some sufferers reroute the cerebral world of speech through emotive, limbic detours—they can sing what they want to say. The cortex and limbic system are not separate, as scads of axonal projections course between the two. Crucially, those projections are bidirectional—the limbic system talks to the cortex, rather than merely being reined in by it. The false dichotomy between thought and feeling is presented in the classic *Descartes' Error*, by the

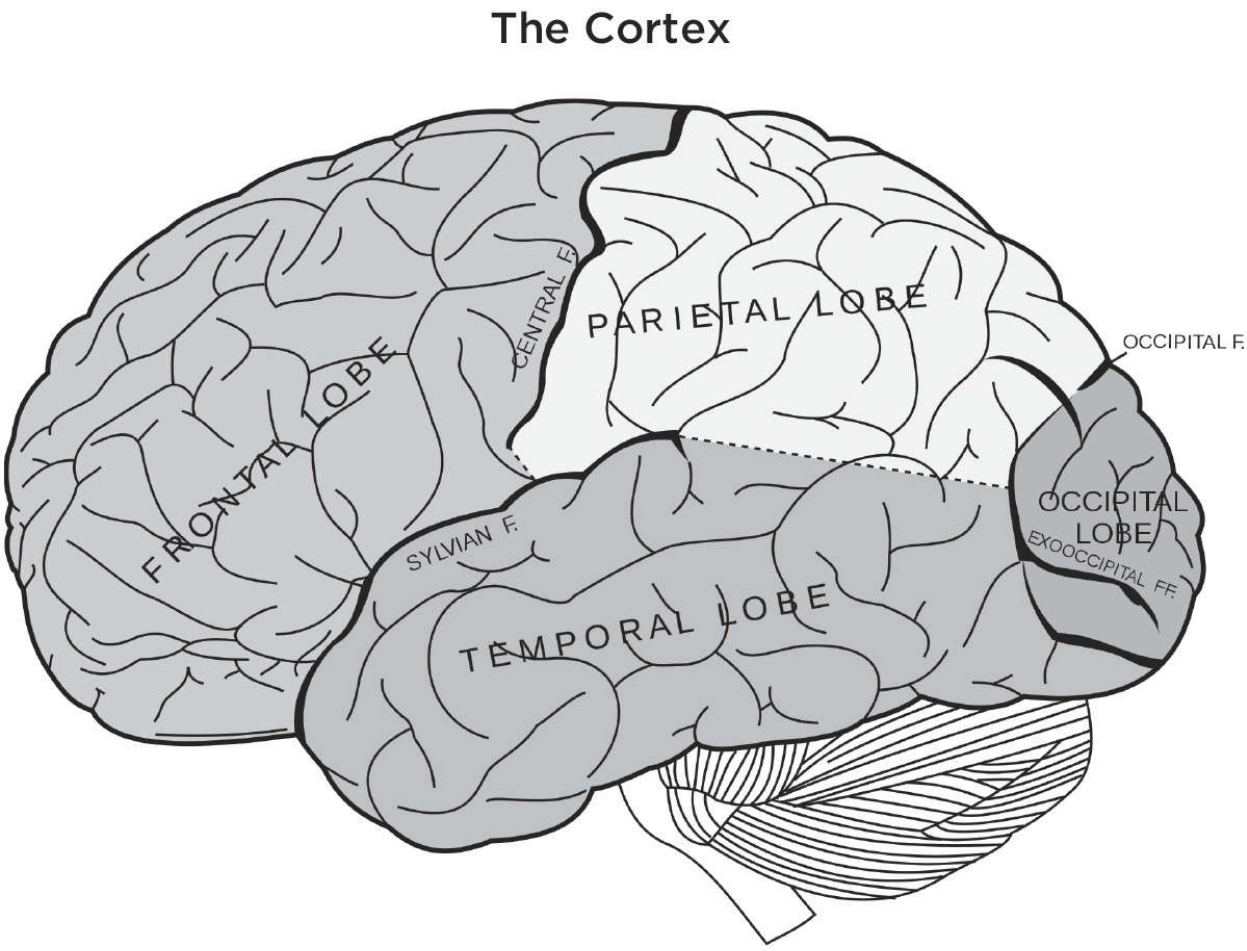
neurologist Antonio Damasio of the University of Southern California; his work is discussed later.[2]

While the hypothalamus dwells at the interface of layers 1 and 2, it is the incredibly interesting frontal cortex that is the interface between layers 2 and 3.

Key insight into the frontal cortex was provided in the 1960s by a giant of neuroscience, Walle Nauta of MIT.*[3] Nauta studied what brain regions sent axons to the frontal cortex and what regions got axons from it. And the frontal cortex was bidirectionally enmeshed with the limbic system, leading him to propose that the frontal cortex is a quasi member of the limbic system. Naturally, everyone thought him daft. The frontal cortex was the most recently evolved part of the very highbrow cortex—the only reason why the frontal cortex would ever go slumming into the limbic system would be to preach honest labor and Christian temperance to the urchins there.

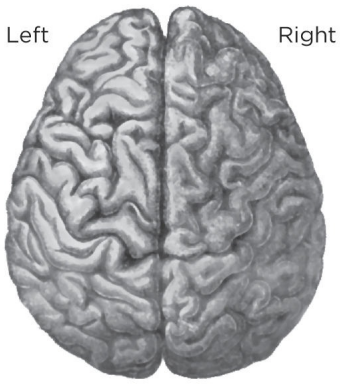
Naturally, Nauta was right. In different circumstances the frontal cortex and limbic system stimulate or inhibit each other, collaborate and coordinate, or bicker and work at cross-purposes. It really is an honorary member of the limbic system. And the interactions between the frontal cortex and (other) limbic structures are at the core of much of this book.

Two more details. First, the cortex is not a smooth surface but instead is folded into convolutions. The convolutions form a superstructure of four separate lobes: the temporal, parietal, occipital, and frontal, each with different functions.



Brain Lateralization

- Analytical thought
- Detail-oriented perception
- Ordered sequencing
- Rational thought
- Verbal
- Cautious
- Planning
- Math/science
- Logic
- Right-field vision



- Intuitive thought
- Holistic perception
- Random sequencing
- Emotional thought
- Nonverbal
- Adventurous
- Impulse
- Creative writing/art
- Imagination
- Left-field vision

- Right-side motor skills
- Left-side motor skills

Second, brains obviously have left and right sides, or “hemispheres,” that roughly mirror each other.

Thus, except for the relatively few midline structures, brain regions come in pairs (a left and right amygdala, hippocampus, temporal lobe, and so on). Functions are often lateralized, such that the left and right hippocampi, for example, have different but related functions. The greatest lateralization occurs in the cortex; the left hemisphere is analytical, the right more involved in intuition and creativity. These contrasts have caught the public fancy, with cortical lateralization exaggerated by many to an absurd extent, where “left brain”–edness has the connotation of anal-retentive bean counting and “right brain”–edness is about making mandalas or singing with whales. In fact the functional differences between the hemispheres are generally subtle, and I’m mostly ignoring lateralization.

We’re now ready to examine the brain regions most central to this book, namely the amygdala, the frontal cortex, and the mesolimbic/mesocortical dopamine system (discussion of other bit-player regions will be subsumed under the headings for these three). We start with the one arguably most central to our worst behaviors.

THE AMYGDALA

The amygdala* is the archetypal limbic structure, sitting under the cortex in the temporal lobe. It is central to mediating aggression, along with other behaviors that tell us tons about aggression.

A First Pass at the Amygdala and Aggression

The evidence for the amygdala's role in aggression is extensive, based on research approaches that will become familiar.

First there's the correlative "recording" approach. Stick recording electrodes into numerous species' amygdalae* and see when neurons there have action potentials; this turns out to be when the animal is being aggressive.* In a related approach, determine which brain regions consume extra oxygen or glucose, or synthesize certain activity-related proteins, during aggression—the amygdala tops the list.

Moving beyond mere correlation, if you lesion the amygdala in an animal, rates of aggression decline. The same occurs transiently when you temporarily silence the amygdala by injecting Novocain into it. Conversely, implanting electrodes that stimulate neurons there, or spritzing in excitatory neurotransmitters (stay tuned), triggers aggression.[4]

Show human subjects pictures that provoke anger, and the amygdala activates (as shown with neuroimaging). Sticking an electrode in someone's amygdala and stimulating it (as is done before certain types of neurosurgery) produces rage.

The most convincing data concern rare humans with damage restricted to the amygdala, either due to a type of encephalitis or a congenital disorder called Urbach-Wiethe disease, or where the amygdala was surgically destroyed to control severe, drug-resistant seizures originating there.[5] Such individuals are impaired in detecting angry facial expressions (while being fine at recognizing other emotional states—stay tuned).

And what does amygdala damage do to aggressive behavior? This was studied in humans where amygdalotomies were done not to control seizures but

to control aggression. Such psychosurgery provoked fiery controversy in the 1970s. And I don't mean scientists not saying hello to each other at conferences. I mean a major public shit storm.

The issue raised bioethical lightning rods: What counted as pathological aggression? Who decided? What other interventions had been tried unsuccessfully? Were some types of hyperaggressive individuals more likely to go under the knife than others? What constituted a cure?[6]

Most of these cases concerned rare epileptics where seizure onset was associated with uncontrollable aggression, and where the goal was to contain that behavior (these papers had titles such as "Clinical and physiological effects of stereotaxic bilateral amygdalotomy for intractable aggression"). The fecal hurricane concerned the involuntary lopping out of the amygdala in people without epilepsy but with a history of severe aggression. Well, doing this could be profoundly helpful. Or Orwellian. This is a long, dark story and I will save it for another time.

Did destruction of the human amygdala lessen aggression? Pretty clearly so, when violence was a reflexive, inchoate outburst preceding a seizure. But with surgery done solely to control behavior, the answer is, er, maybe—the heterogeneity of patients and surgical approaches, the lack of modern neuroimaging to pinpoint exactly which parts of the amygdala were destroyed in each individual, and the imprecision in the behavioral data (with papers reporting from 33 to 100 percent "success" rates) make things inconclusive. The procedure has almost entirely fallen out of practice.

The amygdala/aggression link pops up in two notorious cases of violence. The first concerns Ulrike Meinhof, a founder in 1968 of the Red Army Faction (aka the Baader-Meinhof Gang), a terrorist group responsible for bombings and bank robberies in West Germany. Meinhof had a conventional earlier life as a journalist before becoming violently radicalized. During her 1976 murder trial, she was found hanged in her jail cell (suicide or murder? still unclear). In 1962 Meinhof had had a benign brain tumor surgically removed; the 1976 autopsy showed that remnants of the tumor and surgical scar tissue impinged on her amygdala.[7]

A second case concerns Charles Whitman, the 1966 "Texas Tower" sniper who, after killing his wife and mother, opened fire atop a tower at the University of Texas in Austin, killing sixteen and wounding thirty-two, one of the first school massacres. Whitman was literally an Eagle Scout and childhood choirboy, a happily married engineering major with an IQ in the 99th percentile. In the

prior year he had seen doctors, complaining of severe headaches and violent impulses (e.g., to shoot people from the campus tower). He left notes by the bodies of his wife and his mother, proclaiming love and puzzlement at his actions: "I cannot rationaly [*sic*] pinpoint any specific reason for [killing her]," and "let there be no doubt in your mind that I loved this woman with all my heart." His suicide note requested an autopsy of his brain, and that any money he had be given to a mental health foundation. The autopsy proved his intuition correct—Whitman had a glioblastoma tumor pressing on his amygdala. Did Whitman's tumor "cause" his violence? Probably not in a strict "amygdaloid tumor = murderer" sense, as he had risk factors that interacted with his neurological issues. Whitman grew up being beaten by his father and watching his mother and siblings experience the same. This choirboy Eagle Scout had repeatedly physically abused his wife and had been court-martialed as a Marine for physically threatening another soldier.* And, perhaps indicative of a thread running through the family, his brother was murdered at age twenty-four during a bar fight.[8]

A Whole Other Domain of Amygdaloid Function to the Center Stage

Thus considerable evidence implicates the amygdala in aggression. But if you asked amygdala experts what behavior their favorite brain structure brings to mind, "aggression" wouldn't top their list. It would be fear and anxiety.[9] Crucially, the brain region most involved in feeling afraid and anxious is most involved in generating aggression.

The amygdala/fear link is based on evidence similar to that supporting the amygdala/aggression link.[10] In lab animals this has involved lesioning the structure, detecting activity in its neurons with "recording electrodes," electrically stimulating it, or manipulating genes in it. All suggest a key role for the amygdala in perceiving fear-provoking stimuli and in expressing fear. Moreover, fear activates the amygdala in humans, with more activation predicting more behavioral signs of fear.

In one study subjects in a brain scanner played a Ms. Pac-Man–from–hell video game where they were pursued in a maze by a dot; if caught, they'd be shocked.[11] When people were evading the dot, the amygdala was silent. However, its activity increased as the dot approached; the stronger the shocks,

the farther away the dot would be when first activating the amygdala, the stronger the activation, and the larger the self-reported feeling of panic.

In another study subjects waited an unknown length of time to receive a shock.[12] This lack of predictability and control was so aversive that many *chose* to receive a stronger shock immediately. And in the others the period of anticipatory dread increasingly activated the amygdala.

Thus the human amygdala preferentially responds to fear-evoking stimuli, even stimuli so fleeting as to be below conscious detection.

Powerful support for an amygdaloid role in fear processing comes from post-traumatic stress disorder (PTSD). In PTSD sufferers the amygdala is overreactive to mildly fearful stimuli and is slow in calming down after being activated.[13] Moreover, the amygdala expands in size with long-term PTSD. This role of stress in this expansion will be covered in chapter 4.

The amygdala is also involved in the expression of anxiety.[14] Take a deck of cards—half are black, half are red; how much would you wager that the top card is red? That's about risk. Here's a deck of cards—at least one is black, at least one is red; how much would you wager that the top card is red? That's about ambiguity. The circumstances carry identical probabilities, but people are made more anxious by the second scenario and activate the amygdala more. The amygdala is particularly sensitive to unsettling circumstances that are social. A high-ranking male rhesus monkey is in a sexual consortship with a female; in one condition the female is placed in another room, where the male can see her. In the second she's in the other room along with a rival of the male. No surprise, that situation activates the amygdala. Is that about aggression or anxiety? Seemingly the latter—the extent of activation did not correlate with the amount of aggressive behaviors and vocalizations the male made, or the amount of testosterone secreted. Instead, it correlated with the extent of anxiety displayed (e.g., teeth chattering, or self-scratching).

The amygdala is linked to social uncertainty in other ways. In one neuroimaging study, a subject would participate in a competitive game against a group of other players; outcomes were rigged so that the subject would wind up in the middle of the rankings.[15] Experimenters then manipulated game outcomes so that subjects' rankings either remained stable or fluctuated wildly. Stable rankings activated parts of the frontal cortex that we'll soon consider. Instability activated the frontal cortex plus the amygdala. Being unsure of your place is unsettling.

Another study explored the neurobiology of conforming.[16] To simplify, a subject is part of a group (where, secretly, the rest are confederates); they are shown "X," then asked, "What did you see?" Everyone else says "Y." Does the subject lie and say "Y" also? Often. Subjects who stuck to their guns with "X" showed amygdala activation.

Finally, activating specific circuits within the amygdala in mice turns anxiety on and off; activating others made mice unable to distinguish between safe and anxiety-producing settings.*[17]

The amygdala also helps mediate both innate and learned fear.[18] The core of innate fear (aka a phobia) is that you don't have to learn by trial and error that something is aversive. For example, a rat born in a lab, who has interacted only with other rats and grad students, instinctually fears and avoids the smell of cats. While different phobias activate somewhat different brain circuitry (for example, dentist phobia involves the cortex more than does snake phobia), they all activate the amygdala.

Such innate fear contrasts with things we learn to fear—a bad neighborhood, a letter from the IRS. The dichotomy between innate and learned fear is actually a bit fuzzy.[19] Everyone knows that humans are innately afraid of snakes and spiders. But some people keep them as pets, give them cute names.* Instead of inevitable fear, we show "prepared learning"—learning to be afraid of snakes and spiders more readily than of pandas or beagles.

The same occurs in other primates. For example, lab monkeys who have never encountered snakes (or artificial flowers) can be conditioned to fear the former more readily than the latter. As we'll see in the next chapter, humans show prepared learning, being predisposed to be conditioned to fear people with a certain type of appearance.

The fuzzy distinction between innate and learned fear maps nicely onto the amygdala's structure. The evolutionarily ancient central amygdala plays a key role in innate fears. Surrounding it is the basolateral amygdala (BLA), which is more recently evolved and somewhat resembles the fancy, modern cortex. It's the BLA that learns fear and then sends the news to the central amygdala.

Joseph LeDoux at New York University has shown how the BLA learns fear.*[20] Expose a rat to an innate trigger of fear—a shock. When this "unconditioned stimulus" occurs, the central amygdala activates, stress hormones are secreted, the sympathetic nervous system mobilizes, and, as a clear end point, the rat freezes in place—"What was that? What do I do?" Now do some conditioning. Before each shock, expose the rat to a stimulus that normally

does not evoke fear, such as a tone. And with repeated coupling of the tone (the conditioned stimulus) with the shock (the unconditioned one), fear conditioning occurs—the sound of the tone alone elicits freezing, stress hormone release, and so on.*

LeDoux and others have shown how auditory information about the tone stimulates BLA neurons. At first, activation of those neurons is irrelevant to the central amygdala (whose neurons are destined to activate following the shock). But with repeated coupling of tone with shock, there is remapping and those BLA neurons acquire the means to activate the central amygdala.*

BLA neurons that respond to the tone only once conditioning has occurred would also have responded if conditioning instead had been to a light. In other words, these neurons respond to the meaning of the stimulus, rather than to its specific modality. Moreover, if you electrically stimulate them, rats are easier to fear-condition; you've lowered the threshold for this association to be made. And if you electrically stimulate the auditory sensory input at the same time as shocks (i.e., there's no tone, just activation of the pathway that normally carries news of the tone to the amygdala), you cause fear conditioning to a tone. You've engineered the learning of a false fear.

There are synaptic changes as well. Once conditioning to a tone has occurred, the synapses coupling the BLA and central nucleus neurons have become more excitable; how this occurs is understood at the level of changes in the amount of receptors for excitatory neurotransmitters in dendritic spines in these circuits.* Furthermore, conditioning increases levels of "growth factors," which prompt the growth of new connections between BLA and central amygdala neurons; some of the genes involved have even been identified.

We've now got learning to be afraid under our belts.*[21] Now conditions change—the tone still occurs now and then, but no more shock. Gradually the conditioned fear response abates. How does "fear extinction" occur? How do we learn that this person wasn't so scary after all, that different doesn't necessarily equal frightening? Recall how a subset of BLA neurons respond to the tone only once conditioning has occurred. Another population does the opposite, responding to the tone once it's no longer signaling shock (logically, the two populations of neurons inhibit each other). Where do these "Ohhh, the tone isn't scary anymore" neurons get inputs from? The frontal cortex. When we stop fearing something, it isn't because some amygdaloid neurons have lost their excitability. We don't passively forget that something is scary. We actively learn that it isn't anymore.*

The amygdala also plays a logical role in social and emotional decision making. In the Ultimatum Game, an economic game involving two players, the first makes an offer as to how to divide a pot of money, which the other player either accepts or rejects.[22] If the latter, neither gets anything. Research shows that rejecting an offer is an emotional decision, triggered by anger at a lousy offer and the desire to punish. The more the amygdala activation in the second player after an offer, the more likely the rejection. People with damaged amygdalae are atypically generous in the Ultimatum Game and don't increase rejection rates if they start receiving unfair offers.

Why? These individuals understand the rules and can give sound, strategic advice to other players. Moreover, they use the same strategies as control subjects in a nonsocial version of the game, when believing the other player is a computer. And they don't have a particularly long view, undistracted by the amygdala's emotional tumult, reasoning that their noncontingent generosity will induce reciprocity and pay off in the long run. When asked, they anticipate the same levels of reciprocity as do controls.

Instead, these findings suggest that the amygdala injects implicit distrust and vigilance into social decision making.[23] All thanks to learning. In the words of the authors of the study, "The generosity in the trust game of our BLA-damaged subjects might be considered pathological altruism, in the sense that inborn altruistic behaviors have not, due to BLA damage, been un-learned through negative social experience." In other words, the default state is to trust, and what the amygdala does is learn vigilance and distrust.

Unexpectedly, the amygdala and one of its hypothalamic targets also play a role in male sexual motivation (other hypothalamic nuclei are central to male sexual performance)* but not female.* What's that about? One neuroimaging study sheds some light. "Young heterosexual men" looked at pictures of attractive women (versus, as a control, of attractive men). Passively observing the pictures activated the reward circuitry just alluded to. In contrast, *working* to see the pictures—by repeatedly pressing a button—also activated the amygdala. Similarly, other studies show that the amygdala is most responsive to positive stimuli when the value of the reward is shifting. Moreover, some BLA neurons that respond in that circumstance also respond when the severity of something aversive is shifting—these neurons are paying attention to change, independent of direction. For them, "the amount of reward is changing" and "the amount of punishment is changing" are the same. Studies like these clarify that the amygdala isn't about the pleasure of experiencing pleasure. It's about the

uncertain, unsettled yearning for a potential pleasure, the anxiety and fear and anger that the reward may be smaller than anticipated, or may not even happen. It's about how many of our pleasures and our pursuits of them contain a corrosive vein of disease.*[24]

The Amygdala as Part of Networks in the Brain

Now that we know about the subparts of the amygdala, it's informative to consider its extrinsic connections—i.e., what parts of the brain send projection to it, and what parts does it project to?[25]

SOME INPUTS TO THE AMYGDALA

Sensory inputs. For starters, the amygdala, specifically the BLA, gets projections from all the sensory systems.[26] How else can you get terrified by the shark's theme music in *Jaws*? Normally, sensory information from various modalities (eyes, ears, skin . . .) courses into the brain, reaching the appropriate cortical region (visual cortex, auditory cortex, tactile cortex . . .) for processing. For example, the visual cortex would engage layers and layers of neurons to turn pixels of retinal stimulation into recognizable images before it can scream to the amygdala, "It's a gun!" Importantly, some sensory information entering the brain takes a shortcut, bypassing the cortex and going directly to the amygdala. Thus the amygdala can be informed about something scary before the cortex has a clue. Moreover, thanks to the extreme excitability of this pathway, the amygdala can respond to stimuli that are too fleeting or faint for the cortex to note. Additionally, the shortcut projections form stronger, more excitable synapses in the BLA than do the ones from the sensory cortex; emotional arousal enhances fear conditioning through this pathway. This shortcut's power is shown in the case of a man with stroke damage to his visual cortex, producing "cortical blindness." While unable to process most visual information, he still recognized emotional facial expressions via the shortcut.*

Crucially, while sensory information reaches the amygdala rapidly by this shortcut, it isn't terribly accurate (since, after all, accuracy is what the cortex supplies). As we'll see in the next chapter, this produces tragic circumstances where, say, the amygdala decides it's seeing a handgun before the visual cortex can report that it's actually a cell phone.

Information about pain. The amygdala receives news of that reliable trigger of fear and aggression, namely pain.[27] This is mediated by projections from an ancient, core brain structure, the "periaqueductal gray" (PAG); stimulation of the PAG can evoke panic attacks, and it is enlarged in people with chronic panic attacks. Reflecting the amygdala's roles in vigilance, uncertainty, anxiety, and fear, it's unpredictable pain, rather than pain itself, that activates the amygdala. Pain (and the amygdala's response to it) is all about context.

Disgust of all stripes. The amygdala also receives a hugely interesting projection from the "insular cortex," an honorary part of the prefrontal cortex, which we will consider at length in later chapters.[28] If you (or any other mammal) bite into rancid food, the insular cortex lights up, causing you to spit it out, gag, feel nauseated, make a revolted facial expression—the insular cortex processes gustatory disgust. Ditto for disgusting smells.

Remarkably, humans also activate it by thinking about something *morally* disgusting—social norm violations or individuals who are typically stigmatized in society. And in that circumstance its activation drives that of the amygdala. Someone does something lousy and selfish to you in a game, and the extent of insular and amygdaloid activation predicts how much outrage you feel and how much revenge you take. This is all about sociality—the insula and amygdala don't activate if it's a computer that has stabbed you in the back.

The insula activates when we eat a cockroach or imagine doing so. And the insula and amygdala activate when we think of the neighboring tribe as loathsome cockroaches. As we'll see, this is central to how our brains process "us and them."

And finally, the amygdala gets tons of inputs from the frontal cortex. Much more to come.

SOME OUTPUTS FROM THE AMYGDALA

Bidirectional connections. As we'll see, the amygdala talks to many of the regions that talk to it, including the frontal cortex, insula, periaqueductal gray, and sensory projections, modulating their sensitivity.

The amygdala/hippocampus interface. Naturally, the amygdala talks to other limbic structures, including the hippocampus. As reviewed, typically the amygdala learns fear and the hippocampus learns detached, dispassionate facts. But at times of extreme fear, the amygdala pulls the hippocampus into a type of fear learning.[29]

Back to the rat undergoing fear conditioning. When it's in cage A, a tone is followed by a shock. But in cage B, the tone isn't. This produces context-dependent conditioning—the tone causes fearful freezing in cage A but not in cage B. The amygdala learns the stimulus cue—the tone—while the hippocampus learns about the contexts of cage A versus B. The coupled learning between amygdala and hippocampus is very focalized—we all remember the view of the plane hitting the second World Trade Center tower, but not whether there were clouds in the background. The hippocampus decides whether a factoid is worth filing away, depending on whether the amygdala has gotten worked up over it. Moreover, the coupling can rescale. Suppose someone robs you at gunpoint in an alley in a bad part of town. Afterward, depending on the circumstance, the gun can be the cue and the alley the context, or the alley is the cue and the bad part of town the context.

Motor outputs. There's a second shortcut regarding the amygdala, specifically when it's talking to motor neurons that command movement.[30] Logically, when the amygdala wants to mobilize a behavior—say, fleeing—it talks to the frontal cortex, seeking its executive approval. But if sufficiently aroused, the amygdala talks directly to subcortical, reflexive motor pathways. Again, there's a trade-off—increased speed by bypassing the cortex, but decreased accuracy. Thus the input shortcut may prompt you to see the cell phone as a gun. And the output shortcut may prompt you to pull a trigger before you consciously mean to.

Arousal. Ultimately, amygdala outputs are mostly about setting off alarms throughout the brain and body. As we saw, the core of the amygdala is the central amygdala.[31] Axonal projections from there go to an amygdala-ish structure nearby called the bed nucleus of the stria terminalis (BNST). The BNST, in turn, projects to parts of the hypothalamus that initiate the hormonal stress response (see chapter 4), as well as to midbrain and brain-stem sites that activate the sympathetic nervous system and inhibit the parasympathetic nervous system. Something emotionally arousing occurs, layer 2 limbic amygdala signals layer 1 regions, and heart rate and blood pressure soar.*

The amygdala also activates a brain-stem structure called the locus coeruleus, akin to the brain's own sympathetic nervous system.[32] It sends norepinephrine-releasing projections throughout the brain, particularly the cortex. If the locus coeruleus is drowsy and silent, so are you. If it's moderately activated, you're alert. And if it's firing like gangbusters, thanks to inputs from an aroused amygdala, all neuronal hands are on deck.

The amygdala's projection pattern raises an important point.[33] When is the sympathetic nervous system going full blast? During fear, flight, fight, and sex. Or if you've won the lottery, are happily sprinting down a soccer field, or have just solved Fermat's theorem (if you're that kind of person). Reflecting this, about a quarter of neurons in one hypothalamic nucleus are involved in both sexual behavior and, when stimulated at a higher intensity, aggressive behavior in male mice.

This has two implications. Both sex and aggression activate the sympathetic nervous system, which in turn can influence behavior—people feel differently about things if, say, their heart is racing versus beating slowly. Does this mean that the pattern of your autonomic arousal influences *what* you feel? Not really. But autonomic feedback influences the *intensity* of what is felt. More on this in the next chapter.

The second consequence reflects a core idea of this book. Your heart does roughly the same thing whether you are in a murderous rage or having an orgasm. Again, the opposite of love is not hate, it's indifference.

This concludes our overview of the amygdala. Amid the jargon and complexity, the most important theme is the amygdala's dual role in both aggression and facets of fear and anxiety. Fear and aggression are not inevitably intertwined—not all fear causes aggression, and not all aggression is rooted in fear. Fear typically increases aggression only in those already prone to it; among the subordinate who lack the option of expressing aggression safely, fear does the opposite.

The dissociation between fear and aggression is evident in violent psychopaths, who are the antithesis of fearful—both physiologically and subjectively they are less reactive to pain; their amygdalae are relatively unresponsive to typical fear-evoking stimuli and are smaller than normal.[34] This fits with the picture of psychopathic violence; it is not done in aroused reaction to provocation. Instead, it is purely instrumental, using others as a means to an end with emotionless, remorseless, reptilian indifference.

Thus, fear and violence are not always connected at the hip. But a connection is likely when the aggression evoked is reactive, frenzied, and flecked with spittle. In a world in which no amygdaloid neuron need be afraid and instead can sit under its vine and fig tree, the world is very likely to be a more peaceful place.[*]

We now move to the second of the three brain regions we’re considering in detail.

THE FRONTAL CORTEX

I've spent decades studying the hippocampus. It's been good to me; I'd like to think I've been the same in return. Yet I think I might have made the wrong choice back then—maybe I should have studied the frontal cortex all these years. Because it's the most interesting part of the brain.

What does the frontal cortex do? Its list of expertise includes working memory, executive function (organizing knowledge strategically, and then initiating an action based on an executive decision), gratification postponement, long-term planning, regulation of emotions, and reining in impulsivity.[35]

This is a sprawling portfolio. I will group these varied functions under a single definition, pertinent to every page of this book: *the frontal cortex makes you do the harder thing when it's the right thing to do*.

To start, here are some important features of the frontal cortex:

It's the most recently evolved brain region, not approaching full splendor until the emergence of primates; a disproportionate percentage of genes unique to primates are active in the frontal cortex. Moreover, such gene expression patterns are highly individuated, with greater interindividual variability than average levels of whole-brain differences between humans and chimps.

The human frontal cortex is more complexly wired than in other apes and, by some definitions as to its boundaries, proportionately bigger as well.[36]

The frontal cortex is the last brain region to fully mature, with the most evolutionarily recent subparts the very last. Amazingly, it's not fully online until people are in their *midtwenties.* You'd better bet this factoid will be relevant to the chapter about adolescence.

> Finally, the frontal cortex has a unique cell type. In general, the human brain isn't unique because we've evolved unique types of neurons, neurotransmitters, enzymes, and so on. Human and fly neurons are remarkably similar; the uniqueness is quantitative—for every fly neuron, we have a gazillion more neurons and a bazillion more connections.[37]

The sole exception is an obscure type of neuron with a distinctive shape and pattern of wiring, called von Economo neurons (aka spindle neurons). At first they seemed to be unique to humans, but we've now found them in other primates, whales, dolphins, and elephants.* That's an all-star team of socially complex species.

Moreover, the few von Economo neurons occur only in two subregions of the frontal cortex, as shown by John Allman at Caltech. One we've heard about already—the insula, with its role in gustatory and moral disgust. The second is an equally interesting area called the anterior cingulate. To give a hint (with more to come), it's central to empathy.

So from the standpoint of evolution, size, complexity, development, genetics, and neuron type, the frontal cortex is distinctive, with the human version the most unique.

The Subregions of the Frontal Cortex

Frontal cortical anatomy is hellishly complicated, and there are debates as to whether some parts of the primate frontal cortex even exist in "simpler" species. Nonetheless, there are some useful broad themes.

In the very front is the *pre*frontal cortex (PFC), the newest part of the frontal cortex. As noted, the frontal cortex is central to executive function. To quote George W. Bush, within the frontal cortex, it's the PFC that is "the decider." Most broadly, the PFC chooses between conflicting options—Coke or Pepsi; blurting out what you really think or restraining yourself; pulling the trigger or not. And often the conflict being resolved is between a decision heavily driven by cognition and one driven by emotions.

Once it has decided, the PFC sends orders via projections to the rest of the frontal cortex, sitting just behind it. Those neurons then talk to the "premotor cortex," sitting just behind it, which then passes it to the "motor cortex," which talks to your muscles. And a behavior ensues.*

Before considering how the frontal cortex influences social behavior, let's start with a simpler domain of its function.

The Frontal Cortex and Cognition

What does "doing the harder thing when it's the right thing to do" look like in the realm of cognition (defined by Princeton's Jonathan Cohen as "the ability to orchestrate thought and action in accordance with internal goals")?[38] Suppose you've looked up a phone number in a city where you once lived. The frontal cortex not only remembers it long enough to dial but also considers it strategically. Just before dialing, you consciously recall that it is in that other city and retrieve your memory of the city's area code. And then you remember to dial "1" before the area code.[*]

The frontal cortex is also concerned with focusing on a task. If you step off the curb planning to jaywalk, you look at traffic, paying attention to motion, calculating whether you can cross safely. If you step off looking for a taxi, you pay attention to whether a car has one of those lit taxicab thingies on top. In a great study, monkeys were trained to look at a screen of dots of various colors moving in particular directions; depending on a signal, a monkey had to pay attention to either color or movement. Each signal indicating a shift in tasks triggered a burst of PFC activity and, coupled with that, suppression of the stream of information (color or movement) that was now irrelevant. This is the PFC getting you to do the harder thing; remembering that the rule has changed, don't do the previous habitual response.[39]

The frontal cortex also mediates "executive function"—considering bits of information, looking for patterns, and then choosing a strategic action.[40] Consider this truly frontally demanding test. The experimenter tells a masochistic volunteer, "I'm going to the market and I'm going to buy peaches, cornflakes, laundry detergent, cinnamon . . ." Sixteen items recited, the volunteer is asked to repeat the list. Maybe they correctly recall the first few, the last few, list some near misses—say, nutmeg instead of cinnamon. Then the experimenter repeats the same list. This time the volunteer remembers a few more, avoids repeating the nutmeg incident. Now do it again and again.

This is more than a simple memory test. With repetition, subjects notice that four of the items are fruits, four for cleaning, four spices, four carbs. They come in categories. And this changes subjects' encoding strategy as they start

clumping by semantic group—"Peaches. Apples. Blueberries—no, I mean blackberries. There was another fruit, can't remember what. Okay, cornflakes, bread, doughnuts, muffins. Cumin, nutmeg—argh, again!—I mean cinnamon, oregano . . ." And throughout, the PFC imposes an overarching executive strategy for remembering these sixteen factoids.*

The PFC is essential for categorical thinking, for organizing and thinking about bits of information with different labels. The PFC groups apples and peaches as closer to each other in a conceptual map than are apples and toilet plungers. In a relevant study, monkeys were trained to differentiate between pictures of a dog and of a cat. The PFC contained individual neurons that responded to "dog" and others that responded to "cat." Now the scientists morphed the pictures together, creating hybrids with varying percentages of dog and cat. "Dog" PFC neurons responded about as much to hybrids that were 80 percent dog and 20 percent cat, or 60:40, as to 100 percent dog. But not to 40:60—"cat" neurons would kick in there.[41]

The frontal cortex aids the underdog outcome, fueled by thoughts supplied from influences that fill the rest of this book—stop, those aren't your cookies; you'll go to hell; self-discipline is good; you're happier when you're thinner—all giving some lone inhibitory motor neuron more of a fighting chance.

Frontal Metabolism and an Implicit Vulnerability

This raises an important point, pertinent to the social as well as cognitive functions of the frontal cortex.[42] All this "I wouldn't do that if I were you"–ing by the frontal cortex is taxing. Other brain regions respond to instances of some contingency; the frontal cortex tracks rules. Just think how around age three, our frontal cortices learned a rule followed for the rest of our lives—don't pee whenever you feel like it—and gained the means to enact that rule by increasing their influence over neurons regulating the bladder.

Moreover, the frontal mantra of "self-discipline is good" when cookies beckon is also invoked when economizing to increase retirement savings. Frontal cortical neurons are generalists, with broad patterns of projections, which makes for more work.[43]

All this takes energy, and when it is working hard, the frontal cortex has an extremely high metabolic rate and rates of activation of genes related to energy production.[44] Will*power* is more than just a metaphor; self-control is a finite

resource. Frontal neurons are expensive cells, and expensive cells are vulnerable cells. Consistent with that, the frontal cortex is atypically vulnerable to various neurological insults.

Pertinent to this is the concept of "cognitive load." Make the frontal cortex work hard—a tough working-memory task, regulating social behavior, or making numerous decisions while shopping. Immediately afterward performance on a different frontally dependent task declines.[45] Likewise during multitasking, where PFC neurons simultaneously participate in multiple activated circuits.

Importantly, increase cognitive load on the frontal cortex, and afterward subjects become less prosocial*—less charitable or helpful, more likely to lie.[46] Or increase cognitive load with a task requiring difficult emotional regulation, and subjects cheat more on their diets afterward.*[47]

So the frontal cortex is awash in Calvinist self-discipline, a superego with its nose to the grindstone.[48] But as an important qualifier, soon after we're potty-trained, doing the harder thing with our bladder muscles becomes automatic. Likewise with other initially demanding frontal tasks. For example, you're learning a piece of music on the piano, there's a difficult trill, and each time as you approach it, you think, "Here it comes. Remember, tuck my elbow in, lead with my thumb." A classic working-memory task. And then one day you realize that you're five measures past the trill, it went fine, and you didn't have to think about it. And that's when doing the trill is transferred from the frontal cortex to more reflexive brain regions (e.g., the cerebellum). This transition to automaticity also happens when you get good at a sport, when metaphorically your body knows what to do without your thinking about it.

The chapter on morality considers automaticity in a more important realm. Is resisting lying a demanding task for your frontal cortex, or is it effortless habit? As we'll see, honesty often comes more easily thanks to automaticity. This helps explain the answer typically given after someone has been profoundly brave. "What were you thinking when you dove into the river to save that drowning child?" "I wasn't thinking—before I knew it, I had jumped in." Often the neurobiology of automaticity mediates doing the hardest moral acts, while the neurobiology of the frontal cortex mediates working hard on a term paper about the subject.

The Frontal Cortex and Social Behavior

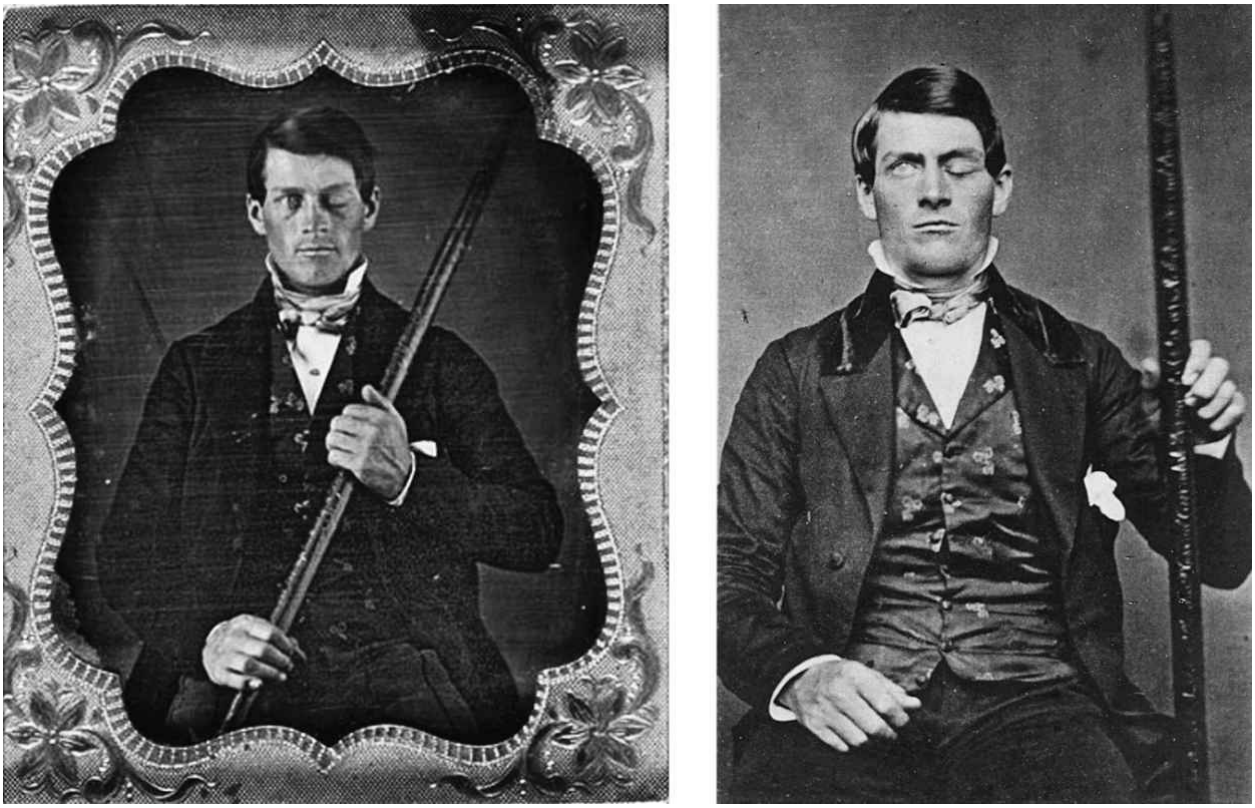
Things get interesting when the frontal cortex has to add social factors to a cognitive mix. For example, one part of the monkey PFC contains neurons that activate when the monkey makes a mistake on a cognitive task or observes another monkey doing so; some activate only when it's a particular animal who made the mistake. In a neuroimaging study humans had to choose something, balancing feedback obtained from their own prior choices with advice from another person. Different PFC circuits tracked "reward-driven" and "advice-driven" cogitating.[49]

Findings like these segue into the central role of the frontal cortex in social behavior.[50] This is appreciated when comparing various primates. Across primate species, the bigger the size of the average social group, the larger the relative size of the frontal cortex. This is particularly so with "fission-fusion" species, where there are times when subgroups split up and function independently for a while before regrouping. Such a social structure is demanding, requiring the scaling of appropriate behavior to subgroup size and composition. Logically, primates from fission-fusion species (chimps, bonobos, orangutans, spider monkeys) have better frontocortical inhibitory control over behavior than do non-fission-fusion primates (gorillas, capuchins, macaques).

Among humans, the larger someone's social network (measured by number of different people texted), the larger a particular PFC subregion (stay tuned).[51] That's cool, but we can't tell if the big brain region causes the sociality or the reverse (assuming there's causality). Another study resolves this; if rhesus monkeys are randomly placed into social groups, over the subsequent fifteen months, the bigger the group, the larger the PFC becomes—social complexity expands the frontal cortex.

We utilize the frontal cortex to do the harder thing in social contexts—we praise the hosts for the inedible dinner; refrain from hitting the infuriating coworker; don't make sexual advances to someone, despite our fantasies; don't belch loudly during the eulogy. A great way to appreciate the frontal cortex is to consider what happens when it is damaged.

The first "frontal" patient, the famous Phineas Gage, was identified in 1848 in Vermont. Gage, the foreman on a railroad construction crew, was injured when an accident with blasting powder blew a thirteen-pound iron tamping rod through the left side of his face and out the top front of his skull. It landed eighty feet away, along with much of his left frontal cortex.[52]



The two known pictures of Gage, along with the tamping rod.

Remarkably, he survived and recovered his health. But the respected, even-keeled Gage was transformed. In the words of the doctor who followed him over the years:

> The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible.

Gage was described by friends as “no longer Gage,” was incapable of resuming his job and was reduced to appearing (with his rod) as an exhibit displayed by P. T. Barnum. Poignant as hell.

Amazingly, Gage got better. Within a few years of his injury, he could resume work (mostly as a stagecoach driver) and was described as being broadly appropriate in his behavior. His remaining right frontal cortical tissue had taken on some of the functions lost in the injury. Such malleability of the brain is the focus of chapter 5.

Another example of what happens when the frontal cortex is damaged is observed in frontotemporal dementia (FTD), which starts by damaging the frontal cortex; intriguingly, the first neurons killed are those mysterious von Economo neurons that are unique to primates, elephants, and cetaceans.[53] What are people with FTD like? They exhibit behavioral disinhibition and socially inappropriate behaviors. There's also an apathy and lack of initiating behavior that reflects the fact that the "decider" is being destroyed.*

Something similar is seen in Huntington's disease, a horrific disorder due to a thoroughly weird mutation. Subcortical circuits that coordinate signaling to muscles are destroyed, and the sufferer is progressively incapacitated by involuntary writhing movements. Except that it turns out that there is frontal damage as well, often before the subcortical damage. In about half the patients there's also behavioral disinhibition—stealing, aggressiveness, hypersexuality, bursts of compulsive, inexplicable gambling.* Social and behavioral disinhibition also occur in individuals with stroke damage in the frontal cortex—for example, sexually assaultive behavior in an octogenarian.

There's another circumstance where the frontal cortex is hypofunctional, producing similar behavioral manifestations—hypersexuality, outbursts of emotion, flamboyantly illogical acts.[54] What disease is this? It isn't. You're dreaming. During REM sleep, when dreaming occurs, the frontal cortex goes off-line, and dream scriptwriters run wild. Moreover, if the frontal cortex is stimulated while people are dreaming, the dreams become less dreamlike, with more self-awareness. And there's another nonpathological circumstance where the PFC silences, producing emotional tsunamis: during orgasm.

One last realm of frontal damage. Adrian Raine of the University of Pennsylvania and Kent Kiehl of the University of New Mexico report that criminal psychopaths have decreased activity in the frontal cortex and less coupling of the PFC to other brain regions (compared with nonpsychopathic

criminals and noncriminal controls). Moreover, a shockingly large percentage of people incarcerated for violent crimes have a history of concussive trauma to the frontal cortex.[55] More to come in chapter 16.

The Obligatory Declaration of the Falseness of the Dichotomy Between Cognition and Emotion

The PFC consists of various parts, subparts, and sub-subparts, enough to keep neuroanatomists off the dole. Two regions are crucial. First there is the dorsal part of the PFC, especially the dorsolateral PFC (dlPFC)—don't worry about "dorsal" or "dorsolateral"; it's just jargon.* The dlPFC is the decider of deciders, the most rational, cognitive, utilitarian, unsentimental part of the PFC. It's the most recently evolved part of the PFC and the last part to fully mature. It mostly hears from and talks to other cortical regions.

In contrast to the dlPFC, there's the ventral part of the PFC, particularly the ventromedial PFC (vmPFC). This is the frontocortical region that the visionary neuroanatomist Nauta made an honorary member of the limbic system because of its interconnections with it. Logically, the vmPFC is all about the impact of emotion on decision making. And many of our best and worst behaviors involve interactions of the vmPFC with the limbic system and dlPFC.*

The functions of the cognitive dlPFC are the essence of doing the harder thing.[56] It's the most active frontocortical region when someone forgoes an immediate reward for a bigger one later. Consider a classic moral quandary—is it okay to kill one innocent person to save five? When people ponder the question, greater dlPFC activation predicts a greater likelihood of answering yes (but as we'll see in chapter 13, it also depends on how you ask the question).

Monkeys with dlPFC lesions can't switch strategies in a task when the rewards given for each strategy shift—they perseverate with the strategy offering the most immediate reward.[57] Similarly, humans with dlPFC damage are impaired in planning or gratification postponement, perseverate on strategies that offer immediate reward, and show poor executive control over their behavior.* Remarkably, the technique of transcranial magnetic stimulation can temporarily silence part of someone's cortex, as was done in a fascinating study by Ernst Fehr of the University of Zurich.[58] When the dlPFC was silenced, subjects playing an economic game impulsively accepted lousy offers that they'd normally reject in the hopes of getting better offers in the future. Crucially, this

was about sociality—silencing the dlPFC had no effect if subjects thought the other player was a computer. Moreover, controls and subjects with silenced dlPFCs rated lousy offers as being equally unfair; thus, as concluded by the authors, "subjects [with the silenced dlPFC] behave as if they can no longer implement their fairness goals."

What are the functions of the emotional vmPFC?[59] What you'd expect, given its inputs from limbic structures. It activates if the person you're rooting for wins a game, or if you listen to pleasant versus dissonant music (particularly if the music provokes a shiver-down-the-spine moment).

What are the effects of vmPFC damage?[60] Lots of things remain normal—intelligence, working memory, making estimates. Individuals can "do the harder thing" with purely cognitive frontal tasks (e.g., puzzles where you have to give up a step of progress in order to gain two more).

The differences appear when it comes to making social/emotional decisions—vmPFC patients just can't decide.* They understand the options and can sagely advise someone else in similar circumstances. But the closer to home and the more emotional the scenario, the more they have problems.

Damasio has produced an influential theory about emotion-laden decision making, rooted in the philosophies of Hume and William James; this will soon be discussed.[61] Briefly, the frontal cortex runs "as if" experiments of gut feelings—"How would I feel if this outcome occurred?"—and makes choices with the answer in mind. Damaging the vmPFC, thus removing limbic input to the PFC, eliminates gut feelings, making decisions harder.

Moreover, eventual decisions are highly utilitarian. vmPFC patients are atypically willing to sacrifice one person, including a family member, to save five strangers.[62] They're more interested in outcomes than in their underlying emotional motives, punishing someone who accidentally kills but not one who tried to kill but failed, because, after all, no one died in the second case.

It's Mr. Spock, running on only the dlPFC. Now for a crucial point. People who dichotomize between thought and emotion often prefer the former, viewing emotion as suspect. It gums up decision making by getting sentimental, sings too loudly, dresses flamboyantly, has unsettling amounts of armpit hair. In this view, get rid of the vmPFC, and we'd be more rational and function better.

But that's not the case, as emphasized eloquently by Damasio. People with vmPFC damage not only have trouble making decisions but also make bad ones.[63] They show poor judgment in choosing friends and partners and don't shift behavior based on negative feedback. For example, consider a gambling

task where reward rates for various strategies change without subjects knowing it, and subjects can shift their play strategy. Control subjects shift optimally, even if they can't verbalize how reward rates have changed. Those with vmPFC damage don't, even when they *can* verbalize. Without a vmPFC, you may know the meaning of negative feedback, but you don't know the *feeling* of it in your gut and thus don't shift behavior.

As we saw, without the dlPFC, the metaphorical superego is gone, resulting in individuals who are now hyperaggressive, hypersexual ids. But without a vmPFC, behavior is inappropriate in a detached way. This is the person who, encountering someone after a long time, says, "Hello, I see you've put on some weight." And when castigated later by their mortified spouse, they will say with calm puzzlement, "But it's true." The vmPFC is not the vestigial appendix of the frontal cortex, where emotion is something akin to appendicitis, inflaming a sensible brain. Instead it's essential.[64] It wouldn't be if we had evolved into Vulcans. But as long as the world is filled with humans, evolution would never have made us that way.

Activation of the dlPFC and vmPFC can be inversely correlated. In an inspired study where a keyboard was provided to jazz pianists inside a brain scanner, the vmPFC became more active and the dlPFC less so when subjects improvised. In another study, subjects judged hypothetical harmful acts. Pondering perpetrators' responsibility activated the dlPFC; deciding the amount of punishment activated the vmPFC.* When subjects did a gambling task where reward probabilities for various strategies shifted and they could always change strategies, decision making reflected two factors: (a) the outcome of their most recent action (the better that had turned out, the more vmPFC activation), and (b) reward rates from all the previous rounds, something requiring a long retrospective view (the better the long-term rewards, the more dlPFC activation). Relative activation between the two regions predicted the decision subjects made.[65]

A simplistic view is that the vmPFC and dlPFC perpetually battle for domination by emotion versus cognition. But while emotion and cognition can be somewhat separable, they're rarely in opposition. Instead they are intertwined in a collaborative relationship needed for normal function, and as tasks with both emotive and cognitive components become more difficult (making an increasingly complex economic decision in a setting that is increasingly unfair), activity in the two structures becomes more synchronized.

The Frontal Cortex and Its Relationship with the Limbic System

We now have a sense of what different subdivisions of the PFC do and how cognition and emotion interact neurobiologically. This leads us to consider how the frontal cortex and limbic system interact.

In landmark studies Joshua Greene of Harvard and Princeton's Cohen showed how the "emotional" and "cognitive" parts of the brain can somewhat dissociate.[66] They used philosophy's famous "runaway trolley" problem, where a trolley is bearing down on five people and you must decide if it's okay to kill one person to save the five. Framing of the problem is key. In one version you pull a lever, diverting the trolley onto a side track. This saves the five, but the trolley kills someone who happened to be on this other track; 70 to 90 percent of people say they would do this. In the second scenario you push the person in front of the trolley with your own hands. This stops the trolley, but the person is killed; 70 to 90 percent say no way. The same numerical trade-off, but utterly different decisions.

Greene and Cohen gave subjects the two versions while neuroimaging them. Contemplating intentionally killing someone with your own hands activates the decider dlPFC, along with emotion-related regions that respond to aversive stimuli (including a cortical region activated by emotionally laden words), the amygdala, and the vmPFC. The more amygdaloid activation and the more negative emotions the participant reported in deciding, the less likely they were to push.

And when people contemplate detachedly pulling a lever that inadvertently kills someone? The dlPFC alone activates. As purely cerebral a decision as choosing which wrench to use to fix a widget. A great study.*

Other studies have examined interactions between "cognitive" and "emotional" parts of the brain. A few examples:

> Chapter 3 discusses some unsettling research—stick your average person in a brain scanner, and show him a picture of someone of another race for only a tenth of a second. This is too fast for him to be aware of what he saw. But thanks to that anatomical shortcut, the amygdala knows . . . and activates. In contrast, show the picture for a longer time. Again the amygdala activates, but then the cognitive dlPFC does as well, inhibiting

the amygdala—the effort to control what is for most people an unpalatable initial response.

Chapter 6 discusses experiments where a subject plays a game with two other people and is manipulated into feeling that she is being left out. This activates her amygdala, periaqueductal gray (that ancient brain region that helps process physical pain), anterior cingulate, and insula, an anatomical picture of anger, anxiety, pain, disgust, sadness. Soon afterward her PFC activates as rationalizations kick in—"This is just a stupid game; I have friends; my dog loves me." And the amygdala et al. quiet down. And what if you do the same to someone whose frontal cortex is not fully functional? The amygdala is increasingly activated; the person feels increasingly distressed. What neurological disease is involved? None. This is a typical teenager.

Finally, the PFC mediates fear extinction. Yesterday the rat learned, "That tone is followed by a shock," so the sound of the tone began to trigger freezing. Today there are no shocks, and the rat has acquired another truth that takes precedence—"but not today." The first truth is still there; as proof, start coupling tone with shock again, and freezing to tone is "reinstated" faster than the association was initially learned.

Where is "but not today" consolidated? In the PFC, after receiving information from the hippocampus.[67] The medial PFC activates inhibitory circuits in the BLA, and the rat stops freezing to the tone. In a similar vein but reflecting cognition specific to humans, condition people to associate a blue square on a screen with a shock, and the amygdala will activate when seeing that square—but less so in subjects who reappraise the situation, activating the medial PFC by thinking of, say, a beautiful blue sky.

This segues into the subject of regulating emotion through thought.[68] It's hard to regulate thought (try not thinking about a hippo) but even tougher with emotion; research by my Stanford colleague and close friend James Gross has explored this. First off, "thinking differently" about something emotional differs from simply suppressing the expression of the emotions. For example, show someone graphic footage of, say, an amputation. Subjects cringe, activate the amygdala and sympathetic nervous system. Now one group is instructed to hide

their emotions (“I’m going to show you another film clip, and I want you to hide your emotional reactions”). How to do so most effectively? Gross distinguishes between “antecedent” and “response”-focused strategies. Response-focused is dragging the emotional horse back to the barn after it’s fled—you’re watching the next horrific footage, feeling queasy, and you think, “Okay, sit still, breathe slowly.” Typically this causes even greater activation of the amygdala and sympathetic nervous system.

Antecedent strategies generally work better, as they keep the barn door closed from the start. These are about thinking/feeling about something else (e.g., that great vacation), or thinking/feeling differently about what you’re seeing (reappraisals such as “That isn’t real; those are just actors”). And when done right, the PFC, particularly the dlPFC, activates, the amygdala and sympathetic nervous system are damped, and subjective distress decreases.*

Antecedent reappraisal is why placebos work.[69] Thinking, “My finger is about to be pricked by a pin,” activates the amygdala along with a circuit of pain-responsive brain regions, and the pin hurts. Be told beforehand that the hand cream being slathered on your finger is a powerful analgesic cream, and you think, “My finger is about to be pricked by a pin, but this cream will block the pain.” The PFC activates, blunting activity in the amygdala and pain circuitry, as well as pain perception.

Thought processes like these, writ large, are the core of a particularly effective type of psychotherapy—cognitive behavioral therapy (CBT)—for the treatment of disorders of emotion regulation.[70] Consider someone with a social anxiety disorder caused by a horrible early experience with trauma. To simplify, CBT is about providing the tools to reappraise circumstances that evoke the anxiety—remember that in this social situation those awful feelings you’re having are about what happened back then, not what is happening now.*

Controlling emotional responses with thought like this is very top down; the frontal cortex calms the overwrought amygdala. But the PFC/limbic relationship can be bottom up as well, when a decision involves a gut feeling. This is the backbone of Damasio’s somatic marker hypothesis. Choosing among options can involve a cerebral cost-benefit analysis. But it also involves “somatic markers,” internal simulations of what each outcome would feel like, run in the limbic system and reported to the vmPFC. The process is not a thought experiment; it’s an emotion experiment, in effect an emotional memory of a possible future.

A mild somatic marker activates only the limbic system.[71] “Should I do behavior A? Maybe not—the possibility of outcome B feels scary.” A more vivid

somatic marker activates the sympathetic nervous system as well. “Should I do behavior A? Definitely not—I can feel my skin getting clammy at the possibility of outcome B.” Experimentally boosting the strength of that sympathetic signal strengthens the aversion.

This is a picture of normal collaboration between the limbic system and frontal cortex.[72] Naturally, things are not always balanced. Anger, for example, makes people less analytical and more reflexive in decisions about punishment. Stressed people often make hideously bad decisions, marinated in emotion; chapter 4 examines what stress does to the amygdala and frontal cortex.*

The effects of stress on the frontal cortex are dissected by the late Harvard psychologist Daniel Wegner in an aptly titled paper, “How to Think, Say or Do Precisely the Worst Thing on Any Occasion.”[73] He considers what Edgar Allan Poe called the “imp of the perverse”:

> We see a rut coming up in the road ahead and proceed to steer our bike right into it. We make a mental note not to mention a sore point in conversation and then cringe in horror as we blurt out exactly that thing. We carefully cradle the glass of red wine as we cross the room, all the while thinking “don’t spill,” and then juggle it onto the carpet under the gaze of our host.

Wegner demonstrated a two-step process of frontocortical regulation: (A) one stream identifies X as being *very* important; (B) the other stream tracks whether the conclusion is “*Do* X” or “*Never* do X.” And during stress, distraction, or heavy cognitive load, the two streams can dissociate; the A stream exerts its presence without the B stream saying which fork in the road to take. The chance that you will do precisely the wrong thing rises not despite your best efforts but because of a stress-boggled version of them.

This concludes our overview of the frontal cortex; the mantra is that it makes you do the harder thing when that is the right thing. Five final points:

- “Doing the harder thing” effectively is not an argument for valuing either emotion or cognition more than the other. For example, as discussed in chapter 11, we are our most prosocial

concerning in-group morality when our rapid, implicit emotions and intuitions dominate, but are most prosocial concerning out-group morality when cognition holds sway.

- It's easy to conclude that the PFC is about preventing imprudent behaviors ("Don't do it; you'll regret it"). But that isn't always the case. For example, in chapter 17 we'll consider the surprising amount of frontocortical effort it can take to pull a trigger.
- Like everything about the brain, the structure and function of the frontal cortex vary enormously among individuals; for example, resting metabolic rate in the PFC varies approximately thirtyfold among people.* What causes such individual differences? See the rest of this book.[74]
- "Doing the harder thing when it's the right thing to do." "Right" in this case is used in a neurobiological and instrumental sense, rather than a moral one.
- Consider lying. Obviously, the frontal cortex aids the hard job of resisting the temptation. But it is also a major frontocortical task, particularly a dlPFC task, to lie competently, to control the emotional content of a signal, to generate an abstract distance between message and meaning. Interestingly, pathological liars have atypically large amounts of white matter in the PFC, indicating more complex wiring.[75]

But again, the "right thing," in the setting of the frontal cortically assisted lying, is amoral. An actor lies to an audience about having the feelings of a morose Danish prince. A situationally ethical child lies, telling Grandma how excited she is about her present, concealing the fact that she already has that toy. A leader tells bold-faced lies, starting a war. A financier with Ponzi in his blood defrauds investors. A peasant woman lies to a uniformed thug, telling him she does not know the whereabouts of the refugees she knows are hiding in her attic. As with much about the frontal cortex, it's context, context, context.

Where does the frontal cortex get the metaphorical motivation to do the harder thing? For this we now look at our final branch, the dopaminergic "reward" system in the brain.

THE MESOLIMBIC/MESOCORTICAL DOPAMINE SYSTEM

Reward, pleasure, and happiness are complex, and the motivated pursuit of them occurs in at least a rudimentary form in many species. The neurotransmitter dopamine is central to understanding this.

Nuclei, Inputs, and Outputs

Dopamine is synthesized in multiple brain regions. One such region helps initiate movement; damage there produces Parkinson's disease. Another regulates the release of a pituitary hormone. But the dopaminergic system that concerns us arises from an ancient, evolutionarily conserved region near the brain stem called the ventral tegmental area (henceforth the "tegmentum").

A key target of these dopaminergic neurons is the last multisyllabic brain region to be introduced in this chapter, the nucleus accumbens (henceforth the "accumbens"). There's debate as to whether the accumbens should count as part of the limbic system, but at the least it's highly limbic-ish.

Here's our first pass at the organization of this circuitry:[76]

a. The tegmentum sends projections to the accumbens and (other) limbic areas such as the amygdala and hippocampus. This is collectively called the "mesolimbic dopamine pathway."
b. The tegmentum also projects to the PFC (but, significantly, not other cortical areas). This is called the "mesocortical dopamine pathway." I'll be lumping the mesolimbic plus mesocortical pathways together as the "dopaminergic system," ignoring their not always being activated simultaneously.*
c. The accumbens projects to regions associated with movement.
d. Naturally, most areas getting projections from the tegmentum and/or accumbens project back to them. Most interesting will be the projections from the amygdala and PFC.

Reward

As a first pass, the dopaminergic system is about reward—various pleasurable stimuli activate tegmental neurons, triggering their release of dopamine.[77] Some supporting evidence: (a) drugs like cocaine, heroin, and alcohol release dopamine in the accumbens; (b) if tegmental release of dopamine is blocked, previously rewarding stimuli become aversive; (c) chronic stress or pain depletes dopamine and decreases the sensitivity of dopamine neurons to stimulation, producing the defining symptom of depression—"anhedonia," the inability to feel pleasure.

Some rewards, such as sex, release dopamine in every species examined.[78] For humans, just thinking about sex suffices.*[79] Food evokes dopamine release in hungry individuals of all species, with an added twist in humans. Show a picture of a milkshake to someone after they've consumed one, and there's rarely dopaminergic activation—there's satiation. But with subjects who have been dieting, there's *further* activation. If you're working to restrict your food intake, a milkshake just makes you want another one.

The mesolimbic dopamine system also responds to pleasurable aesthetics.[80] In one study people listened to new music; the more accumbens activation, the more likely subjects were to buy the music afterward. And then there is dopaminergic activation for artificial cultural inventions—for example, when typical males look at pictures of sports cars.

Patterns of dopamine release are most interesting when concerning social interactions.[81] Some findings are downright heartwarming. In one study a subject would play an economic game with someone, where a player is rewarded under two circumstances: (a) if both players cooperate, each receives a moderate reward, and (b) stabbing the other person in the back gets the subject a big reward, while the other person gets nothing. While both outcomes increased dopaminergic activity, the bigger increase occurred after cooperation.*

Other research examined the economic behavior of punishing jerks.[82] In one study subjects played a game where player B could screw over player A for a profit. Depending on the round, player A could either (a) do nothing, (b) punish player B by having some of player B's money taken (at no cost to player B), or (c) pay one unit of money to have two units taken from player B. Punishment activated the dopamine system, especially when subjects had to pay to punish; the greater the dopamine increase during no-cost punishment, the more willing someone was to pay to punish. Punishing norm violations is satisfying.

Another great study, carried out by Elizabeth Phelps of New York University, concerns "overbidding" in auctions, where people bid more money than anticipated.[83] This is interpreted as reflecting the additional reward of besting someone in the competitive aspect of bidding. Thus, "winning" an auction is intrinsically socially competitive, unlike "winning" a lottery. Winning a lottery and winning a bid both activated dopaminergic signaling in subjects; losing a lottery had no effect, while losing a bidding war inhibited dopamine release. Not winning the lottery is bad luck; not winning an auction is social subordination.

This raises the specter of envy. In one neuroimaging study subjects read about a hypothetical person's academic record, popularity, attractiveness, and wealth.[84] Descriptions that evoked self-reported envy activated cortical regions involved in pain perception. Then the hypothetical individual was described as experiencing a misfortune (e.g., they were demoted). More activation of pain pathways at the news of the person's good fortune predicted more dopaminergic activation after learning of their misfortune. Thus there's dopaminergic activation during schadenfreude—gloating over an envied person's fall from grace.

The dopamine system gives insights into jealousy, resentment, and invidiousness, leading to another depressing finding.[85] A monkey has learned that when he presses a lever ten times, he gets a raisin as a reward. That's just happened, and as a result, ten units of dopamine are released in the accumbens. Now—surprise!—the monkey presses the lever ten times and gets *two* raisins. Whoa: twenty units of dopamine are released. And as the monkey continues to get paychecks of two raisins, the size of the dopamine response returns to ten units. Now reward the monkey with only a single raisin, and dopamine levels *decline*.

Why? This is our world of habituation, where nothing is ever as good as that first time.

Unfortunately, things have to work this way because of our range of rewards.[86] After all, reward coding must accommodate the rewarding properties of both solving a math problem and having an orgasm. Dopaminergic responses to reward, rather than being absolute, are relative to the reward value of alternative outcomes. In order to accommodate the pleasures of both mathematics and orgasms, the system must constantly rescale to accommodate the range of intensity offered by particular stimuli. The response to any reward must habituate with repetition, so that the system can respond over its full range to the next new thing.

This was shown in a beautiful study by Wolfram Schultz of Cambridge University.[87] Depending on the circumstance, monkeys were trained to expect either two or twenty units of reward. If they unexpectedly got either four or forty units, respectively, there'd be an identical burst of dopamine release; giving one or ten units produced an identical decrease. It was the relative, not absolute, size of the surprise that mattered over a tenfold range of reward.

These studies show that the dopamine system is bidirectional.[88] It responds with scale-free increases for unexpected good news and decreases for bad. Schultz demonstrated that following a reward, the dopamine system codes for discrepancy from expectation—get what you expected, and there's a steady-state dribble of dopamine. Get more reward and/or get it sooner than expected, and there's a big burst; less and/or later, a decrease. Some tegmental neurons respond to positive discrepancy from expectation, others to negative; appropriately, the latter are local neurons that release the inhibitory neurotransmitter GABA. Those same neurons participate in habituation, where the reward that once elicited a big dopamine response becomes less exciting.[*]

Logically, these different types of coding neurons in the tegmentum (as well as the accumbens) get projections from the frontal cortex—that's where all the expectancy/discrepancy calculations take place—"Okay, I thought I was going to get 5.0 but got 4.9. How big of a bummer is that?"

Additional cortical regions weigh in. In one study subjects were shown an item to purchase, with the degree of accumbens activation predicting how much a person would pay.[89] Then they were told the price; if it was less than what they were willing to spend, there was activation of the emotional vmPFC; more expensive, and there'd be activation of that disgust-related insular cortex. Combine all the neuroimaging data, and you could predict whether the person would buy the item.

Thus, in typical mammals the dopamine system codes in a scale-free manner over a wide range of experience for both good and bad surprises and is constantly habituating to yesterday's news. But humans have something in addition, namely that we invent pleasures far more intense than anything offered by the natural world.

Once, during a concert of cathedral organ music, as I sat getting gooseflesh amid that tsunami of sound, I was struck with a thought: for a medieval peasant, this must have been the loudest human-made sound they ever experienced, awe-inspiring in now-unimaginable ways. No wonder they signed up for the religion being proffered. And now we are constantly pummeled with sounds that dwarf

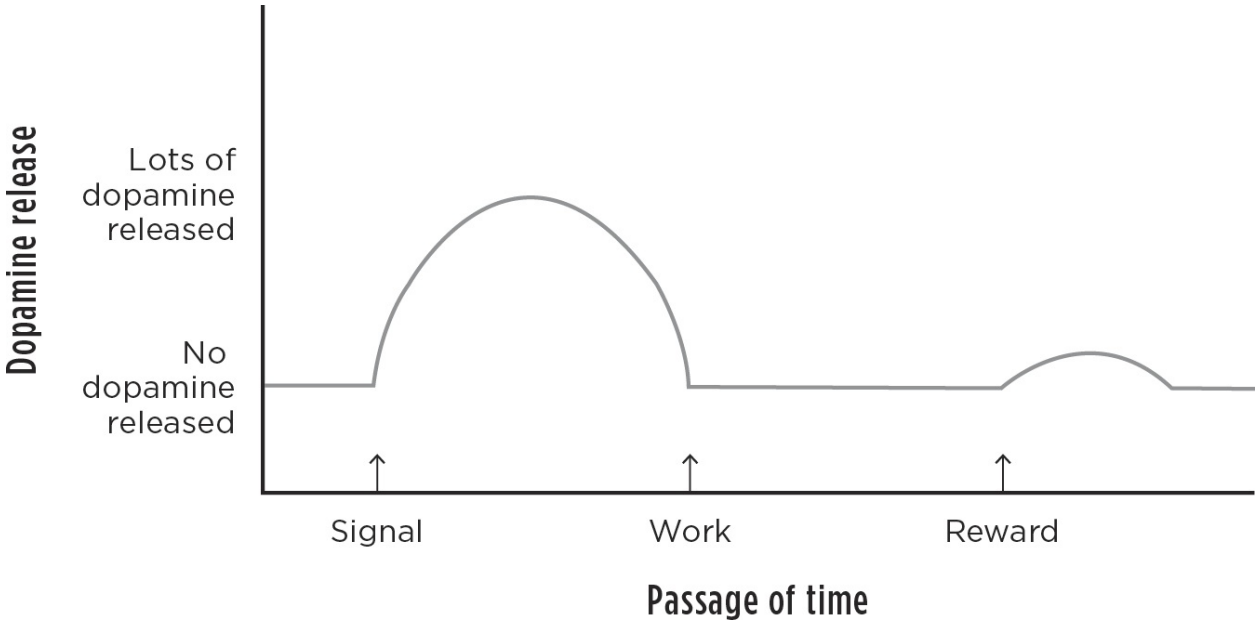
quaint organs. Once, hunter-gatherers might chance upon honey from a beehive and thus briefly satisfy a hardwired food craving. And now we have hundreds of carefully designed commercial foods that supply a burst of sensation unmatched by some lowly natural food. Once, we had lives that, amid considerable privation, also offered numerous subtle, hard-won pleasures. And now we have drugs that cause spasms of pleasure and dopamine release a thousandfold higher than anything stimulated in our old drug-free world.

An emptiness comes from this combination of over-the-top nonnatural sources of reward and the inevitability of habituation; this is because unnaturally strong explosions of synthetic experience and sensation and pleasure evoke unnaturally strong degrees of habituation.[90] This has two consequences. First, soon we barely notice the fleeting whispers of pleasure caused by leaves in autumn, or by the lingering glance of the right person, or by the promise of reward following a difficult, worthy task. And the other consequence is that we eventually habituate to even those artificial deluges of intensity. If we were designed by engineers, as we consumed more, we'd desire less. But our frequent human tragedy is that the more we consume, the hungrier we get. More and faster and stronger. What was an unexpected pleasure yesterday is what we feel entitled to today, and what won't be enough tomorrow.

The Anticipation of Reward

Thus, dopamine is about invidious, rapidly habituating reward. But dopamine is more interesting than that. Back to our well-trained monkey working for a reward. A light comes on in his room, signaling the start of a reward trial. He goes over to the lever, presses ten times, and gets the raisin reward; this has happened often enough that there's only a small increase in dopamine with each raisin.

However, importantly, lots of dopamine is released when the light first comes on, signaling the start of the reward trial, before the monkey starts lever pressing.



Visit bit.ly/2ovJngg for a larger version of this graph.

In other words, once reward contingencies are learned, dopamine is less about reward than about its anticipation. Similarly, work by my Stanford colleague Brian Knutson has shown dopamine pathway activation in people in anticipation of a monetary reward.[91] Dopamine is about mastery and expectation and confidence. It's "I know how things work; this is going to be great." In other words, the pleasure is in the anticipation of reward, and the reward itself is nearly an afterthought (unless, of course, the reward fails to arrive, in which case it's the most important thing in the world). If you know your appetite will be sated, pleasure is more about the appetite than about the sating.* This is hugely important.

Anticipation requires learning.[92] Learn Warren G. Harding's middle name, and synapses in the hippocampus become more excitable. Learn that when the light comes on it's reward time, and it's hippocampal amygdaloid and frontal cortical neurons projecting to dopamine neurons that become more excitable.

This explains context-dependent craving in addiction.[93] Suppose an alcoholic has been clean and sober for years. Return him to where the alcohol consumption used to occur (e.g., that rundown street corner, that fancy men's club), and those potentiated synapses, those cues that were learned to be associated with alcohol, come roaring back into action, dopamine surges with anticipation, and the craving inundates.

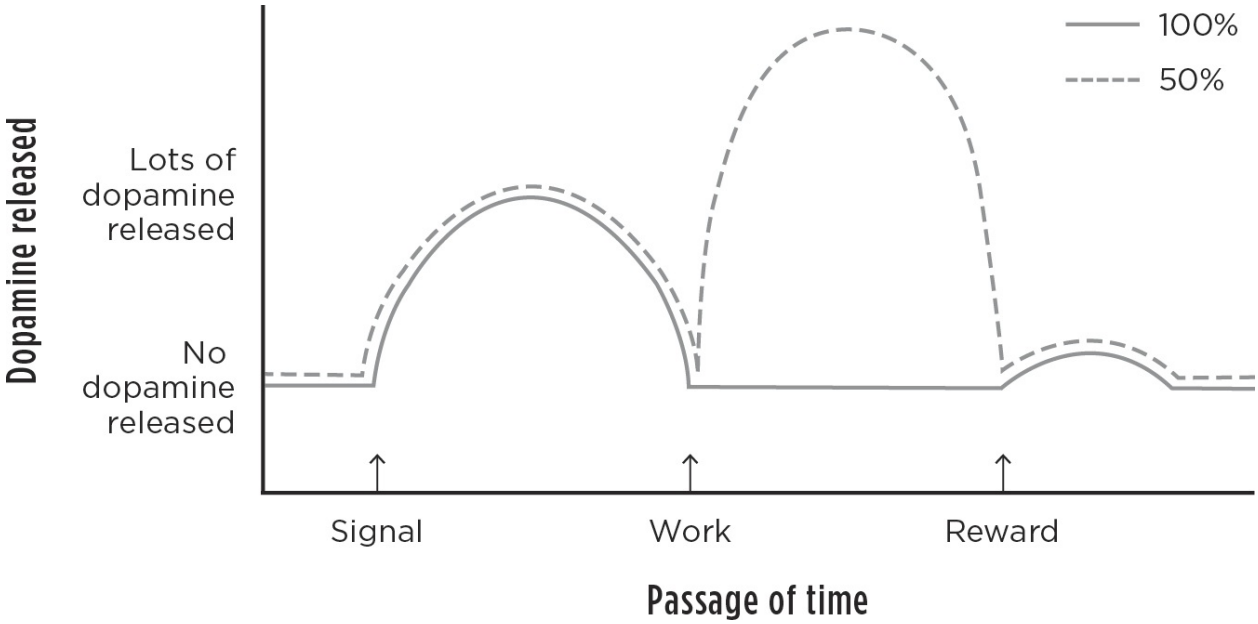
Can a reliable cue of an impending reward eventually become rewarding itself? This has been shown by Huda Akil of the University of Michigan. A light

in the left side of a rat's cage signals that lever pressing will produce a reward from a food chute on the right side. Remarkably, rats eventually will work for the chance to hang around on the left side of the cage, just because it feels so nice to be there. The signal has gained the dopaminergic power of what is being signaled. Similarly, rats will work to be exposed to a cue that signals that *some kind* of reward is likely, without knowing what or when. This is what fetishes are, in both the anthropological and sexual sense.[94]

Schultz's group has shown that the magnitude of an anticipatory dopamine rise reflects two variables. First is the size of the anticipated reward. A monkey has learned that a light means that ten lever presses earns one unit of reward, while a tone means ten presses earns ten units. And soon a tone provokes more anticipatory dopamine than does a light. It's "This is going to be great" versus "This is going to be *great*."

The second variable is extraordinary. The rule is that the light comes on, you press the lever, you get the reward. Now things change. Light comes on, press the lever, get the reward . . . only 50 percent of the time. Remarkably, once that new scenario is learned, far more dopamine is released. Why? Because nothing fuels dopamine release like the "maybe" of intermittent reinforcement.[95]

This additional dopamine is released at a distinctive time. The light comes on in the 50 percent scenario, producing the usual anticipatory dopamine rise before the lever pressing starts. Back in the predictable days when lever pressing always earned a reward, once the pressing was finished, dopamine levels remained low until the reward arrived, followed by a little dopamine blip. But in this 50 percent scenario, once the pressing is finished, dopamine levels start rising, driven by the uncertainty of "maybe yes, maybe no."



Visit bit.ly/2o3Zvcq for a larger version of this graph.

Modify things further; reward now occurs 25 or 75 percent of the time. A shift from 50 to 25 percent and a shift from 50 to 75 percent are exactly opposite, in terms of the likelihood of reward, and work from Knutson's group shows that the greater the probability of reward, the more activation in the medial PFC.[96] But switches from 50 to 25 percent and from 50 to 75 percent both reduce the magnitude of uncertainty. And the secondary rise of dopamine for a 25 or 75 percent likelihood of reward is smaller than for 50 percent. Thus, anticipatory dopamine release peaks with the greatest uncertainty as to whether a reward will occur.* Interestingly, in circumstances of uncertainty, enhanced anticipatory dopamine release is mostly in the mesocortical rather than mesolimbic pathway, implying that uncertainty is a more cognitively complex state than is anticipation of predictable reward.

None of this is news to the honorary psychologists running Las Vegas. Logically, gambling shouldn't evoke much anticipatory dopamine, given the astronomical odds against winning. But the behavioral engineering—the 24-7 activity and lack of time cues, the cheap alcohol pickling frontocortical judgment, the manipulations to make you feel like today is your lucky day—distorts and shifts the perception of the odds into a range where dopamine pours out and, oh, why not, let's try again.

The interaction between "maybe" and the propensity for addictive gambling is seen in a study of "near misses"—when two out of three reels line up in a slot machine. In control subjects there was minimal dopaminergic activation after

misses of any sort; among pathological gamblers, a near miss activated the dopamine system like crazy. Another study concerned two betting situations with identical probabilities of reward but different levels of information about reward contingencies. The circumstance with less information (i.e., that was more about ambiguity than risk) activated the amygdala and silenced dopaminergic signaling; what is perceived to be well-calibrated risk is addictive, while ambiguity is just agitating.[97]

Pursuit

So dopamine is more about anticipation of reward than about reward itself. Time for one more piece of the picture. Consider that monkey trained to respond to the light cue with lever pressing, and out comes the reward; as we now know, once that relationship is established, most dopamine release is anticipatory, occurring right after the cue.

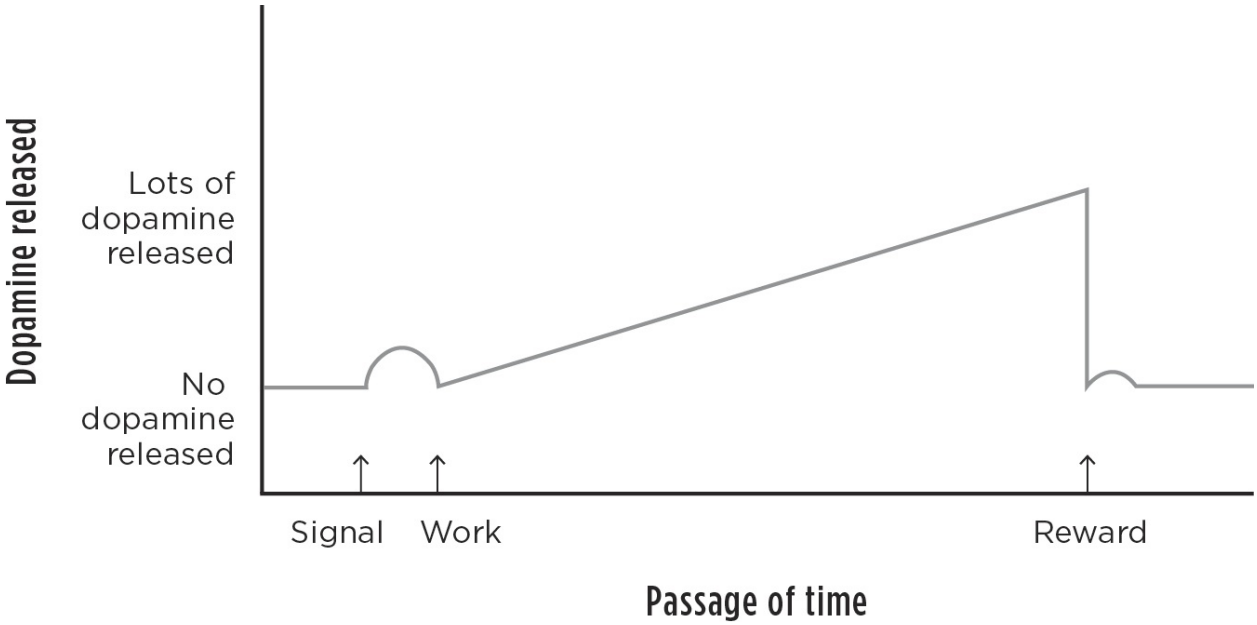
What happens if the post–light cue release of dopamine doesn't occur?[98] Crucially, the monkey doesn't press the lever. Similarly, if you destroy its accumbens, a rat makes impulsive choices, instead of holding out for a delayed larger reward. Conversely, back to the monkey—if instead of flashing the light cue you electrically stimulate the tegmentum to release dopamine, the monkey presses the lever. Dopamine is not just about reward anticipation; it fuels the *goal-directed behavior* needed to gain that reward; dopamine "binds" the value of a reward to the resulting work. It's about the motivation arising from those dopaminergic projections to the PFC that is needed to do the harder thing (i.e., to work).

In other words, dopamine is not about the happiness of reward. It's about the happiness of pursuit of reward that has a decent chance of occurring.*[99]

This is central to understanding the nature of motivation, as well as its failures (e.g., during depression, where there is inhibition of dopamine signaling thanks to stress, or in anxiety, where such inhibition is caused by projections from the amygdala).[100] It also tells us about the source of the frontocortical power behind willpower. In a task where one chooses between an immediate and a (larger) delayed reward, contemplating the immediate reward activates limbic targets of dopamine (i.e., the mesolimbic pathway), whereas contemplating the delayed reward activates frontocortical targets (i.e., the mesocortical pathway).

The greater the activation of the latter, the more likely there'll be gratification postponement.

These studies involved scenarios of a short burst of work soon followed by reward.[101] What about when the work required is prolonged, and reward is substantially delayed? In that scenario there is a secondary rise of dopamine, a gradual increase that fuels the sustained work; the extent of the dopamine ramp-up is a function of the length of the delay and the anticipated size of the reward:



Visit bit.ly/2ngTC7V for a larger version of this graph.

This reveals how dopamine fuels delayed gratification. If waiting X amount of time for a reward has value Z; waiting 2X should logically have value ½Z; instead we "temporally discount"—the value is smaller, e.g., ¼Z. We don't like waiting.

Dopamine and the frontal cortex are in the thick of this phenomenon. Discounting curves—a value of ¼Z instead of ½Z—are coded in the accumbens, while dlPFC and vmPFC neurons code for time delay.[102]

This generates some complex interactions. For example, activate the vmPFC or inactivate the dlPFC, and short-term reward becomes more alluring. And a cool neuroimaging study of Knutson's gives insight into impatient people with steep temporal discounting curves; their accumbens, in effect, underestimates the magnitude of the delayed reward, and their dlPFC overestimates the length of the delay.[103]

Collectively these studies show that our dopaminergic system, frontal cortex, amygdala, insula, and other members of the chorus code for differing aspects of

reward magnitude, delay, and probability with varying degrees of accuracy, all influencing whether we manage to do the harder, more correct thing.[104]

Individual differences among people in the capacity for gratification postponement arise from variation in the volume of these individual neural voices.[105] For example, there are abnormalities in dopamine response profiles during temporal discounting tasks in people with the maladaptive impulsiveness of attention-deficit/hyperactivity disorder (ADHD). Similarly, addictive drugs bias the dopamine system toward impulsiveness.

Phew. One more complication: These studies of temporal discounting typically involve delays on the order of seconds. Though the dopamine system is similar across numerous species, humans do something utterly novel: we delay gratification for insanely long times. No warthog restricts calories to look good in a bathing suit next summer. No gerbil works hard at school to get good SAT scores to get into a good college to get into a good grad school to get a good job to get into a good nursing home. We do something even beyond this unprecedented gratification delay: we use the dopaminergic power of the happiness of pursuit to motivate us to work for rewards that come *after we are dead*—depending on your culture, this can be knowing that your nation is closer to winning a war because you've sacrificed yourself in battle, that your kids will inherit money because of your financial sacrifices, or that you will spend eternity in paradise. It is extraordinary neural circuitry that bucks temporal discounting enough to allow (some of) us to care about the temperature of the planet that our great-grandchildren will inherit. Basically, it's unknown how we humans do this. We may merely be a type of animal, mammal, primate, and ape, but we're a profoundly unique one.

A Final Small Topic: Serotonin

This lengthy section has concerned dopamine, but an additional neurotransmitter, serotonin, plays a clear role in some behaviors that concern us.

Starting with a 1979 study, low levels of serotonin in the brain were shown to be associated with elevated levels of human aggression, with end points ranging from psychological measures of hostility to overt violence.[106] A similar serotonin/aggression relationship was observed in other mammals and, remarkably, even crickets, mollusks, and crustaceans.

As work continued, an important qualifier emerged. Low serotonin didn't predict premeditated, instrumental violence. It predicted *impulsive* aggression, as well as cognitive impulsivity (e.g., steep temporal discounting or trouble inhibiting a habitual response). Other studies linked low serotonin to impulsive suicide (independent of severity of the associated psychiatric illness).[107]

Moreover, in both animals and humans pharmacologically decreasing serotonin signaling increases behavioral and cognitive impulsivity (e.g., impulsively torpedoing a stable, cooperative relationship with a player in an economic game).[108] Importantly, while increasing serotonin signaling did not lessen impulsiveness in normal subjects, it did in subjects prone toward impulsivity, such as adolescents with conduct disorder.

How does serotonin do this? Nearly all serotonin is synthesized in one brain region,* which projects to the usual suspects—the tegmentum, accumbens, PFC, and amygdala, where serotonin enhances dopamine's effects on goal-directed behavior.[109]

This is as dependable a finding as you get in this business.[110] Until we get to chapter 8 and look at genes related to serotonin, at which point everything becomes a completely contradictory mess. Just as a hint of what's to come, one gene variant has even been referred to, straight faced, by some scientists as the "warrior gene," and its presence has been used successfully in some courtrooms to lessen sentences for impulsive murders.

CONCLUSIONS

This completes our introduction to the nervous system and its role in pro- and antisocial behaviors. It was organized around three themes: the hub of fear, aggression, and arousal centered in the amygdala; the hub of reward, anticipation, and motivation of the dopaminergic system; and the hub of frontal cortical regulation and restraint of behavior. Additional brain regions and neurotransmitters will be introduced in subsequent chapters. Amid this mountain of information, be assured that the key brain regions, circuits, and neurotransmitters will become familiar as the book progresses.

Hang on. So what does this all mean? It's useful to start with three things that this information doesn't mean:

1. First, there's the lure of needing neurobiology to confirm the obvious. Someone claims that, for example, their crappy, violent neighborhood leaves them so anxious that they can't function effectively. Toss them in a brain scanner and flash pictures of various neighborhoods; when their own appears, the amygdala explodes into activity. "Ah," it is tempting to conclude, "we've now *proven* that the person really does feel frightened."

   It shouldn't require neuroscience to validate someone's internal state. An example of this fallacy was reports of atrophy of the hippocampus in combat vets suffering from PTSD; this was in accord with basic research (including from my lab) showing that stress can damage the hippocampus. The hippocampal atrophy in PTSD got a lot of play in Washington, helping to convince skeptics that PTSD is an organic disorder rather than neurotic malingering. It struck me that if it took brain scans to convince legislators that there's something tragically, organically damaged in combat vets with PTSD, then these legislators have some neurological problems of their own.

Yet it required precisely this to "prove" to many that PTSD was an organic brain disorder.

The notion that "if a neuroscientist can demonstrate it, we know that the person's problem is for real" has a corollary—the fancier the neurobiology utilized, the more reliable the verification. That's simply not true; for example, a good neuropsychologist can discern more of what's happening to someone with subtle but pervasive memory problems than can a gazillion-dollar brain scanner.

It shouldn't take neuroscience to "prove" what we think and feel.

2. There's been a proliferation of "neuro-" fields. Some, like neuroendocrinology and neuroimmunology, are stodgy old institutions by now. Others are relatively new—neuroeconomics, neuromarketing, neuroethics, and, I kid you not, neuroliterature and neuroexistentialism. In other words, a hegemonic neuroscientist might conclude that their field explains everything. And with that comes the danger, raised by the *New Yorker* writer Adam Gopnik under the sardonic banner of "neuroskepticism," that explaining everything leads to forgiving everything.[111] This premise is at the heart of debates in the new field of "neurolaw." In chapter 16 I will argue that it is wrong to think that understanding must lead to forgiveness—mainly because I think that a term like "forgiveness," and others related to criminal justice (e.g., "evil," "soul," "volition," and "blame"), are incompatible with science and should be discarded.
3. Finally, there is the danger of thinking that neuroscience supports a tacit sort of dualism. A guy does something impulsive and awful, and neuroimaging reveals that, unexpectedly, he's missing all his PFC neurons. There's a dualist temptation now to view his behavior as more "biological" or "organic" in some nebulous manner than if he had committed the same act with a normal PFC. However, the guy's awful, impulsive act is equally "biological" with or without a PFC. The sole difference is that the workings of the

PFC-less brain are easier to understand with our primitive research tools.

So What Does All of This Tell Us?

Sometimes these studies tell us what different brain regions do. They are getting fancier, telling us about circuits, thanks to the growing time resolution of neuroimaging, transitioning from "This stimulus activates brain regions A, B, C" to "This stimulus activates both A and B, and then C, and C activates only if B does". And identifying what specific regions/circuits do gets harder as studies become subtler. Consider, for example, the fusiform face area. As discussed in the next chapter, it is a cortical region that responds to faces in humans and other primates. We primates sure are social creatures.

But work by Isabel Gauthier of Vanderbilt University demonstrates something more complicated. Show pictures of different cars, and the fusiform activates—in automobile aficionados.[112] Show pictures of birds, and ditto among bird-watchers. The fusiform isn't about faces; it's about recognizing examples of things from categories that are emotionally salient to each individual.

Thus, studying behavior is useful for understanding the nature of the brain—ah, isn't it interesting that behavior A arises from the coupling of brain regions X and Y. And sometimes studying the brain is useful for understanding the nature of behavior—ah, isn't it interesting that brain region A is central to both behavior X and behavior Y. For example, to me the most interesting thing about the amygdala is its dual involvement in both aggression and fear; you can't understand the former without recognizing the relevance of the latter.

A final point related to the core of this book: While this neurobiology is mighty impressive, the brain is not where a behavior "begins." It's merely the final common pathway by which all the factors in the chapters to come converge and create behavior.