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Understanding the Anxious Mind

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Jerome Kagan's "Aha!" moment came with Baby 19. It was 1989, and Kagan, a professor of psychology at Harvard, had just begun a major longitudinal study of temperament and its effects. Temperament is a complex, multilayered thing, and for the sake of clarity, Kagan was tracking it along a single dimension: whether babies were easily upset when exposed to new things. He chose this characteristic both because it could be measured and because it seemed to explain much of normal human variation. He suspected, extrapolating from a study he had just completed on toddlers, that the most edgy infants were more likely to grow up to be inhibited, shy and anxious. Eager to take a peek at the early results, he grabbed the videotapes of the first babies in the study, looking for the irritable behavior he would later call high-reactive.

No high-reactors among the first 18. They gazed calmly at things that were unfamiliar. But the 19th baby was different. She was distressed by novelty — new sounds, new voices, new toys, new smells — and showed it by flailing her legs, arching her back and crying. Here was what Kagan was looking for but was not sure he would find: a baby who essentially fell apart when exposed to anything new.

Baby 19 grew up true to her temperament. This past summer, Kagan showed me a video of her from 2004, when she was 15. We sat in a screening room in Harvard's William James Hall — a building named, coincidentally, for the 19th-century psychologist who described his own struggles with anxiety as "a horrible dread at the pit of my stomach ... a sense of the insecurity of life." Kagan is elfin and spry, balding and bespectacled. He neither looks nor acts his age, which is 80. He is one of the most influential developmental psychologists of the 20th century.

On the monitor, Baby 19 is a plain-looking teenager, hiding behind her long, dark hair. The interview, the same one given to all 15-year-olds in the longitudinal study, begins with questions about school. She has very few extracurricular activities, she says in a small voice, but she does like writing and playing the violin. She fidgets almost constantly as she speaks, twirling her hair, touching her ear, jiggling her knee. "This is the overflow of her high-reactive nature," Kagan told me, standing near the monitor so he could fast-forward to the good parts.

Here was a good part: The interviewer asks Baby 19 what she worries about.

"I don't know," Baby 19 says after a long pause, twirling her hair faster, touching her face, her knee. She smiles a little, shrugs. Another pause. And then the list of troubles spills out: "When I don't quite know what to do and it's really frustrating and I feel really uncomfortable, especially if other people around me know what they're doing. I'm always thinking, Should I go here? Should I go there? Am I in someone's way? ... I worry about things like getting projects done... I think, Will I get it done? How am I going to do it? ... If I'm going to be in a big crowd, it makes me nervous about what I'm going to do and say and what other people are going to do and say." Baby 19 is wringing her hands now. "How I'm going to deal with the world when I'm grown. Or if I'm going to sort of do anything that really means anything."

Her voice trails off. She wants to make a difference, she says, and worries about whether she will. "I can't stop thinking about that."

Watching this video again makes Kagan fairly vibrate with the thrill of rediscovery: here on camera is the

young girl who, as an infant, first embodied for him what it meant to be wired to worry. He went on to find many more such children, and would watch a big chunk of them run into trouble with anxiety or other problems as they grew up.

The tenuousness of modern life can make anyone feel overwrought. And in societal moments like the one we are in — thousands losing jobs and homes, our futures threatened by everything from diminishing retirement funds to global warming — it often feels as if ours is the Age of Anxiety. But some people, no matter how robust their stock portfolios or how healthy their children, are always mentally preparing for doom. They are just born worriers, their brains forever anticipating the dropping of some dreaded other shoe. For the past 20 years, Kagan and his colleagues have been following hundreds of such people, beginning in infancy, to see what happens to those who start out primed to fret. Now that these infants are young adults, the studies are yielding new information about the anxious brain.

These psychologists have put the assumptions about innate temperament on firmer footing, and they have also demonstrated that some of us, like Baby 19, are born anxious — or, more accurately, born predisposed to be anxious. Four significant long-term longitudinal studies are now under way: two at Harvard that Kagan initiated, two more at the University of Maryland under the direction of Nathan Fox, a former graduate student of Kagan's. With slight variations, they all have reached similar conclusions: that babies differ according to inborn temperament; that 15 to 20 percent of them will react strongly to novel people or situations; and that strongly reactive babies are more likely to grow up to be anxious.

They have also shown that while temperament persists, the behavior associated with it doesn't always. Kagan often talks about the three ways to identify an emotion: the physiological brain state, the way an individual describes the feeling and the behavior the feeling leads to. Not every brain state sparks the same subjective experience; one person might describe a hyperaroused brain in a negative way, as feeling anxious or tense, while another might enjoy the sensation and instead uses a positive word like "alert." Nor does every brain state spark the same behavior: some might repress the bad feelings and act normally; others might withdraw. But while the behavior and the subjective experience associated with an emotion like anxiety might be in a person's conscious control, physiology usually is not. This is what Kagan calls "the long shadow of temperament." The oldest high-reactive subjects in Kagan's and Fox's studies, like Baby 19, are in their 20s now, and for many of them, no matter how much they manage to avoid looking anxious to an outsider, fears still rattle in their skulls at 3 o'clock in the morning. They remain anxious just below the surface, their subconscious brains still twitchy, still hypervigilant, still unable to shift attention away from perceived threats that aren't really there.

ANXIETY IS NOT fear, exactly, because fear is focused on something right in front of you, a real and objective danger. It is instead a kind of fear gone wild, a generalized sense of dread about something out there that seems menacing — but that in truth is not menacing, and may not even be out there. If you're anxious, you find it difficult to talk yourself out of this foreboding; you become trapped in an endless loop of what-ifs.

"I was flesh bereft of spirit," wrote the journalist Patricia Pearson in "A Brief History of Anxiety (Yours and Mine)," in a pitch-perfect description of this emotional morass, "a friable self, grotesque... I got an AIDS test. I had my moles checked. I grew suspicious of pains in my back. If I was nauseous, I worried about cancer and started reading up obsessively on symptoms. I lay in bed whenever I could, trying to shut up the clamor of terror with sleep."

When the "clamor of terror" starts to interfere with functioning, as it did for Pearson when she was a crime reporter in her early 30s, worrying turns into a clinical anxiety disorder, of which there are several forms:

panic, social anxiety, phobia, obsessive-compulsive, post-traumatic stress and a catch-all called generalized anxiety disorder. Taken together, they make anxiety the most common mental illness in America, affecting an estimated 40 million adults, according to the National Institute of Mental Health. And that figure doesn't even count the far greater swath who are garden-variety worriers, people who fret when a child is late, who worry when they hear a siren headed toward home, who are sure that a phone call in the middle of the night means someone is dead.

In the brain, these thoughts can often be traced to overreactivity in the amygdala, a small site in the middle of the brain that, among its many other functions, responds to novelty and threat. When the amygdala works as it should, it orchestrates a physiological response to changes in the environment. That response includes heightened memory for emotional experiences and the familiar chest pounding of fight or flight. But in people born with a particular brain circuitry, the kind seen in Kagan's high-reactive study subjects, the amygdala is hyperreactive, prickly as a haywire motion-detector light that turns on when nothing's moving but the rain. Other physiological changes exist in children with this temperament, many of them also related to hyperreactivity in the amygdala. They have a tendency to more activity in the right hemisphere, the half of the brain associated with negative mood and anxiety; greater increases in heart rate and pupil dilation in response to stress; and on occasion higher levels of the stress hormones cortisol and norepinephrine.

But having all the earmarks of anxiety in the brain does not always translate into a subjective experience of anxiety. "The brain state does not make it a disorder," Kagan told me. "The brain state exists, and the statement 'I'm anxious,' exists, and the correlation is imperfect." Two people can experience the same level of anxiety, he said, but one who has interesting work to distract her from the jittery feelings might do fine, while another who has just lost his job spends all day at home fretting and might be quicker to reach a point where the thrum becomes overwhelming. It's all in the context, the interpretation, the ability to divert your attention from the knot in your gut. These variations also happen when someone grows up from an anxious infant to someone either fretful or tranquil. One aim of Kagan's and Fox's longitudinal studies is to watch how the life stories of these high-strung babies unfold.

The quintessential longitudinal study, the one often mentioned because it set the standard, is the Framingham Heart Study, which enshrined the idea of risk factors. It was through Framingham, for instance, that scientists learned that high blood pressure was a risk factor for cardiovascular disease, since it followed its subjects for long enough to detect that those who had high blood pressure in their 30s and 40s were more likely to have heart disease later in life.

But such studies draw conclusions about trends, not destinies. If someone with high blood pressure treats it early, the risk of heart disease can be reduced significantly. Similarly, if someone with an anxiety-prone temperament grows up in the right surroundings, he or she might never develop a full-blown anxiety disorder.

Kagan's first exposure to longitudinal studies came shortly after he received his Ph.D. from Yale in 1954. He was working at the Fels Research Institute on the campus of Antioch College in Ohio, where a longitudinal study of middle-class children had been going on for nearly 30 years. He stumbled upon a gigantic room "loaded with prose summaries of what these children were like from the age of 1 month on," he told me recently. He knew a treasure trove when he saw one.

Among these prose summaries, which ultimately Kagan and a colleague, Howard Moss, turned into the book "Birth to Maturity," were descriptions indicating that babies had different innate temperaments. Kagan studiously ignored this finding; it didn't fit with his left-leaning politics, which saw all individuals as

born inherently the same — blank slates, to use the old terminology — and capable of achieving anything if afforded the right social, economic and educational opportunities. “I was so resistant to awarding biology much influence, I didn’t follow up on the inhibited temperaments I was seeing,” he told me. It took another 20 years of listening to arguments about nature versus nurture for Kagan finally to entertain the possibility that some behavior might be attributed to genes.

BY THE TIME Kagan moved to Harvard in 1964, the notion of an inborn temperament was on the ascent, in part because of the findings of Stella Chess and Alexander Thomas of New York University, who divided children into three categories: easy children, difficult children and those who were slow to warm up. Remembering the Fels data, Kagan embarked on his own longitudinal study of temperament. In 1979, he screened about 400 preschoolers, exposing them to new toys and new people in a laboratory playroom, videotaping them and coding their behavior. About 15 percent ended up in the group Kagan called “behaviorally inhibited”: wary, subdued, tending to hover near their mothers. Another 15 percent were “behaviorally uninhibited.” They were the fearless ones, who ran around trying to play with every new toy and chatting happily with the examiner. When Kagan talks about such children, he uses one of his favorite words: “ebullient.”

Over the next five years, 107 of these children — half of them timid, half bold — came back to the lab for more testing. (To keep environmental differences to a minimum, Kagan restricted his sample to children who were white, middle class and healthy at birth.) Their behavior was again recorded and again coded. Temperament, it turned out, tended to be stable over those five years, at least in children who started out at the extremes. There was a shift toward the middle between ages 2 and 7, but only 3 of the 107 changed categories completely from uninhibited to inhibited or vice versa. In addition, the most inhibited 7-year-olds showed some physiological differences that indicated an exaggerated response to stress.

Kagan and his colleagues, Nancy Snidman and J. Steven Reznick, published their results in Science in 1988. The physiological measurements led them to believe something biological was at work. Their hypothesis: the inhibited children were “born with a lower threshold” for arousal of various brain regions, in particular the amygdala, the hypothalamus and the hypothalamic-pituitary-adrenal axis, the circuit responsible for the stress hormone cortisol.

Though its findings seem almost self-evident today, the Science paper made a splash at the time. “There are two kinds of great research,” Susan Engel, a developmental psychologist at Williams College, told me when I discussed Kagan’s study with her. “There’s research that is counterintuitive, that shows you something you’d never guess on your own, and there’s research that shows you irrefutably what you had an intuition about, something you thought was true but didn’t have evidence to support.” Kagan’s research was of the second type, she says: “a beautiful, elegant experimental demonstration of an old intuition.”

But these subjects were preschoolers when Kagan first met them, already too old for him to know how much to attribute to nature rather than nurture. Couldn’t the inhibited children somehow have been raised to be wary instead of born that way? So the following year, Kagan began a new study he said he hoped would minimize the effects of the environment. He recruited infants who were just 4 months old, planning to categorize them according to temperament and to follow them as they grew to see whether temperament in infancy predicted anything about subsequent personality.

How to measure temperament in babies so young, at an age when some parents are still wondering whether a smile means happiness or gas? Kagan couldn’t measure the amygdala directly, so he looked for signs of its rampant firing that would be meaningful — and measurable — in infants. Since projections from the amygdala connect it to brain regions that control motor activity and the autonomic nervous system

(heartbeat, breathing and other involuntary actions), he reasoned that if the amygdala was highly reactive, it would show up as increased motor activity, fretting and crying, as well as increases in heart rate, respiration and blood pressure.

Showing that a few physical measurements could offer insight into a baby's psyche was one of Kagan's real contributions. "Where his work had so much depth was not only in the longitudinal follow-up," says Joan Kaufman, a Yale psychologist who was a research assistant at Harvard when the study began, "but in thinking about the behavioral phenotype of an inborn temperament and really assessing it with such rigor."

Kagan brought about 500 babies — as before, all white, middle class and healthy — into the laboratory, placed them in infant seats in front of a video camera and exposed them to a series of novel stimuli. He showed them a schematic face that emitted words in a synthetic voice designed to be what he called "discrepant but not terrifying." He dangled a dancing mobile with plastic Winnie the Pooh characters — again, nothing scary, but something new. He brought to their noses a cotton swab that had been dipped in diluted alcohol. The battery of novel stimuli took 45 minutes. Some of the babies gazed contentedly throughout. Others were in constant motion, kicking and moving their arms fitfully, furrowing their brows, arching their backs or crying if they were really upset.

Kagan and his research assistants again looked at videotapes and coded movements and cries. Based on the final tally, each infant was categorized as either low-reactive, high-reactive or somewhere in between. The low-reactives were the classic easy babies, the ones who take unfamiliarity in stride. The high-reactives, among them Baby 19, thrashed and whimpered when exposed to the same unfamiliar things. It was clear, as they twisted about in their infant seats, that these babies were high-maintenance, difficult to comfort.

About 40 percent were low-reactive, and about 20 percent were high-reactive. Kagan brought most of them, as well as those with intermediate temperament, back for testing at ages 1 and 2. About half of them — primarily those at each extreme — returned for further testing at ages 4, 7, 11 and 15. That pattern continues to this day, even after Kagan retired in 2000 and handed over his records to a collaborator, Carl Schwartz, an adolescent psychiatrist at Harvard and Massachusetts General Hospital, who tested some of Kagan's subjects when they were 18 or 21.

By the earliest assessments, certain patterns had already emerged. At age 4, children who had been high-reactive were four times as likely to be behaviorally inhibited as those who had been low-reactive. By age 7, almost half of the jittery babies had developed symptoms of anxiety — fear of thunder or dogs or darkness, extreme shyness in the classroom or playground — compared with just 10 percent of the more easygoing ones. About one in five of the high-reactive babies were consistently inhibited and fearful at every visit up to the age of 7.

"Fear is an incredibly heterogeneous construct," says Daniel Pine, a child psychiatrist at the National Institute of Mental Health. Pine collaborates on the two longitudinal studies at the University of Maryland, conducting psychiatric interviews and functional M.R.I. scans on subjects at several stages. "Fear of social things is different from fear of physical things." The same brain circuitry is probably involved in both, he said, but different fears tend to show up at different points in development: fear of things like clowns, balloons or spiders emerging early in life; fear of things like social situations with peers emerging later. In addition, it's relatively easy to avoid the physical things that frighten you; if you're afraid of dogs, you can just take a different route to school to keep from passing that bull terrier down the street. It's much harder to avoid social fears — you can avoid the dog on the way to school, but you still have to go to school.

The children tended to get a better grip on their fearfulness as they got older. By adolescence, the rate of

anxiety in Kagan's study subjects declined overall, including in the high-risk group. At 15, about two-thirds of those who had been high-reactors in infancy behaved pretty much like everybody else.

One such person was Mary, now a 21-year-old junior at Harvard, who was in the high-reactive group as a baby and was moderately fearful at ages 1 and 2. She didn't think of herself as anxious, just dutiful. "I don't stray from the rules too much," she said when we spoke by telephone not long ago. "But it's natural for me — I never felt troubled about it. I was definitely the kid who worked really hard to get good grades, who got all my homework done before I watched TV." Mary also was an accomplished ballet dancer as a child, which gave her a way to work off energy and to find a niche in which she excelled. That talent, plus being raised in what Kagan called a "benevolent home environment," might have helped shift Mary's innate inhibition to something more constructive. If Mary's high-reactive temperament is evident now, it comes out in the form of conscientiousness and self-control.

PEOPLE WITH A nervous temperament don't usually get off so easily, Kagan and his colleagues have found. There exists a kind of sub-rosa anxiety, a secret stash of worries that continue to plague a subset of high-reactive people no matter how well they function outwardly. They cannot quite outrun their own natures: consciously or unconsciously, they remain the same uneasy people they were when they were little.

Most of the high-reactive kids in Kagan's study did well in adolescence, getting good grades, going to parties, making friends. Scratch the surface, though, and many of them — probably most of them — were buckets of nerves. "It's only the high-reactives who say, 'I'm tense in school,' 'I vomit before examinations,' 'If we're going on a class trip to D.C., I can't sleep the night before,' " Kagan told me. "They don't like it, but they've accepted the fact that they're just tense people." Invoking Jungian terminology, he called it the difference between persona (the outer-directed personality) and anima (the inner-directed thoughts and feelings). The persona can be controlled, but the anima often cannot.

Nathan Fox of the University of Maryland says that when the anima erupts in high-risk children, it often takes the form of excessive vigilance and misdirected attention. In the first of his two longitudinal studies of temperament, begun in 1989, he followed 180 children from the age of 4 months and gave them a set of neuropsychological tests when they were between 13 and 15. One test, called the spatial-cuing task, measures vigilance and the ability to disengage attention from a perceived threat. It shows two faces briefly on a computer screen, one on each side — the same face looking threatening on one side and pleasant on the other. The faces fade away, and an arrow appears on one side of the screen, sometimes on the side the threatening face had been on, sometimes on the other. The subject must notice the arrow and press a button to indicate whether the arrow points up or down.

Adults with clinical anxiety consistently are faster at pressing the correct button if the arrow is on the side of the screen where the threatening face had been, and slower if the arrow is on the other side. (Non-anxious adults show no such subconscious preference.) In the kids in Fox's study, those who were born anxiety-prone — even the outwardly calm, well-adjusted ones — tended to perform this task like anxious adults, paying more attention to the threatening face whether or not they meant to.

A similar result came from another test Fox gave his subjects, called the potentiated startle response. In this test, teenagers are placed in front of a screen and told that when the screen is blue, there is a chance a puff of air will be blasted at their throats — a sensation that, Fox assured me, is surprising and uncomfortable but not painful. When the screen is green, they're safe; they are told that no puff of air will ever come when the green screen is on. Then, to evoke a startle, the experimenter plays a loud noise and measures the teenager's response (an involuntary eye blink). All subjects have a robust startle response when the blue screen is on, which reflects the fact that they are tensing up in anticipation of that uncomfortable air puff.

But anxiety-prone kids startle just as much with the green, supposedly safe screen. They stay on guard, anxious and wired, even when the situation is not threatening. Again, this finding held no matter how the subjects behaved in real life — and no matter how they were feeling while the test was taking place.

Fox's collaborator, Daniel Pine of the N.I.M.H., conducted functional M.R.I. scans on 27 of these study subjects when they were adolescents. While they were in the scanner, Pine showed them pictures of fearful faces. Sometimes he told them to try to measure how wide the nose was — in other words, to focus on a detail that is emotionally neutral. Other times he told them to think about how afraid they felt looking at the person in the picture.

Teenagers who were in the group at low risk for anxiety showed no increase in activity in the amygdala when they looked at the face, even if they had been told to focus on their own fear. But those in the high-risk group showed increased activity in the amygdala when they were thinking about their own feelings (though not when they were thinking about the nose). Once again, this pattern was seen in anxiety-prone youngsters quite apart from whether they had problems with anxiety in their daily lives. In the high-risk kids, even those who were apparently calm in most settings, their amygdalas lighted up more than the others' did.

Temperamental type tends to reveal itself not only in functional M.R.I. scans but also in structural M.R.I.'s, which look at brain anatomy rather than activity. In 2007 Carl Schwartz, the Harvard psychiatrist who has taken over the follow-up work on Kagan's two longitudinal studies, put 76 of Kagan's study subjects in an M.R.I. machine. At the time, they were 18 years old. (Baby 19 was part of the sample; Mary was asked to participate, but she declined.) He found that the subjects who were high-reactors at 4 months tended to show significant thickening in the prefrontal cortex compared to those who were low-reactors. "This was amazing," Schwartz told me. "The temperament they exhibited as infants still seemed to leave a fingerprint in the brain 18 years later."

He is still trying to work out the exact meaning of this fingerprint; he cannot yet tell, for instance, whether a thicker cortex is a cause of a high-reactive temperament, or an effect, or something else entirely. One job of the prefrontal cortex is inhibitory, putting a damper on signals that come from the amygdala. Could it be that the cortex thickens more in the anxiety-prone as it is busy tamping down the overactive amygdala and growing new neural connections? Or does a thicker cortex come first, and contribute to a tendency to be anxious in the first place?

One way Schwartz tried to untangle his uncertainties was by winnowing from his sample the 14 subjects who had ever been given a diagnosis of social-anxiety disorder. What was left, presumably, were 62 young people who all functioned just fine, at least in the sense of never having suffered from social anxiety. Schwartz reviewed their brain images, and the difference between the cortical thickening in the high-reactive group and the low-reactives not only remained; it also became more pronounced. One explanation of this could be that a thicker cortex is protective in the anxiety-prone. He surmises that those 14 subjects who developed problems did so in part because their cortex was thinner, and the high-reactives who had avoided social anxiety had the thickest cortexes of all.

So what do these brain-anxious young people report about their state of mind? Anxiety, remember, can occur at three levels: brain, behavior and subjective experience. Were the ones whose brains looked anxious on the M.R.I. scans actually experiencing the sensation of being anxious?

This is a question the scientists struggle with, hampered as they are by peoples' inability to report their own feelings accurately. Pine told me that his subjects often admit, after the fact, that they had been more afraid during the experiment than they said at the time — leaving him unsure what conclusions to draw. According

to Kagan, the high-reactive temperament is characterized by a tendency to be supersensitive to your own body's signals. Wouldn't you expect, then, that anxiety-prone kids would have some insight into their own brains? Yet even in the high-risk subjects, objective brain state and subjective experience of anxiety still don't always track.

It is also difficult to say whether high-reactive people are aware, more generally, that their brains are more tightly coiled than other people's. "What people say about what they're feeling is significant, but it is hardly the whole story," Schwartz says. "Some of those kids probably do have a subjective awareness of their brain state; others who have equally large amygdala signals — depending on how they have adapted, how they've been brought up and supported — might have little awareness of it." In some cases, he says, people might even have "reframed" certain physical sensations that could be considered symptoms of anxiety — like feeling jazzed up or having your pulse quicken — as "vaguely exhilarating or exciting."

Studies like Pine's and Schwartz's might actually be revealing not an anxious brain at all but an experimental artifact, says the developmental psychologist Robert Plomin. Plomin, who runs a longitudinal twin study of genes and behavior at King's College, London, agrees that anxiety does have a neurological fingerprint, but he worries about a disconnect between anxiety in the lab and anxiety as a quotidian experience. "Let's say that in your real life you learn to manage your temperamental dispositions so you don't freak out," he said. "Let's say you learn to take a deep breath, learn tricks to make yourself function better in life. But in the lab you're not dealing with social situations you've learned to control. You're just shown — boom! — some horrible picture of a bloody accident." If your response to a brutal image is milliseconds faster than the response of someone who is more sanguine, Plomin asked, what does that really tell you about how your brain would respond in the real world to a worrisome situation?

To make the anxiety-provoking lab challenge more authentic and emotionally charged, Pine and his colleagues at the N.I.M.H., Eric Nelson and Amanda Guyer, concocted an elaborate experimental setup to persuade teenagers in a functional M.R.I. machine that their social status really is on the line: a fake Internet chat room. They created a set of potential chat-room partners for their subjects: smiley, fictitious teenagers, complete with sham MySpace pages. The setup was that the other kids would eventually tell the subjects in the scanner whether they did or did not want to chat with them. The scans were taken, then, while the subjects were lying still, awaiting the verdict. In a handful of pilot experiments, this has proved to be an emotionally significant challenge for teenagers with social anxiety. The anxious youngsters, while waiting to hear from one of the pretend teenagers they wanted to avoid, showed more reactivity in the amygdala and prefrontal cortex. Pine has conducted this same experiment on 40 of Fox's longitudinal-study subjects and is currently analyzing the results.

Still, tracking the anxious mind, even with a more realistic experimental setup, means having the subject lie in an M.R.I. scanner, which is inherently not only artificial but also stressful. So Plomin's point is interesting. Brain scans and other lab findings might reflect something deep and persistent going on in the anxious mind. But if you have learned to control your behavior, to structure your life so you can limit triggers and cope with your emotional skittishness, how much does it really matter?

THE BEHAVIORAL STRAND of the brain-behavior-experience triad is the one that seems most amenable to intervention, and scientists are now investigating how it is that two-thirds of those with a high-reactive temperament manage to avoid trouble. Many environmental factors no doubt come into play — some of them malleable, some less so. In Kagan's first study, for instance, he found that birth order seemed relevant. Behaviorally inhibited children were much more likely to have older siblings: two-thirds of them did, compared with just one-third of the uninhibited children. Could having older siblings, he and his co-authors wondered, mean being teased and pushed, which becomes a source of chronic stress, which in turn

amplifies a biological predisposition to inhibition? Kagan never replicated this finding, as intriguing as it was — which shows how difficult it can be to tease out which environmental factors are relevant, and which turn out to be incidental. Fox, meanwhile, noted that the high-reactive babies who went to day care when they were young were significantly less fearful at age 4 than were the high-reactives who stayed home with their mothers.

Attempts to see what kind of parenting works best with an anxiety-prone temperament leave almost as many questions asked as answered. Which is better for a fearful, high-strung child — a parent who coddles the child and says everything will be all right, or a parent who sets firm, strict limits and has no tolerance for skittishness? You could picture it as going either way, really. On the one hand, it might be good to shield children from the things that worry them. On the other hand, it might be better to urge them, maybe even force them, to confront the things they dread.

Scientists from both Kagan's and Fox's labs have looked at this question in a systematic way, and they have come up with two somewhat different findings. Both studies involved a series of home visits and hours of videotapes of mother-baby interactions. But one study, by Kagan's graduate student Doreen Arcus in the early 1990s, found that what seemed to be best for high-reactive babies were mothers who set firm limits and did not rush too quickly to comfort them when they cried. And the other, by Fox's postdoctoral fellow Amie Ashley Hane a decade later, found something slightly different: that the best fit for high-strung babies were sensitive mothers, who met their fearful children on their own terms and interacted with them in a way that was accepting and supportive without being intrusive. Sometimes, of course, there's a fine line between firm and hardhearted, and a fine line between supportive and intrusive. This makes it especially tough to turn research findings like Arcus's and Hane's into clear guidance on how best to care for a fretful child.

The best outcome, however it happens, is to rear a child who learns to wrestle his demons on his own. Some children figure out themselves what works best. "Inner struggles pulled at me for years until I was able to just let go and calm myself," wrote one of Kagan's high-reactive study subjects in an essay, revealing a wisdom far beyond his 13 years. "For example, when I first heard about the anthrax in Washington, I began to have an upset stomach. I realized it was simply because of my anxiety that I was feeling sick. As soon as I realized that, the stomachache went away. Because I now understand my predisposition toward anxiety, I can talk myself out of simple fears." There are many adults, anxious or not, who can't control their own interior monologues as well as this boy can.

For the children who need help grappling with their fears, some psychologists try to intervene early, with programs that give worried children tools for quieting the scary thoughts in their heads. Kids are often taught the same skills that anxious adults are, a variation on cognitive behavior therapy, designed to stop the endless recursive loop of rumination, replacing it with a smart, rational interior voice. In a way, it's teaching anxious people to do what non-anxious people do naturally.

"I joke a lot about my anxiety," wrote a young woman named Brittany on the group blog We Worry, part of a thriving community of anxiety blogs. "And there are times I do find it funny. I can do this because there is that voice in my head that tells me what I'm worrying about is irrational. But then I worry about worrying about irrational things. It is a never-ending cycle." She might laugh at herself, she wrote, but life can get "overwhelming to me sometimes. Things that don't even register to most people are uphill battles for me."

Even those with normal, run-of-the-mill fretfulness — not a clinical anxiety disorder like Brittany's — struggle to outsmart their brooding. "I have a friend who's a clinical psychologist, and we talk about this a lot — what people do on their own to make themselves less anxious," said Engel of Williams College, who is writing a book about temperament called "Red Flags and Red Herrings." Engel said she is by nature very

anxious, as is the eldest of her three sons. “The way we deal with it is that we both get everything done in lots of time. We can’t stand the anxiety of a looming deadline; we’re so worried about being late that we do it five days early.” This is one way to alleviate anxiety, she said. “There are other things we could do. We could drink, we could procrastinate, we could pretend we don’t have the deadline. I guess we both happen to be lucky that our method is adaptive.”

This kind of adapting might have something to do with intelligence, says Steven Pinker, a psychologist at Harvard and author of “The Blank Slate: The Modern Denial of Human Nature.” He says he believes, based on pure conjecture, that people with higher intelligence are better at overcoming their anxious temperament and more likely to “see their own worry list as a problem to be solved, minimizing unnecessary anxiety while still being anxious enough to get things done.” At least one study lends support to Pinker’s impression. In a 2004 article called “Can Worriers Be Winners?” two British scientists gave personality questionnaires to a group of financial services managers and found that those who reported themselves as scoring high on anxiety traits, like being nervous about performing well on the job, turned out to be better employees, but only if their worrying was accompanied by high cognitive ability.

Fox said that what distinguishes the high-reactives who learn to adapt from those who don’t often comes down to something simple, like finding one or two supportive friends — or, like Mary and her ballet, finding something they’re good at and can feel self-confident about. But there could be some physiological differences between the adapters and the nonadapters, too. Baby 19, for instance, ran into some problems as she grew up. At a year old, she was one of the most fearful children in Kagan’s study, and she had an episode of depression in middle school and a diagnosis of social anxiety disorder as a teenager. While these could have been related to any of a number of environmental factors, including a broken home, they could be related too to something curious that turned up in the brain scan Schwartz did on Baby 19 when she was 18 years old.

When Baby 19 was in the functional M.R.I. scanner and shown a series of unfamiliar faces, Schwartz said, her amygdala was highly reactive — about three times as much as that of a typical low-reactor. This was what Schwartz expected in someone with her temperament and psychiatric history. More surprising, though, was how her prefrontal cortex appeared on the structural M.R.I. scan. Rather than the thickened cortex that so many young adults with her temperament had, Baby 19’s was relatively thin.

“This is the brain area implicated in emotional regulation,” Schwartz told me. Could it be that in her case, her thin cortex was unable to regulate excessive activity in the amygdala, leading to more problems than someone with a thicker cortex would encounter? “At the level of an individual, it’s always a bit dangerous to draw conclusions,” he said. “In fact, it’s pretty much impossible. But maybe one thing that affects outcome is whether the genes that contribute to these two areas, the amygdala and the cortex, travel together or separately.” Maybe a high-reactive person with a jumpy amygdala can manage to avoid the behavioral and subjective experience of anxiety because of a strong cortex that can quiet the overactive brain. But in Baby 19’s case, the jumpy amygdala might instead have been accompanied by a cortex less able to mount an inhibitory response. “Maybe when those things occur together,” Schwartz said, “your outcome is that you have a little bit more trouble.”

LOOKING AT THE neurology of anxiety raises the inevitable question of why a trait that causes so much mental anguish would have evolved in the first place. For the species as a whole, it is most likely an advantage to have some group members who are hypervigilant and who see everything as a threat, always ready to sound an alarm and leap into action. For the individual, though, being inhibited can mean having fewer mating opportunities, not to mention the psychic burden, wearing yourself ragged with a brain that’s always on high alert.

In the modern world, the anxious temperament does offer certain benefits: caution, introspection, the capacity to work alone. These can be adaptive qualities. Kagan has observed that the high-reactives in his sample tend to avoid the traditional hazards of adolescence. Because they are more restrained than their wilder peers, he says, high-reactive kids are less likely to experiment with drugs, to get pregnant or to drive recklessly. They grow up to be the Felix Ungers of the world, he says, clearing a safe, neat path for the Oscar Madisons.

People with a high-reactive temperament — as long as it doesn't show itself as a clinical disorder — are generally conscientious and almost obsessively well-prepared. Worriers are likely to be the most thorough workers and the most attentive friends. Someone who worries about being late will plan to get to places early. Someone anxious about giving a public lecture will work harder to prepare for it. Test-taking anxiety can lead to better studying; fear of traveling can lead to careful mapping of transit routes.

Kagan told me that in the 40 years he worked at Harvard, he hired at least 200 research assistants, "and I always looked for high-reactives. They're compulsive, they don't make errors, they're careful when they're coding data." He said he would bet that when the United States sends people up in space, the steely, brave astronauts were low-reactive as infants, and the mission-control people down on the ground, doing the detail work that keeps the craft aloft, were high-reactive.

An anxious temperament might serve a more exalted function too. "Our culture has this illusion that anxiety is toxic," Kagan said. But without inner-directed people who prefer solitude, where would we get the writers and artists and scientists and computer programmers who make society hum? Kagan likes to point out that T. S. Eliot suffered from anxiety, and that biographies indicate that he was a typical high-reactive baby. "That line 'I will show you fear in a handful of dust' — he couldn't have written that without feeling the tension and dysphoria he did," Kagan said.

These are overgeneralizations, of course. And they're easy to shoot down with exceptions. But all the exceptions mean, really, is that the link between neurology and behavior is complicated. There may well be hundreds of different temperaments, and these studies have investigated only two — the most stable and most amenable to measurement, but still just two. If it were as simple as saying that a high-reactive infant will become a behaviorally inhibited child who will become an anxious adult, all the scientific work on temperament would amount to little more than charting horoscopes.

The predictive power of an anxiety-prone temperament, such as it is, essentially works in just one direction: not by predicting what these children will become but by predicting what they will not. In the longitudinal studies of anxiety, all you can say with confidence is that the high-reactive infants will not grow up to be exuberant, outgoing, bubbly or bold. Still, while a Sylvia Plath almost certainly won't grow up to be a Bill Clinton, she can either grow up to be anxious and suicidal, or simply a poet. Temperament is important, but life intervenes.

As for Baby 19, she has not yet gone against type, and odds are she never will. She is in college and doing pretty well, Kagan told me. But her temperament still comes through in her personality. Kagan said Baby 19 tends to be "dour" and "melancholy." And she is still, and probably always will be, a worrier.

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