

LEDE AND NUT GRAF

Jerome Kagan's "Aha!" moment came with Baby 19. It was 1989, and Kagan had just begun a major longitudinal study of inborn temperament and its long-term effects – a study that would eventually include 498 children and would follow them from infancy to young adulthood. He believed that some of the four-months-olds in the study would respond to their environment more intensely than other babies did, and that their "high-reactive" nature would play out in the way they grew up, causing them to become high-strung, shy, and prone to anxiety. Eager to test his hypothesis, he grabbed the videotapes of the first 50 babies in the study, looking for high-reactive infants.

The first eighteen babies looked perfectly ordinary. They babbled when their mothers spoke to them. They focused on a face that emitted words in an amalgam of three voices, designed to be what Kagan called "discrepant but not terrifying." They stared at a mobile cluttered with dancing Winnie the Pooh characters. In response to all these novel stimuli, the babies moved their arms and legs a bit, but mostly they just watched placidly and occasionally smiled.

But Baby 19 looked different. As Kagan described her when we met recently in his office at Harvard, Baby 19 was in constant motion when exposed to the same stimuli. When her mother spoke to her, she moved her arms and legs fitfully. When the face with the dissonant voices appeared, she moved even more, and had a furrowed expression on her face. The Winnie the Pooh mobile caused her so much distress that she arched her back when it came into view. Kagan had wanted to show me the actual video of Baby 19 at four months old, but he couldn't find it after sifting through the number tk videotapes from his longitudinal study, a great stack of them stored in no particular order in an

archive at Harvard's Murray Center. What he did find, though, was something even more revealing – a tape from later in the longitudinal study, when Baby 19 was fifteen years old.

Baby 19 has grown into a plain-looking teenager, her hair long and straight. She seems not to have taken after her mother, a divorcee who raised her daughter alone and whom Kagan remembers as drop-dead, movie-star gorgeous. The tape begins, as do all the others

All study subjects had home interviews when they were fifteen, and this video begins, as the others do, with questions about school and outside interests. Baby 19 does little in the way of extracurricular activities in her all-girls high school, she says in a small voice, but she enjoys playing the violin and she likes to write. She fidgets almost constantly, one part of her body or another always in motion – twirling her hair, touching her ear, jiggling her knee, wringing her hands. “This is how she regulates her high-reactive nature,” Kagan told me, standing near the monitor to fast-forward to the good parts, tense with excitement over how perfect a model Baby 19 is of his hypothesis that high-reactive infants are more likely to grow up anxious.

And here's one of the good parts Kagan was fast-forwarding for: the interviewer asks Baby 19 what she worries about.

“I don't know,” Baby 19 says after a long pause, now twirling her hair faster, touching her face, her knee. She smiles a little, shrugs. Another pause. And then, slowly, 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."

To Kagan, Baby 19 is a case study in what it means to be wired to fret. "She was the one that allowed me to infer high reactivity," he said as we watched the video together. And she stayed true to that temperament: fearful at age one and age two, shy as a four- and five-year-old. "She was shyer at eleven than she is now," he said, pointing to the video. "Now you see it's all inside, worrying about the future, about crowds." But Kagan held out hope for her. She is now in college, he said, and, though prone to dour and melancholic moods, not in need of psychiatric treatment. She will probably grow up to become a writer, he said, turning her adolescent anxieties into a kind of art.

Baby 19's video was part of a stack of old footage that Kagan was showing me in an examining 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." [Pearson, p. 1] The scent of the tobacco in his rarely-lit pipe still clung to his clothes. He is elfin and spry, bald and bespectacled. He neither looks nor acts his age, which is 80.

Kagan's longitudinal study from 1989 is still ongoing; the subjects he first met as infants are now in their twenties. Findings from this study and others have been part of

the rise and fall and rise again of a controversial idea in psychology: that inborn temperament is a powerful force in determining personality and adult behavior. These findings have helped paint a picture of how people who are destined to ruminate and worry – a group in which I would place myself and just about every fellow writer, parent, or sensitive soul I know – look when they are as young as four months old.

And these are the people most likely to develop a clinical anxiety – the most common mental illness in the United States. Anxiety disorders confine an estimated 40 million Americans to constrained and frightened lives, hemmed in by imagined terrors that, because of how their brains work, they are unable to ignore.

When scientists talk about anxiety, they're not talking about garden-variety fretting that keeps worried mothers awake at night. They're talking about worry that doesn't turn off, about negative self-talk that cannot be quieted, about thoughts that automatically see catastrophe around every corner. It's this severe, often-debilitating anxiety that scientists are now trying to understand. They are looking at brain activity through functional MRI scans and electroencephalograms; at genetic mutations or variations through genome sequencing of anxious patients and of lab animals bred for anxiety; and at life stories through traditional longitudinal studies, including two studies begun by Kagan at Harvard and two others his protege at the University of Maryland. They are trying to understand what is different about the anxious brain – and to figure out why, even as their neural patterns remain consistent throughout life, some children manage to grow out of their inhibitions and fretfulness, and others turn into adults mired in fear.

We generally think of anxiety as a detriment, something to transcend or medicate. But it's worth asking whether there might be some benefit to a sense of undifferentiated dread – and a hazard to trying to tamp it down. As we dispense drugs ranging from the “mother’s little helper” Valium of the 1960s to the Halcion of the 1990s and the Paxil and Xanax of today, maybe we are eliminating something crucial, too, something that helps us negotiate our way in a dangerous and frightening world.

HISTORY & RATES AND TYPES OF ANXIETY

Anxiety seems a particularly apt metaphor for the way we live, and worry, now. But many other eras have called themselves the Age of Anxiety – raising the possibility that feeling anxious is just part of the human condition. In the early twentieth century, for instance, there was an outbreak of what was known as neurasthenia – or, in William James’s wry terminology, American nervousness.

brief section -- different definitions of anxiety during different eras, some cool examples

data from WHO study of 60,000-plus adults in 14 countries to see which countries are most anxious. Americans top the list; Mexicans are at the bottom. Thoughts about this tk.

definitions of anxiety – DSM-IV says there are 6 types of anxiety disorders: social anxiety disorder, post-traumatic stress disorder, phobias, panic disorder, and obsessive-compulsive disorder, and generalized anxiety disorder, the one that most resembles plain old garden-variety fretting. a little about each tk?

cultural component to definitions of anxiety – Americans with social anxiety disorder, for instance, say that what they're most afraid of is doing something in public that will embarrass them. But in Japan, those with social anxiety disorder say their greatest fear is doing something in public that will embarrass somebody else [elliott, p. 71]

KAGAN'S LONGITUDINAL STUDIES AT HARVARD

But while social constructs clearly make a difference in how anxiety is defined and expressed, biology cannot be ignored. There is something about the anxious brain that is different. That is where longitudinal studies of anxiety come in.

Background on longitudinal studies, mentioning Framingham Study and how it found risk factors for heart disease

But such studies can draw conclusions about trends and tendencies, not destinies. If someone with high blood pressure treats it early, the risk of heart disease can be significantly reduced. 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. Four longitudinal studies of anxiety are now underway – two at Harvard, two at the University of Maryland – and while they can help scientists draw some general conclusions about risk factors, they cannot predict which high-risk children will be able to alter their own narratives as they age. Instead, what they can do is look for factors in the environment that might mitigate a person's biological tendency to grow up anxious.

Some background about Kagan, his first longitudinal study of temperament in the early 1960s at Ohio State's Fels Institute, how he didn't like the findings that biology made that much of a difference, it didn't jive with his left-leaning sentiments

Kagan moved to Harvard in date tk and began a small pilot study of temperament in 1979 (100 2-year-olds seen again at ages 3 and 7)

Science magazine publication of his results in 1988, caused a stir

s\Started bigger study in 1988 that recruited subjects earlier in life, at age 4 months, to make it more likely that the differences found were innate rather than environmental. Of 498 babies in the study, 40% low-reactive, 20% high-reactive. The kids were seen again at ages 1, 2, 4, 7, 11, and 15.

Description tk of video of one high-reactive baby, Nathan, that Kagan showed me

Descriptions of Nathan again at tk age 2 and 4

Findings, including this – that high-reactive babies are twice as likely as low-reactive babies to become behaviorally inhibited as toddlers. Of those who were high-reactive infants, 40% were behaviorally inhibited at age 11. And behaviorally inhibited kids were more likely to “run into trouble” as adolescents – about 10% of them do, compared to tk percent of kids Kagan describes as “exuberant.” Examples of problems in his adolescent study subjects tk

Kagan's thoughts about what's going on in the brain – amygdala more easily activated, connected to motor neurons which accounts for increased flailing motions as babies, increased fidgeting as adolescents

And all of these high-reactive infants, as Kagan and his colleagues would soon discover, showed brain activity even at age 20 that was characteristic of their

temperament as babies, whether or not they were anxious as young adults – [this is just to signal what is one of my favorite findings]

SECTION ON FOX'S LONGITUDINAL STUDIES AT MARYLAND

Similar findings to Kagan's

slight differences in groups of infants he compared (160 in all) – high-motor, high-negative (Kagan's high-reactive group) versus high-motor, high-positive (not exactly Kagan's low-reactive group)

Fox also looked at how these kids, as they got older, behaved in social groupings – description of one of these very inhibited kids, Joey, in videos at ages 2 and 4, and again at 15

Joey was diagnosed as clinically anxious – more details about him tk

SECTION ON THE ANXIOUS BRAIN

When high-reactive infants grow up, their brains have a characteristic pattern of activity, as measured by functional MRI scans and EEG. Those born with the temperament of Joey or Nathan or Baby 19, no matter how they behave, have brains that look different and function differently from the brains of those who are temperamentally serene.

Description of measurements of the anxious brain – how scientists at Harvard measure Wave 5 and right brain function. Carl Schwartz, one of Kagan's colleagues, put kids in functional MRI machines and also measured their electroencephalogram patterns. Description of that tk, and the findings that inhibited kids were physiologically different

from uninhibited kids – kids who are behaviorally inhibited have more asymmetry in their brain wave patterns, more activity in the right side of the brain than in the left, something called a small Wave 5 (definition tk), and a high vagal tone (definition tk) quotes from Kagan's colleague Carl Schwartz, who has done most of this testing

Nathan Fox found some of the same differences. Description of myself being given one of the psychological tests, in which his 15-year-old subjects who had been high-reactive, high-negative as babies performed like others from that temperament group, no matter how they objectively behaved at 15.

Bottom line – the anxiety-prone have a highly-reactive amygdala, greater vigilance, greater attention to threat, an inability to shift focus. What that means in day to day life for garden-variety worriers and also for clinically anxious.

Descriptions tk of some people I've talked to who are clinically anxious

SECTION ON GENETICS

Clinical anxiety seems to be no more genetically determined than most other mental disorders, such as clinical depression; scientists say about 30 or 40 percent of its occurrence can be traced to genes. But the temperament associated with anxiety, is highly genetic; twin studies show a concordance for high reactivity in identical twins of about 70 to 80 percent. People who are high-reactive as babies are significantly more likely to grow up to be anxious, to have a tendency to worry and fret, and also to develop a full-blown anxiety disorder.

The work of Jordan Smoller, a geneticist at Harvard, looking at genes involved in GABA and other neuropeptides thought to be involved in anxiety

Smoller also looking at the RGS-2 gene – describe briefly what his gene sequencing lab looks like?

Another candidate gene is the SERT gene (serotonin transporter) – those with the short version of SERT are more likely to be neurotic and clinically anxious than those with the long version

University of Michigan studies of rats bred to be anxious, and their lower levels of FGF-2 (fibroblast growth factor 2) – quote from one of them, Javier Perez, tk

Rett Syndrome – a rare genetic syndrome, found only in girls, that causes, among other devastating neurological symptoms, severe anxiety. Huda Zaghbi of Baylor discovered the single gene mutation that causes Rett, a mutation in the MECP2 gene, is responsible for producing tk. When she damages the MECP2 gene in mice, they become anxious, as indicated by the fact that they cower in the corners of their cages, tremble when touched, and engage in a gesture, called forepaw stereopathy, that is analogous to the hand-wringing seen in very anxious people and also in girls with Rett. Now she is trying to damage the gene only in specific parts of the brain, such as the hypothalamus, to see how it affects the mouse's social and feeding behavior. She has a paper about her results about to be published, and says it might suggest something about generalized anxiety, too.

SECTION ON WHY WE EVOLVED TO BE ANXIOUS

The adaptive value of anxiety is something scientists have speculated about. It's good to have someone in the social group who is attentive and vigilant, always ready to call an alarm and leap to action. It's good, sometimes, to be that person, too, since the

ones who are most alert to danger are often the ones who are best at averting it. But having your meter set too high can be damaging.

COMT gene -- COMT breaks down dopamine in the prefrontal cortex – comes in two forms, low-activity COMT and high-activity COMT. Low-activity COMT gene (meaning there's more dopamine) is associated with an increased startle and anxiety response in lab mice. A 2005 study of 497 Yale students found those with low-activity COMT were more neurotic and less extroverted than those with high-activity COMT. But people with low-activity COMT have also been shown to have denser nerve connections in the prefrontal cortex, meaning they can concentrate better, which is good, but have trouble shifting focus, which is bad. So the tradeoff with this gene is maybe better cognitive function but more anxiety

Some studies suggest that the anticipation of pain – which is one version of generalized anxiety – releases endorphins, the body's natural painkiller. They suggest that anticipatory anxiety is a kind of inoculation: when you dread the approach of pain, the anticipation blunts the pain when it finally arrives. It makes evolutionary sense: the “fight-or-flight” response sparked by anxiety, which helps you get away from the thing you're afraid of, keeps on working even if you might otherwise be paralyzed by pain.

Other theories about how anxiety genes came to be include a kind of loopy one from Jerome Kagan. Even he admits it's a little bit of a stretch, but it's intriguing. He says anxious people tend to be fair-skinned and blue-eyed, therefore more likely from Scandinavian stock, where cells from their neural crest evolved to adapt to cold. “I think a mutation occurred in the neural crest, whose purpose was to enable the sympathetic

nervous system to increase body heat – and a high-reactive temperament is just one of the untoward dividends of that.”

There is an analogy in the animal kingdom, he pointed out when he saw my skeptical expression. In fish like cod, for instance, “arctic cod are more fearful than Carolina cod, and they are also lighter in color.” The fair coloration does not cause the fear, but because both traits arise from the same structure in the embryo, they seem to be inherited together.

ENDING

Prediction is a tricky business, affected by initial conditions – either biological or environmental – but not limited by them. Kagan likes to use the analogy of a stone rolling down a hill. It takes five minutes for the stone to move from top to bottom – is there a way to predict where the stone will land based on where it began? “An observer would be able to eliminate a great many final locations after each ten seconds of descent,” Kagan says, “but it is not until the final second that she will be able to predict exactly where the stone will come to rest.” The same is true for humans and temperaments: restate tk.

For every 100 adults in America, about 10 are diagnosed with social phobia. Of those, Kagan estimates that 4 or 5 would have started out life as high-reactive infants. It’s hard to say what the other half were like as babies, says Kagan – but he says it’s a good bet that none of them were infants at the other extreme, low-reactive infants who were unflappable and calm.

“Temperament prevents rather than determines,” Kagan said. Among the high-reactive infants in his sample, there was a tendency to develop into teenagers who were inhibited, shy, fearful, and anxiety-prone, Kagan said. But the stronger link was to they would not become: it was very rare for high-reactive infants to develop into exuberant, outgoing, bold and bubbly teenagers.