

INSIDE THE PERFECT STORM THAT IS  
THE TEENAGE MIND | BY CHUCK STARESINIC

# RAGING HORMONES, BUT WHAT ELSE?

People have always been suckers for a good love story. That's true even of scientists. Ronald Dahl, the Staunton Professor of Psychiatry and Pediatrics at Pitt's Western Psychiatric Institute and Clinic, is a big fan of one in particular, because of what it says of the intensity of human emotion at certain times in our lives. The story begins at a large party, where a guy—let's call him Doug—notices Susan across a crowded room. Her beauty stuns him; his eye is drawn to her face as if a spotlight lighted it.

Doug doesn't know her name yet. Susan isn't aware of her admirer until he crosses the room, and she suddenly finds her hand in his. Doug, perhaps

PHOTOGRAPHY | C.E. MITCHELL



Adolescents seek thrills and experience emotions with an intensity that adults find hard to fathom. It turns out that they're not just hyped up on hormones—the teenage brain is undergoing fundamental changes that we never suspected.

embarrassed now to have been so forward, spews forth a semblance of an apology, though he doesn't let go of her hand. In fact, emboldened by a wave of emotion, he says that if he has offended, perhaps he should kiss her hand to atone for the transgression. Susan does not rebuff these sudden advances. She flirts a bit in reply—at the same time, letting him know that kissing, at least kissing her hand, is uncalled for in this situation. Then, within moments of first laying eyes on each other, their lips meet in a first kiss.

From this day on, the two are infatuated with one another. And though their respective families disapprove of the match, the couple elopes later that same week. Each declares, in all seriousness, that life is not worth living if they cannot be together.

There are different ways to react to these characters. Imagine, for example, that Doug is 35 years old and that he is a successful

about adolescence that will allow us to understand the changes as they happen and help teenagers reach their full potential despite their inherent vulnerabilities?

**W**hat scientists are learning now has the potential to alter the very way we raise our children and the way we think about the perfect storm that is the teenage brain.

*Teenagers write immortal poetry; crusade to overthrow dictatorships; volunteer for suicide bombings; drive (or take drugs or have sex) as though they were invincible; think the unthinkable in science and philosophy; join cults; and dedicate their lives to peace, monastic contemplation, or the eradication of poverty. They are successively inspired, alienated, infuriated, devastated, impassioned, and inconsolably bored. To begin to compre-*

and changes may play an even greater role. Some brain development continues into the early 20s. This changes everything.

In child development, there's been an informal movement afoot for several years, often called "0 to 3," that says human brain development is largely complete within the first few years of life. Its most extreme manifestation is the parent who dutifully (some would say "fanatically") blitzes a child with Mozart and educational toys from ages 0 to 3, believing that these years represent the best chance to have a lasting impact on the child's brain development. Although it's true that the vast majority of our synapses—the neural connections between brain cells that allow regions of the brain to communicate—are formed in these first few years of life, a lot of this occurs independent of stimulation. So though it is enormously important to stimulate and play with infants, Dahl calls it

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automobile salesman. Susan is two years younger and is a professor of linguistics at the local university. Their story may seem too far-fetched to be believed. The family and friends of these formerly rational adults would likely think that they'd somehow lost their minds. They might recommend immediate psychiatric evaluations. They might look for evidence of brain injury or wonder if the punch at the party was spiked with illicit drugs. This is not the sort of behavior in which rational adults engage.

Of course, this story is not about rational adults, and it's not the story of anyone named Doug or Susan. It's the tragedy of *Romeo and Juliet*. In William Shakespeare's play, Juliet is a few weeks shy of her 14th birthday. Romeo is probably just a few years older. And it's a believable story of youthful passion, its verisimilitude having brought audiences to tears across languages and cultures for 400 years.

Dahl uses *Romeo and Juliet* to demonstrate that the intensity of adolescent passion and emotion transcends culture, class, and even time. It has been recognized at least as far back as Shakespeare's day that youth is a time of exceptional potential as well as vulnerability, he says. These qualities must be deeply rooted in our biology. What then can modern biological science reveal

*hend how so much vulnerability and potential can coexist in one brief interval of life ... we must look beyond the intensity of the passions and craving for excitement that characterize so many adolescents.*

This is the introduction to a 2003 essay by Dahl. He wrote the essay describing "the tinderbox in the teenage brain" for a quarterly journal called *Cerebrum*. To him, it expresses much of what is wonderful, exasperating, and intriguing about teens. And the title, "Beyond Raging Hormones," sums up one very important lesson about studying adolescent development: It turns out that the stock answer to explaining away the particulars of adolescent behavior—raging hormones—doesn't hold up under scientific scrutiny. In fact, it looks like the direct effects of hormones on emotion and behavior may be pretty small. High levels of hormones don't cause the emotional problems that some adolescents suffer—look at the vast majority of teens who have no serious emotional difficulties while their hormone levels peak.

So what is beyond raging hormones? For Dahl and a growing number of other researchers in adolescent development, it's now clear that though rising hormone levels are a critical part of the changes we see in adolescents, the ways in which the brain develops

"a serious misconception" that this period represents the last, best chance to influence the way the brain works.

A teenage brain may be the same size as an adult brain, but it is qualitatively different. Neural connections are still forming. Dahl cites evidence that there are unique types of brain plasticity that occur only during adolescence. Specifically, patterns of what motivates us, what gratifies us, and how we regulate our emotions develop naturally in puberty. In a 2004 paper in the *Annals of the New York Academy of Sciences*, Dahl and a colleague reviewed evidence showing that the cerebellum at adolescence is still undergoing extensive development, and this appears to create a particular susceptibility to disruption from episodes of binge drinking. Long known for its role in coordination, balance, and motor skills, the cerebellum also appears to be involved in cognition, emotion, and other complex brain functions.

"Adolescence, especially early adolescence, is one of the last uncharted territories," says David Kupfer, chair of the Department of Psychiatry. "And part of the reason that it is so poorly charted is the difficulty in parceling out the contributions that are made by biology and environment in an interactive way." A modern approach to adolescence now involves genetics, psychiatry, neuroscience,

social science, and more. Dahl leads this effort at Pitt, one of a handful of medical research centers that includes the National Institute of Mental Health, UCLA, Harvard University, and others doing broad, interdisciplinary work in this area.

Dahl's office occupies one corner of the seventh floor of Pitt's Western Psychiatric Institute and Clinic (WPIC). From here, he leads a group of researchers and clinicians trying to understand the teenage brain. Dahl can gesture down one hall to psychologists interested in using neuroscience to improve therapy for depressed teens and down the

other to PhD neuroscientists who want to understand how genes put their mark on brain function. Dahl is the tall guy at the intersection, encouraging communication and collaboration between these deep thinkers and others, asking questions, and

offering encouragement. As a mentor of students and junior faculty, he's always on the lookout for that collaborative spark—revealed when a person becomes intrigued by another's perspective and begins asking new questions. What Dahl's students and col-

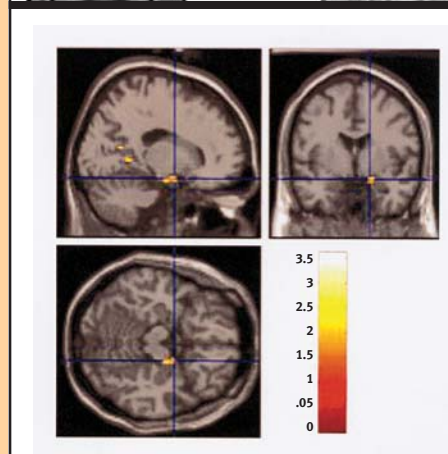
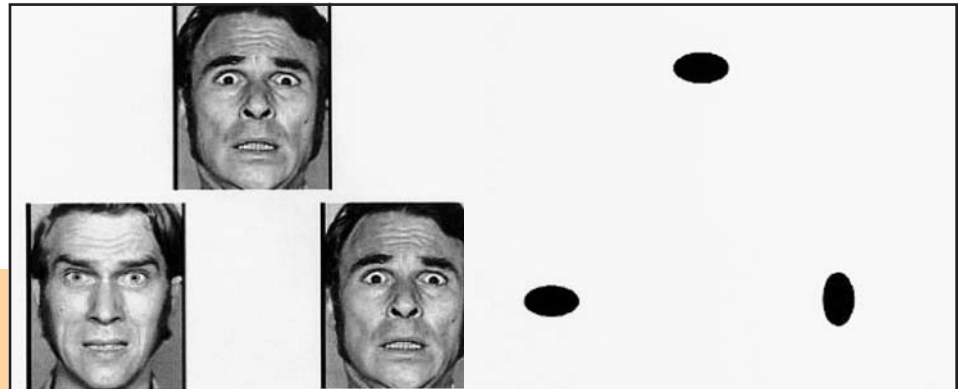
## HARIRI'S HAMMER

A man enters his house late at night, drops his keys and wallet on the table, and freezes. He sees broken glass beneath a window that has been forced open. A sound on the stairs tells him an intruder is in the house. If we could see an MRI scan of his brain at this moment, a spot toward the back of his head would be glowing like a night-light. This is the amygdala, an almond-sized mass of gray matter that is very active whenever we are faced with a "fight-or-flight" situation. "The amygdala has been most comprehensively studied in terms of fear and especially fear conditioning," says Pitt neuroscientist Ahmad Hariri, "although it's important in any behavior that requires the organism to become attentive to its environment and to redirect resources to something that is pressing." It's also believed to play a role in emotional states.

When Hariri gives a talk, he often plays a video clip. It's not about the amygdala or even the brain—it's about reptiles—but it shows what the amygdala does. During a talk show before a live audience, a special guest holds a Texas rat snake. The host of the show is doing a pretty good job of keeping his cool next to this scaly, writhing, 5-foot-long coil of serpent. He asks whether or not the species lives in their part of Texas. You betcha, says the guest. Well, let's see how long it is, the host suggests, and he gamely takes hold of the tail end of the snake. At this moment, he is not thinking about the gecko on the table. A gecko is a harmless lizard with a sticky tongue, a taste for insects, and an extraordinary ability to cling to vertical surfaces, which it unexpectedly demonstrates at this moment by launching itself into the air and latching onto the host's jacket, just shy of belt level.

Ever seen a person panic and flail at a particularly pesky wasp or bee? The host's reaction is orders-of-magnitude worse. He staggers backward several steps and spastically flaps his hand at the lizard. Nonsensical, choking sounds emerge from his throat interspersed with barely intelligible words (*Get, this, thing, off*), a few of which are frowned upon by the FCC. Finally, he falls to the floor.

Hariri laughs like a kid watching cartoons. He usually plays this clip twice and laughs just as hard the second time. As director of the



**A simple matching activity (top): Match the faces that are the same, then match the oval shapes that are the same. If you have a variant of the serotonin transporter gene, your amygdala (the brain's "hub of fear") may light up a functional magnetic resonance imaging scan taken as you look at these scared faces much more than when you look at simple shapes, and more than someone without the genetic variant. The scans on the left show the additional amygdala activity of people with the gene variant.**

COURTESY A. HARIRI

developmental imaging genomics program in the Department of Psychiatry, Hariri wants to learn how specific genes can make a person biologically prone to having a stronger fear response, whether faced with an intimidating gecko or emotional stress at home or work.

"We can't throw snakes in the scanner," Hariri reminds his audience. (He doesn't comment on the feasibility of geckos in the scanner.) So what does a researcher do to light up the amygdala? Enter Hariri's Hammer.

With Susan Brookheimer, his PhD adviser at UCLA, Hariri developed a simple task, which he later fine-tuned with Daniel Weinberger at the National Institute of Mental Health: While in the scanner, volunteers are shown photos of three people with scared or angry expressions and asked to match the two that are most similar. The controls are asked to match shapes that have no biological significance. On a functional magnetic resonance imaging scan, the amygdala of a person performing the face-matching task lights up robustly.

"It's a hammer because it's very crude," says Hariri. "We're not principally interested in faces or facial expressions or anything along those lines. We're interested in engaging the amygdala very forcefully and then exploring the effects of genetic variation on that reactivity. ... It's like taking a hammer and smacking the amygdala, getting it to reverberate, and then measuring those reverberations and understanding what factors determine the magnitude of those reverberations." —CS

leagues describe as charisma manifests itself as an inexhaustible curiosity fed by questions—lots and lots of questions, asked in a patient, thoughtful tone. He's not soft-spoken, but his voice seems to lack all harshness.

Kupfer has been tracking Dahl (MD '84) since the latter was a medical student. Kupfer helped him secure a one-year research fellowship in sleep/neuroendocrinology between his third and fourth years, and he has watched him turn into a unique clinician and researcher—a trained pediatrician working in a psychiatric setting with expertise in adolescent development. (Dahl has run Pitt's pediatric sleep and neurobehavioral lab since 1988. He's extensively documented biological changes in the sleep cycle during adolescence and their implications for development and behavior.)

"He has been well informed by a number of things happening in the fields around him," says Kupfer, including clinical and basic neuroscience, genetics, brain imaging, psychiatric therapy, and therapeutics.

for 20 years. Every time a gene showed some connection to depression, or attempted suicide, or bipolar disorder, later studies would fail to replicate the findings, says Hariri. He thinks scientists just went about it in the wrong way.

"Psychiatric genetics and behavioral genetics have tried very explicitly to relate a gene and a variation in a gene to behavior, which is just silly," says Hariri.

"It's silly, because a gene doesn't code behaviors."

Genes code for proteins—small molecular entities. Variations in genes, if they have any impact at all, are going to have small, subtle effects at this level. In the brain, explains Hariri, those subtle alterations can influence how different parts of the brain communicate. Finally, these subtle alterations can slightly bias behavior. Behavior is at the very end of a long, complex equation that begins with genes. So before anyone can talk about genes for depression, neuroscientists have to work on the middle part of this equation.

process that shapes behavior and predicts the degree to which healthy humans are harm avoidant. How biologically reactive we are to signs of danger is probably an adaptive trait, but it also appears that it can place us at greater risk for anxiety or depression.

For Hariri, the obvious next question is, what happens to people with these variants in adolescence—when so much of this brain development, including the formation of neural circuits that process negative emotion—is occurring? Also, how do some people with highly reactive amygdalas avoid depression and anxiety, as so many of them do?

Hariri theorizes, "You take that person who has a more reactive amygdala because of his genetic background, and you put him into a very nurturing environment that protects that individual ... and in all likelihood, you won't see any differences. He won't be more vulnerable to becoming sick, to developing anxiety or depression than the next person *without* that particular genetic background. You take that same individual and you put him in a

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"I feel like the architect sometimes," says Dahl, "and I need a lot of engineers."

Ahmad Hariri is one of these "engineers," recruited to Pitt just two years ago to work in Dahl's group as well as in the Center for the Neural Basis of Cognition, a joint neuroscience effort of Pitt and Carnegie Mellon University. Ask him about adolescent development, and the assistant professor of psychiatry is quick to define his perspective:

"I'm not a developmental biologist. I'm interested in genes, brains, and behavior."

Hariri is a PhD neuroscientist. He's also 33 years old, well over 6 feet, and lanky. His knees barely fit beneath his desk, and he appears ready to take the basketball that rests on his bookshelf out to the court, dressed as he is in shorts on a spring day. (He admits, somewhat sheepishly, that the ball hasn't swished through the net for some time, though.)

Hariri's work may help enable parents to one day talk very specifically about the genes that bias their kids for anxiety, depression, and other disorders. This is something that science has attempted and mostly failed to do

Hariri studies activity in the amygdala, an almond-size region of the brain linked to fear and emotion.

In a 2002 paper in *Science*, Hariri and colleague Daniel Weinberger at the National Institute of Mental Health looked at a variant of the human serotonin transporter gene, which had long been suspected of having a link to anxiety. Using functional magnetic resonance imaging (fMRI) of the brain, they showed that people with two copies of this variant, as compared to those with only one or no copy, tended to show much greater amygdala activity when they viewed pictures of scared faces (see "Hariri's Hammer"). In other words, some people's brains have a genetic tendency to react strongly to emotional stimuli. Notice, the researchers hadn't tried to connect the gene to behavior yet—only to brain activity.

However, in *Nature Neuroscience* this year, Hariri, Weinberger, and colleagues took one more step in linking genes to brain function and finally to behavior. They found that the gene variant biased communication between the amygdala and prefrontal cortex. That's a

very unstable background, without parents, without social support, always encountering stressors in his life—they could be socioeconomic stressors or they could be very direct, acute stressful events like the loss of a loved one, crime, etc.—then the environment begins to provoke a system that's already more reactive. That's *genetically* more reactive. And that's where you start this downward spiral into increasing susceptibility for disease."

This is not to say that the parent of the near future need only obtain a genetic profile to know whether a child is at risk of a behavioral or emotional problem. There are lots of depressed people who don't carry such genes. For example, says Jennifer Silk, a new assistant professor of psychiatry, we know that about 40 percent of children with a depressed parent will go on to develop depression themselves. This is probably a result of a combination of genes and environment. Designing strategies to identify and help that 40 percent requires insights that come from both neuroscience and clinical psychology.

Last year, Silk was a postdoc working with

Greg Siegle, a PhD assistant professor in Pitt's psychiatry and psychology departments. Siegle had found a curious phenomenon in the way that depressed adults responded to reading emotional words. He used a simple video camera to measure light reflecting from a person's retina. Like the red eyes that show up in a snapshot, the light reveals pupil size from moment to moment. The participants read words like *death*, *war*, *divorce*, and *lonely*. At other times, they would read neutral words—*table*, *door*, *pen-cil*—or words like *happy*, *friend*, and *sunshine*. Almost without fail, people's eyes dilated in response to reading words associated with negative emotions. Most returned to baseline within a few seconds. In depressed adults, the dilation often lasted 15 seconds or more.

It looked like Siegle and Silk had found what poker aficionados call "a tell." (If eyes dilate in response to sad words, perhaps they do the same when faced with a lousy pair of deuces—no wonder gamblers sport sunglasses.) "What we think it's telling us," says Silk, who is more interested in the neuroscience of depression than she is in poker, "is that they have a stronger reaction to emotional information, or they are thinking about negative information over and over again." The eyes reveal activity in the brain.

As a new faculty member working with Dahl's group, Silk is using this approach to study adolescents at high risk for depression. You might expect that depressed teens would react to sad words in a similar way. Silk did, too, but was wrong.

"Their pupils dilate, then quickly go back to normal, like a healthy adult," she says. "Normal kids? Their pupils dilate, and stay dilated for a while. Just like depressed adults. It's the direct opposite effect."

Silk thinks those who are prone to depression have the ability to shut down negative emotional reactions early in life but lose that ability later on, perhaps during adolescence. She's interested in finding out exactly when in adolescent development such neurobehavioral changes occur and whether they are linked to the hormonal changes of puberty. (Evidence shows that some features of adolescent brain development occur even in children with delayed



puberty.) The ultimate goal is the prevention of depression, and finding out when our patterns of emotion regulation form is key to prevention. This year, she'll expand her study to include more kids from ages 8 to 18, in hopes of watching their development throughout the course of several years.

"We miss seeing his smile," the concerned teacher said to the mother of one of her students. Eleven-year-old Jesse was a quiet kid, but he did well in school, and he'd always loved going to football practice. Suddenly, he didn't care about practice anymore. When he won an essay contest at school, he didn't want to go to the award ceremony to read it aloud. This normally pleasant kid was now getting into schoolyard scuffles with other boys. That's when his mother brought him to the outpatient STAR clinic (Services for Teens at Risk) at WPIC, and they met Erika Forbes, who'd recently received a Pitt PhD in clinical and developmental psychology and was doing her clinical internship.

Forbes saw Jesse every week for psychotherapy. She used cognitive-behavioral therapy. In other words she addressed automatic thoughts—helping Jesse understand how thoughts, emotions, and behavior are linked. She then helped him change his mood and change his behavior by addressing his thoughts and teaching adaptive behaviors.

Jesse was a motivated kid who wanted to take steps to get better. Fortunately, he made quick progress during the two or three months that he continued therapy at the STAR clinic.

Patients like Jesse (not his real name) encouraged Forbes to start thinking about depression in a new way: It's not just a pre-

ponderance of negative thoughts and emotions ("negative affect," as it's known in the field), it's a change in *positive* affect. Jesse had lost his smile. He'd lost his motivation to play football and to do well in school. To understand the biology of these behaviors, Forbes, who had spent much of grad school studying behavior and emotional expression, began to study brain anatomy and neuroscience. She's now doing a postdoc in the School of Medicine with Dahl as her adviser and beginning a research project that will use fMRI to understand what's going on in the brains of adolescents like Jesse as they increase or decrease positive thoughts and emotions. She envisions one day diagnosing types of depression in adolescents more precisely, so that clinicians can recognize when enhancing positive affect would have the most benefit.

Dahl describes Pitt's program as clinically oriented: "We want to use this advancing knowledge about adolescent brain development to really inform clinical and social policy." He and his colleagues believe that they can show that adolescence is not only a period of increased risk for psychopathology but also the period in which clinicians can get "the most bang for their buck" in terms of intervention. Pitt's clinical approach embraces a lot of disorders, says Dahl, rattling off a list of experts in depression, anxiety, pediatric bipolar disorder, and drug and alcohol abuse. Several of these experts, like Silk and Forbes, have been mentored by Dahl.

"We're like talent scouts," says Kupfer, describing why he noticed a med student named Ron Dahl and encouraged his research interests. Twenty years later, his prospect has become another scout. ■