

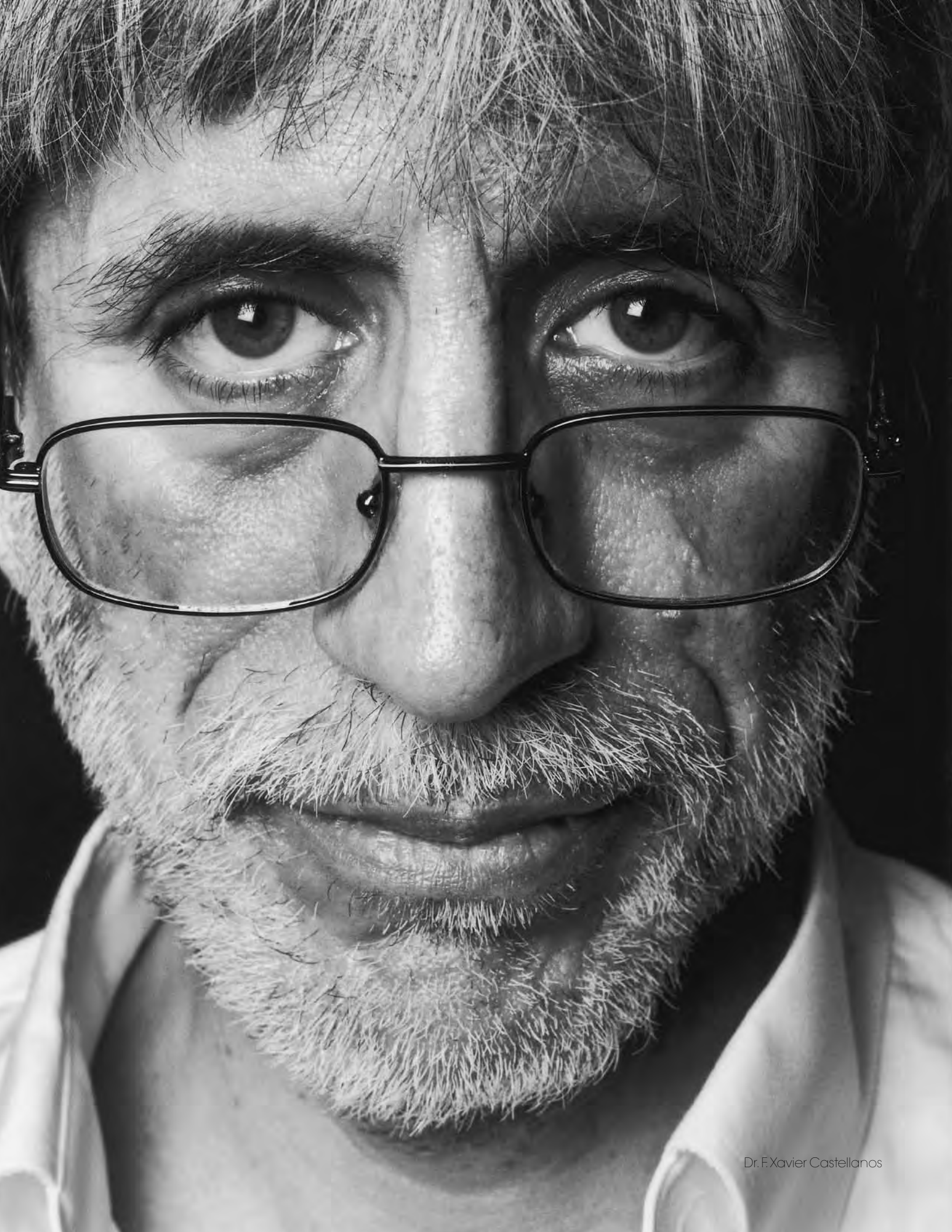
Neuroscience may hold the key to unraveling this elusive childhood disorder.

Bringing ADHD into Focus

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Photograph:
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Dr.F.Xavier Castellanos



was 1992, and

child psychiatrist F. Xavier Castellanos, M.D., was taking a shuttle bus back from the airport to his job at the National Institute of Mental Health (NIMH), where he had recently begun studying the neurobiology of attention-deficit/hyperactivity disorder (ADHD). He struck up a conversation about his work with another passenger, a visiting journalist. She was intrigued. Wasn't ADHD just hype? she asked. No, he replied. It's real, and it's a big deal. In fact, he told her, it's going to be the diagnosis of the decade.

Within a few years, attention deficit disorder, as it was then widely known, was featured on the cover of *Time* magazine. As diagnoses skyrocketed, a new battleground emerged. Some doubted that there was any such thing as ADHD—the problem was parents who couldn't control their rambunctious kids. Others railed against the practice of treating kids with psychoactive drugs. By the end of the decade, the number of recognized cases of ADHD had tripled, and as many as 20 percent of boys in some school districts were on prescription stimulants. Then the backlash began. Parents who refused to medicate their children got visits from child protective services. State legislatures across the country banned schools from recommending meds for children.

The lack of knowledge added heat and smoke to the debate. Then and now, nobody knew what caused ADHD or, for that matter, how to be sure a child has it. The American Psychiatric Association characterizes the disorder by its symptoms: a persistent pattern of hyperactivity, impulsivity, and inattention beyond what's typical for a developmental age. But there's no test for ADHD, and no telltale physical signs of it. For many

psychiatrists, the medication of choice is Ritalin (methylphenidate), a central nervous system stimulant that, ironically, has a calming and focusing effect on those with ADHD, particularly children.

"It's a huge controversy that isn't going to go away until we understand it on a more fundamental level," says Dr. Castellanos, the Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry and Professor of Radiology. "Where there's ignorance, there's fear." The chance to move beyond ignorance and fear—to shift the debate from the domain of opinion to that of biochemistry and neuroanatomy—was why he had come to NIMH. Using advances in neuroimaging and genetics, Dr. Castellanos and his collaborators published paper after paper in the 1990s that uncovered discernible physical differences in the brains of kids with ADHD, providing evidence that the disorder not only is real, but has tangible effects.

In a landmark study published in the *Journal of the American Medical Association* in 2002, Dr. Castellanos and his research team proved that Ritalin was not shrinking kids' brains, as some had alleged. Dr. Castellanos documented that all kids with the disorder—boys and girls, medicated or not—had slightly smaller overall cerebral volumes throughout childhood. The finding reassured parents who were worried about Ritalin, and it also suggested that their kids' brains were growing normally, albeit a bit behind the curve. Significantly, it also indicated that whatever caused ADHD happened very early on, perhaps as the result of a genetic influence. For this paper, the American Psychiatric Association honored Dr. Castellanos with the Blanche F. Ittleson Award for Research in Child Psychiatry, one of the most prestigious awards in the field.

Dr. Castellanos's collaborators emphasize his nose for original ideas, his tendency to seek out approaches and perspectives that others may not even look for. "From the first day I met him,

says Judith L. Rapoport, M.D., Chief of the Child Psychiatry Branch at NIMH and, for many years, Dr. Castellanos's mentor and boss. His ADHD research is so well regarded, in fact, that he is now chairing the committee that will update the definition of the disorder for the next edition of the *Diagnostic and Statistical Manual*, the psychiatrist's dictionary.

"He's a very innovative scientist and a wonderful teacher," says Harold S. Koplewicz, M.D., Chairman of Child and Adolescent Psychiatry and the founder and Director of the NYU Child Study Center. "He makes neuroscience cool."

His latest cool idea brought him in 2002 to the NYU Child Study Center, where he is Director of Research and Director of the Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience. He is continuing to study ADHD, but mainly now in the context of a new project: investigating the very slow oscillations in neural activity that seem to knit together widely dispersed areas of the brain. This emerging science has powerful implications for understanding how the brain organizes itself, and perhaps for explaining psychiatric disorders as well. "I feel driven to pursue it," says Dr. Castellanos.

Although this research may seem remote from the concerns of a 10-year-old struggling to pay attention during math class, Dr. Castellanos believes that uncovering the neurological basis of mental illness is the only way to make real progress. Otherwise, psychiatric problems will continue to be defined through subjective opinion and clinical judgment, leaving them open to challenge and debate.

Dr. Castellanos has always been drawn to theories about how the world works. As a boy, shortly after his family moved to the United States from Bolivia, he devoured everything about quantum mechanics and relativity he could lay his hands on. His family struggled financially, but his excellent grades earned him a scholarship to Vas-

"The moment I appreciated that the brain contained a version of morphine, it blew me away."

his view wasn't, 'How do we incrementally build on things?' but rather, 'How do we make a huge change?'" says Michael Milham, M.D., a young physician-scientist and neuroimaging wizard who works in Dr. Castellanos's lab.

"He has a rare combination of qualities: he reads very widely, and he combines that breadth with methodological care,"

sar, where he learned about Noam Chomsky, the MIT scholar and political activist who was rewriting the rules of linguistics and cognitive science. Dr. Castellanos was hooked; he created Vassar's first major in linguistics, graduating with honors.

Several years later, Dr. Castellanos was working on a master's degree in psycholinguistics when he heard about the



Dr. Castellanos
at home
in his study

discovery of endorphins, neurochemicals that mimic the activity of opioids. “The moment I appreciated that the brain contained a version of morphine, it blew me away,” he laughs. That insight propelled him into psychopharmacology, and from there to medical school, and finally into a residency program that combined psychiatry, pediatrics, and child psychiatry. As Dr. Castellanos was finishing his residency, the first major study using neuro-imaging techniques to probe adults with ADHD was published. For the first time, it was possible to get a picture of what was happening inside someone’s head.

At his wife’s suggestion, he began looking into research fellowships. He joined NIMH the next year, in 1991, and began working with the nascent technology of magnetic resonance imaging (MRI). The technology provides unique information about brain structure in developing children and, unlike other imaging technologies, did not use radiation.

Meanwhile, by 1996, pediatricians were diagnosing ADHD in more than 9 percent of their patients. As a practicing child psychiatrist, Dr. Castellanos was well aware of the confusion and frustration felt by afflicted children and their parents. The stereotype is one of a fidgety, hyperactive

little boy who can’t sit still and can’t control himself. But the disorder affects girls, too: the ratio is about three boys for every girl, according to one recent survey.

Besides, only some kids with ADHD are physically restless. A child with the “inattentive” subtype, which may be more common among girls, is more of a daydreamer, constantly forgetting or misplacing things and unable to focus on details. Even the name of the disorder is a bit misleading: kids with ADHD suffer not so much from a deficit or lack of attentiveness as from the inability to control it. Many, for example, can spend hours focused on something interesting but can’t force themselves to pay attention to something dull.

For Rachel Stone, now 24, the disorder made it almost impossible to pay attention in class. A bird would fly past the window, and she’d be gone, daydreaming for the rest of the period. She did OK without the drugs for a while, but by the ninth grade, she was drowning. Finishing homework was out of the question. The disorder also ruined her social life. “I was always having fights,” she recalls. “There was constant conflict.”

The vagaries of ADHD often lead to moral judgments about a child’s lack of

self-control or motivation—or his parents’ lack of discipline. So Dr. Castellanos searches for specific, unambiguous deficits that can be measured precisely. For example, kids with ADHD may seem sped up, but on cognitive tests, they’re often *slower* to respond. More specifically, Dr. Castellanos and others have proven that the most distinctive hallmark of ADHD is variability. Given a repetitive cognitive test, anyone’s performance wavers from one trial to another, but kids with ADHD are remarkably inconsistent.

ADHD also seems to take different forms in different children. In a recent review in *Nature Reviews Neuroscience*, Dr. Castellanos and co-author Rosemary Tanock, Ph.D., of Toronto’s Hospital for Sick Children proposed three main categories that probably overlap in most kids. In one child, working memory—the ability to keep information foremost in the mind for a short period—may be disrupted, causing him, for example, to struggle to finish a math problem. Another may be incapable of delaying gratification, leading to impulsive behavior. A third may have trouble judging time, resulting in impatience.

Searching for an overarching picture of ADHD, Dr. Castellanos tried to match up these observations with findings from

neuroimaging, which can reveal the physical structure of the brain. In 1996 he and his colleagues at NIMH showed that the right prefrontal cortex of the brain—a region involved in such higher cognitive processes as motivation, attention, and screening out irrelevant events—was smaller in kids with ADHD. His other research documented declines in the size of a part of the cerebellum that may be involved in timing and attention-shifting. Dopamine, a neurochemical that is integral to motivation, attention, and responses to novelty, is almost surely involved. Dopamine signaling seems to be weaker in children with ADHD, which may be why they are so distractable: they're getting less stimulation out of things that most of us would find interesting. Ritalin and similar drugs help them concentrate by boosting the signal.

The origin of the disorder remains an open question. In one group of extended families in Colombia who suffer high rates of ADHD, Dr. Castellanos and his colleagues have identified gene variants that play a role in at least some cases. Maternal smoking and lead exposure also sharply increase the risk. But the process of untangling genetic and environmental causes for the disorder is just beginning.

Although it doesn't get as much attention as it once did, ADHD is still the most common childhood psychiatric disorder. In 2003, 7.8 percent of school-age children had been diagnosed with the condition, according to the Centers for Disease Control and Prevention (CDC). But the news isn't all bad.

Dr. Castellanos believes that one important aspect of treatment is helping the child learn to recognize both his difficulties and his strengths—to take advantage of what he can do and avoid situations that require prolonged focus with low stimulation. Although his own research has shown that Ritalin does not seem to harm the brain, he was initially skeptical of stimulants. "Medicines have been oversold," he says, and considering the complexity of the disorder, prescribing these drugs by themselves is little more than "spitting in the wind." But Dr. Castellanos also believes that when combined with intensive parental education, a good school with good teachers, and a lot of hard work on the part of child and family, stimulants can be an essential part of coping with the disorder.

While there's no cure for the disorder and it doesn't disappear with time, explains Dr. Castellanos, its effects tend to diminish with age. The brain continues to develop through adolescence, and with adulthood, people learn to sidestep their weaknesses. Rachel Stone, for example, is an executive recruiter; it's a fast-paced job that she finds highly gratifying.

Kids with ADHD suffer not so much from a deficit or lack of attentiveness as from the inability to control it.

Certainly, many adults struggle with ADHD. But the anguish and the controversy over the disorder has focused on kids, because it touches on widespread worries about discipline, parenting techniques, and giving psychiatric medication to children. Besides, for some kids, the disorder is extremely destructive. Up to 40 percent of people with ADHD have learning disabilities on top of their attention problems. In addition to struggling in school, they may be faced with social disaster. Kids with ADHD—especially girls—have trouble making and keeping friends.

"It was killing me—what it was doing to our family," says Rikke Stone, Rachel's mother. The disorder "made this little happy girl who'd say hello to everybody very, very unhappy." Like any parent, she hesitated to put her daughter on stimulants, especially since the first time the drugs had caused problems. But in the middle of the 10th grade, when Rachel started taking Adderall (dextroamphetamine/amphetamine), everything changed. Her GPA soared—up 27 points in one semester. Homework, previously a source of "horrible stress," became routine. And her family stopped quarreling. By the end of high school, she was an honors student bound for college.

In the worst-case scenario, though, problems balloon during early adolescence. An

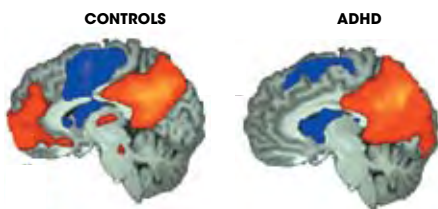
impulsive, aggressive eight-year-old is a headache, but a relatively small one. By the fifth grade, though, that same kid might start smoking—nicotine seems to calm the symptoms of ADHD. By the eighth grade, he could be drinking or doing drugs. And he probably hates school because it makes him feel like a failure. The disorder also predisposes adolescents toward depression and anxiety. The problem is that it's hard to tell which kids will spiral downward and which will learn to cope. In the hopes of predicting the course of this and other child psychiatric disorders, Dr. Castellanos is focusing on the basic processing mechanisms of the brain.

In an innovative working relationship, Dr. Milham is a scientific moonlighter with Dr. Castellanos. While he finishes his residency at NYU, he's continuing basic neuroscience research in the lab—something residents don't often get the chance to do. Their idea is that slow, regular, widespread patterns of brain activation, which fluctuate roughly two to four times per minute, might be a key to understanding ADHD, and to the greater mystery of cognition itself. This phenomenon has been recognized for decades, but most researchers, focusing on the lightning-speed activity of individual neurons, which normally communicate anywhere from 20 to 150 times per second, dismissed it as background noise. It seemed way too slow and way too diffuse to mean anything.

In recent years, though, some neurobiologists have begun to reconsider this notion. They suspect that this activity is actually essential to how the brain processes information. Currently, Dr. Milham and Dr. Castellanos are exploring how changes in functional connectivity between regions of the brain might account for the cognitive symptoms of ADHD. It's a new approach, investigating the strength of connections between various areas of the brain, rather than looking for answers in one region at a time.

Decades from now, Dr. Castellanos expects these observations to generate a truly comprehensive portrait of how the brain organizes itself—a "unified field theory of the mind," as he calls it. "There are jumps in the way in which science progresses," he says. "Roughly 100 years ago, physics took one of those big jumps with relativity and quantum mechanics, and it changed the future. In neuroscience, I think we're going through a similar transformation." ●

A New Site for Dysfunction



IN THE FUNCTIONAL MAGNETIC resonance images (fMRI) above, NYU researchers compared the connectedness of brain regions in two groups of adults. In the controls, they found that areas in the front and back of the brain, the ventromedial prefrontal cortex and the posterior cingulate cortex, respectively (both in red), were strongly connected. This association was far weaker in the ADHD group, leading the scientists to suspect that momentary lapses in attention may originate in the pathways linking the two regions.