ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

The Long Life of Early Pain

Winter 2011
Vol. 17, No. 1

HARVARD MEDICAL SCHOOL

CONTENTS

1 *The Long Life of Early Pain*

4 *The David Mahoney Prize Symposium and Dinner*

5 *David Mahoney Prize Goes to Kay Redfield Jamison*

6 *Alcohol and the Adolescent Brian: A Troubling Cocktail*

7 *Addiction and the Adolescent Brain*

It was a centuries-old notion that had profound ramifications for medicine: Infants, especially those born prematurely, felt little or no pain. As recently as the late 1970s, physicians in the United States and other countries used pain-killing medications on infants only sparingly; the common practice was to provide infants with a sucrose solution to quiet and soothe. Even medical procedures like lancing and needle sticks were routinely performed with little or no anesthetic or similar agents.

Although the 1980s saw a growing number of textbooks recommending anesthesia's use for invasive procedures, many clinicians refused to use it, opting instead for nitrous oxide and muscle relaxing agents that dampen pain rather than block it. When challenged, these wary individuals would cite concerns about the risk that opiates would depress neonatal heart and lung function.

Today, such beliefs strike many as barbaric and unethical—or, at the very least, ridiculous. Yet these practices were perpetuated largely because of a dearth of scientific evidence for change: Few researchers had challenged the premise that infants did not respond physiologically—or neurologically—to surgical incursions.

Turning the Tables

By the mid-1980s, however, textbook recommendations were backed by a mounting body of evidence showing that newborns and infants had distinct physiological reactions to surgical and other invasive procedures. Research showed, for instance, that infants receiving little or no anesthesia had increased levels of various stress-triggered steroids, including epinephrine and cortisol, which acted to break down carbohydrates and fats stored in babies' bodies. Such losses could compromise recovery.

A pivotal study in 1987 by Paul Hickey, MD, a professor of medicine at HMS and chief of anesthesia at Children's Hospital Boston, and Kanwaljeet Anand, MD, PhD, formerly at Children's, now a professor of pediatrics at the University of Tennessee Health Science Center in Memphis, showed not only that babies exhibited stress responses to invasive procedures, but that these troubling, even dangerous, responses were reduced when anesthesia was used.

In their report in the *New England Journal of Medicine*, the researchers detailed the mechanisms by which infants and newborns experience pain. They marshaled data showing that, just as in adults, infants' neural pain pathways ran from sensory receptors in the skin to areas in the brain's cerebral cortex, where memories, perceptual awareness, and consciousness take hold. In addition, the researchers noted, the density of nociceptive nerve endings in the skin of infants is similar to or greater than that of adult skin. Sensing and responding to bodily injury or damage, these nerve endings transmit pain signals to the brain.

continued on page 2

continued from page 1

Hickey and Anand challenged the theory that infants do not feel pain because their nerve cells lack myelination, a hallmark of an underdeveloped nervous system. Myelin forms an insulating coat around key parts of nerve cells, and myelination speeds nerve impulses to and within the brain. Neuroanatomical data showed that nerve tracts in the spinal cord and central nervous system are completely myelinated by the second or third trimester and that pain pathways to the brain stem and to the thalamus, which relays sensation to the cerebral cortex, are myelinated by week 30.

"As much as half a year later, the infants circumcised without analgesic relief showed a heightened aversion to needle-stick procedures such as vaccination when compared with the control infants."

Furthermore, Hickey and Anand noted that various studies published in the early 1980s reported finding a high density of a chemical messenger called substance P in areas of the fetal brain associated with pain perception and response. Although substance P is one of several neurotransmitters in the central nervous system, it is the only one shown to play a role in transmitting pain impulses.

Hickey and Anand concluded their paper with a paradigm-busting understatement: "Current knowledge suggests that humane considerations should apply as forcefully to the care of neonates and young, nonverbal infants as they do to children and adults in similar painful and stressful situations."

The Long View

While medicine was making strides in understanding and regulating infant pain, another problem simmered. Medical professionals began noting an array of psychological and psychosomatic troubles linked with the experience of pain or impending pain in adolescents and adults who, as infants, had undergone surgery without anesthesia.

Understanding the collateral effects of early pain may have first taken shape in Toronto-based studies in the late 1990s. This research looked at infants who were circumcised without analgesic relief at or shortly after birth as well as infants who either had not been circumcised or had received a topical pain block during the procedure. As much as half a year later, the infants circumcised without analgesic relief showed a heightened aversion to needle-stick procedures such as vaccination when compared with the control infants.

The lingering effects of early pain also have been uncovered in studies of premature, low-birth-weight infants who have spent their first few weeks in neonatal intensive care units (NICUs). The medical professionals in these units, while dedicated to coaxing the smallest of babies to a robustness that rivals that of their full-term peers, rely on a plethora of tests, many involving needle sticks, to monitor the health of their charges. Studies in select hospitals in British Columbia,

Canada, have found that by age 4, NICU infants showed a greater tendency to complain of pain even though no physical cause for their pain could be found. In addition, when those infants reached their mid-teens, self-reports showed them to be more likely to list pain as a significant aspect of their health status.

These ill effects may not be localized to pain. According to Frederick J. Stoddard Jr., MD, an associate clinical professor of psychiatry at HMS, early-life traumatic stress and untreated pain may seriously affect a child's development, contributing to lifelong emotional disorders, including anxiety and depression, learning disabilities, and other problems in growth and development.

Although studies have documented post-traumatic stress disorder (PTSD) in survivors of child abuse, few have looked for a connection between the disorder and early-life surgical pain. PTSD, a severe anxiety disorder that can develop after exposure to a psychologically traumatizing event, often overwhelms an individual's ability to cope. A 2008 National Institute of Mental Health study found that adults who had been abused as children, for example, had twice the number of PTSD symptoms as those who hadn't been abused.

"Early-life trauma," Stoddard says, "has a broader impact on neurodevelopment, including attention deficit hyperactivity disorder and learning disabilities."

Two very different patterns emerge after a child experiences physical, emotional, or psychological trauma. While some children become hyperactive and irritable; others withdraw and appear to shut down. The hyperactive child seems to lose control and may engage in disruptive behavior, such as wandering around during class or picking fights on the playground. The withdrawn child, in contrast, appears to give up, cease caring, or become occupied with daydreaming. Each situation, experts say, can lead to learning and social problems in adults.

Studies conducted by Bessel van der Kolk, medical director at the Justice Resource Center's Trauma Center, located in Brookline, Massachusetts, and a global leader in the field of psychological trauma, show that the brains of traumatized kids produce lower levels of hormones that help regulate attention. Many of these children, especially those who are hyperactive, experience chronic states of arousal that can interfere with the function of the hippocampus, the part of the brain responsible for forming new memories. Learning, remembering, and processing information can pose challenges for such children. One investigation even found that traumatic stress releases hormones that damage the hippocampus, creating memory deficits, while yet another study found that REM sleep, which seems to boost memory, is disrupted in kids who have survived a traumatic event.

Stoddard, whose research at the Shriners Hospital for Children in Boston focuses on the psychological reactions of severely burned young children, says his findings on PTSD provide insight into the psychological after-effects of early-life surgical pain. His 2006 study in the *Journal of Burn Care & Research* found that children from 12 to 48 months of age who suffer acute burns—especially those whose burns require a long hospitalization and multiple dressing changes—appear to be at increased risk for developing PTSD symptoms.

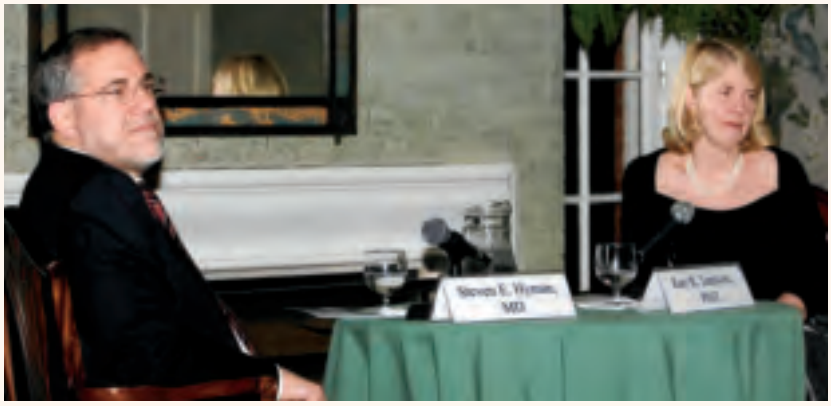
"These ill effects may not be localized to pain. According to Frederick J. Stoddard Jr., MD, an associate clinical professor of psychiatry at HMS, early-life traumatic stress and untreated pain may seriously affect a child's development, contributing to lifelong emotional disorders, including anxiety and depression, learning disabilities, and other problems in growth and development."

Treating these children, as well as children who may have suffered early-life surgical pain, may help ward off "longer term and more damaging reactions later, including the hidden memories that have come to haunt some trauma survivors," Stoddard says, provided that medical professionals assess these symptoms as part of routine patient care.

"Psychological interventions are also important for the child," says Stoddard, "including careful nurturance and the involvement of parents and other caretakers. Educating caretakers about the condition being treated and the support available is very likely protective for children in terms of reducing their stress."

Now that anesthesia is a routine part of surgery for society's youngest patients, it is likely that many of the psychological effects of untreated early-life surgical pain have been stemmed. And for previous generations of patients, who may not have benefited from such "humane considerations," our accumulating knowledge of treatments for the longer-term effects of early-life trauma may yet provide balm for still-tender wounds.

The David Mahoney Prize Symposium and Dinner—October 29, 2010



A conversation, "Mood Disorders in the 21st Century," features Steven Hyman, MD, Harvard University provost and professor of neuroscience as well as council member for the Harvard Mahoney Neuroscience Institute, and Kay Redfield Jamison, PhD, Johns Hopkins professor and recipient of the 2010 David Mahoney Prize.

Isaac Shapiro; Hildegarde Mahoney, chairman of the Harvard Mahoney Neuroscience Institute; and Ed Blier

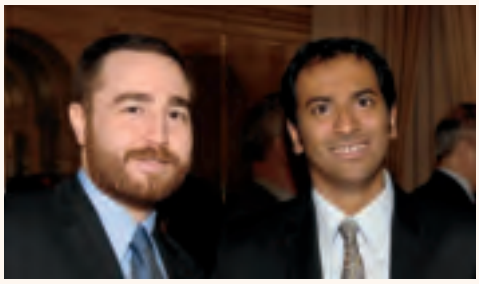
Keynote speaker William Chin, MD, executive dean for research at Harvard Medical School, and Edward Benz, MD, president of the Dana-Farber Cancer Institute

Steven Hyman and Edward Rover, chairman and president of the Dana Foundation and council member for the Harvard Mahoney Neuroscience Institute

James and Ginny Welch, and Patricia Dunnington

John Herman, MD, associate chief of psychiatry at Massachusetts General Hospital, and Patricia Cook

Peter Nadosy and Carroll Carpenter



Jonathan Nassi, PhD, and Kiran Padmanabhan, PhD, 2010 Mahoney Fellows in Harvard Medical School's Department of Neurobiology. Katharina Cosker, a third fellow, was unable to attend the event.

Stuart Quan, MD, and his wife, Victoria

Bob Merrill, H '81, and his trio

Suzanne McDonough and Donna da Veronna Pinto

David Mahoney Prize Goes to Kay Redfield Jamison

More then 150 friends and supporters of the Harvard Mahoney Neuroscience Institute at Harvard Medical School gathered on Oct. 27, 2010, for the Institute's biennial David Mahoney Prize symposium and dinner to honor Kay Redfield Jamison, PhD, a professor of psychiatry and co-director of the Mood Disorders Center at Johns Hopkins University School of Medicine. Jamison received the award for communicating the importance of brain research to the public, for her research investigating the neurological bases of mood disorders, and for her tireless advocacy for improvements in the diagnosis, treatment, and counseling of people with schizophrenia, bipolar disorder, and other neurological disorders.

The event, held in New York City, began with Jamison joining Harvard Provost Steven Hyman, MD, in a discussion titled "Mood Disorders in the 21st Century." Their conversation spanned Jamison's journey through years of stratospheric highs and deep, depressive lows before coming to grips with a diagnosis of bipolar disorder and its treatment demands; the debate over the link between creativity and bipolar disorder; and the crippling effects of stigma. But it was when speaking of her work with young people—work that includes counseling them to maintain treatment regimens through years that are ripe with promise and rife with risk-seeking behavior—that Jamison perhaps best showed the strength of her commitment to better care and compassion for all who face a lifelong struggle with a mood disorder.

In her memoir *An Unquiet Mind*, Jamison tells of the healing power of structure, psychotherapy and a social network—and gives a bracing account of what can happen when a woman with bipolar disorder opts out of her treatment plan. The destructive consequences of such a choice provide a cautionary tale to young people facing a life of treatment for an illness that cannot be seen on an x-ray or in a blood analysis—or by their peers. Jamison's story exemplifies the power and promise of those who, with appropriate treatment and personal resolve, can keep life in their lives.

Jamison, a prolific author, has also used her skills to serve professionals in the field: She is co-author of the seminal text *Manic Depressive Illness: Bipolar Disorders and Recurrent Depression*.

Jamison noted that while the public craves information about mood disorders, "psychiatry is not earning any teaching awards" when it comes to educating that same public about symptoms such as depression and how to seek help for those in need. She described an outreach program at Johns Hopkins that brings psychiatrists and other mental health professionals into public and private middle schools in Baltimore. There they teach students to recognize the symptoms of depression in themselves and others, and advise them about available help and treatments.

"Hope is one of the first things to go," said Jamison, "especially in young people. We need to help them realize that they are not alone. We need to educate the public to the fact that depression affects people everywhere, and that poor or no treatment for depression takes a huge toll worldwide." According to the World Health Organization, suicide is one of the three leading causes of death globally among people between 15 and 34 years of age.

At a dinner following the symposium, in presenting the award, Hildegarde Mahoney, wife of the late David Mahoney and Harvard Mahoney Neuroscience Institute chair, highlighted Jamison's research accomplishments but saved her highest praise for Jamison's efforts to banish the stigma associated with such disorders. These achievements, Mahoney added, were true to both the letter and spirit of the prize. In accepting the award, Jamison recalled the friendship and support she received through the years from the Mahoneys and reflected on the critical role that HMNI can have in sustaining research on neurological disorders.

Kay Redfield Jamison receives the 2010 David Mahoney Prize from Hildegarde Mahoney, chairman of the Harvard Mahoney Neuroscience Institute.

The Steuben tower awarded by the Harvard Mahoney Neuroscience Institute to Kay Redfield Jamison, "for building a bridge between the public and the scientists dedicated to brain research."

Gerald Fishbach, MD, John E. Borne Professor of Pharmacology and Neuroscience at Columbia University Medical Center, and former director of the Harvard Mahoney Neuroscience Institute

Michael Greenberg, PhD, Nathan Pusey Professor of Neurobiology at Harvard Medical School and chair of the School's Department of Neurobiology

Alcohol and the Adolescent Brain: A Troubling Cocktail

The brain of an adolescent shares some characteristics of the brain of someone who is addicted to alcohol or drugs, says Marisa Silveri, PhD, an HMS assistant professor of psychiatry. "Neither has good cognitive control," she says, "and both often have trouble making the right decision." Silveri's statement is not just an educated opinion; she has research to back it up. In a study published in February in *Alcoholism: Clinical & Experimental Research*,

"What it comes down to," says Silveri, "is that kids can have a hard time making sound decisions about their use of alcohol. But for those kids with a family history of alcohol abuse, the difficulty of such decisions increases."

Silveri and colleagues report that teenagers in families with a history of alcoholism have a significantly higher risk for the disease than their peers in families without such a past.

Silveri, an associate research psychologist in the Brain Imaging Center at McLean Hospital, gathered data for her study by using functional MRI (fMRI) to investigate activity in the frontal lobes of adolescents in alcohol-abusing families. She found the neural activity required for decision making increased significantly. It's a finding that troubles: The frontal lobes help us make good decisions about behavior, but the region takes almost two decades to develop fully. During the teen years, frontal lobes are still vulnerable to assaults resulting from bad decisions and risky behavior.

What it comes down to, says Silveri, is that kids can have a hard time making sound decisions about their use of alcohol. But for those kids with a family history of alcohol abuse, the difficulty of such decisions increases.

Color Codes

In their investigation, Silveri and colleagues used the Stroop interference test, which exploits our ability to read a word more quickly than we can name a color, to assess brain activity. Participants in the study—32 adolescents who had not yet begun to drink, including 18 with a family history of alcohol abuse—underwent a three-stage test. First, they were shown blocks of color and were asked to simply name the color of the block. In the second stage, the participants were asked to read "color" words written in black ink.

Participants next were asked to inhibit their impulse to read a word describing a color and to instead state what color ink the word was written in. For example, when shown the word *red* written in blue ink, the teen was instructed to identify the ink color (blue) while holding back reading the word (*red*). An MRI scanner collected data indicating frontal lobe activity throughout the tests and researchers used the data to measure which part of the brain participants used to perform this challenge–interference task.

The scientists found that teens with a family history of alcoholism showed higher levels of frontal lobe activity, indicating neural inefficiency when it came to processing information and producing a desired response. In other words, the brains of these adolescents required a little more "juice" from their frontal lobes in order to answer correctly.

Our brain is primed for reading, says Silveri, "But the adolescents were asked to identify a color, not to read a word—which causes a conflict, requiring an alteration in neural processing. The brain had to work harder to hold back the wrong answer by reading the word instead of naming the color."

For these teens, holding back the wrong behavior—drinking in excess rather than in moderation or not at all—may be difficult; their frontal lobes show even less maturity than those of others in their age group. For these adolescents, says Silveri, impulse control is especially challenging.

For the most part, adolescents know the dangers of drinking, says Silveri, but their immature neural decision-making centers foster poor decisions and "raise the bar on risk taking." The same is true for heavy users of alcohol and drugs, whose diminished inhibition responses are associated with smaller

continued on page 8

Addiction and the Adolescent Brain

by Joseph A. Califano, Jr., founder and chairman of the National Center on Addiction and Substance Abuse (CASA) at Columbia University and former U.S. Secretary of Health, Education, and Welfare

It's never been easy for parents to understand and deal with their teenagers and, courtesy of the easy availability of legal (alcohol and nicotine) and illegal drugs, it's never been more vexatious to get them safely through those dangerous years from 10 to 21. But doing so has never been more important. A child who gets through age 21 without smoking, abusing alcohol, or using illegal drugs is virtually certain never to do so.

For better or worse, parents have a great influence on whether their children will choose to use. Biological and behavioral science can provide parents with reasons why adolescence is a period of heightened vulnerability to substance abuse and addiction—for example, the link between adolescent brain development and risky behavior, the environmental and social influences that teens confront daily, and the evidence of genetic predisposition to addiction. Parents need to appreciate that the early onset of substance use is associated with an increased risk of lifetime addiction.

Why Do Teens Act as They Do?

Teens' penchant for engaging in risky behaviors is related to changes in their neurological architecture. Because the connection between the prefrontal cortex, which is responsible for judgment, decision making, and impulse control, and the limbic system, which generates emotions and impulses, isn't fully developed until around age 25, adolescents are prone to act upon immediate impulses and emotions rather than think through their decisions before taking action.

In addition to being impulsive, teens are susceptible to external influences. As teens get older, they are bombarded with peer pressure and temptations to smoke, drink, and use drugs. These substances are easily obtained—40 percent of 12 to 17 year olds can get marijuana within a day; 20 percent can get it within an hour.

Parents can help their teens understand and appreciate consequences of their actions and guide their children's decisions and behaviors. This kind of parenting not only instills good judgment, it can also trump the influence of others. Teens really do care what their parents think of them and generally don't want to disappoint them. In surveys, we ask children who do not smoke, drink, or use drugs, "Why not?" They overwhelmingly answer: "Because our parents would be extremely upset."

Addiction and Adolescence

During adolescence, the brain's pleasure–reward centers are readily modified by external stimuli, such as addictive substances. Drugs physically affect these brain centers faster and more intensely in adolescents than in adults.

The younger teens are when they first use drugs, the more vulnerable they are to addiction. The converse is also true: Every year that initiation of substance use is delayed, the risk of addiction decreases.

Research also has shown that adolescents who smoke cigarettes and drink alcohol are more likely to use marijuana than those who don't, and that adolescents who smoke marijuana are far more likely to use drugs like cocaine and heroin than those who don't. Among 12 to 17 year olds, those who smoke cigarettes are twelve times likelier to smoke marijuana than those abstain.

Even when an adolescent's substance use doesn't lead to addiction, it can have adverse consequences. Mind-altering substances can affect a teen's reasoning, interfere with normal development, and cause mental health problems. Substance abuse can interfere with a teen's ability to concentrate and remember, processes critical to school-based learning. And poor academic performance is not only itself harmful, it can become a risk factor for further substance use.

"During adolescence, the brain's pleasure–reward centers are readily modified by external stimuli, such as addictive substances. Drugs physically affect these brain centers faster and more intensely in adolescents than in adults."

The Benefits of Engaged Parenting

Brain imaging and biomedical and social science have identified opportunities for preventive interventions to steer teens in the right direction. *How to Raise a Drug Free Kid: The Straight Dope for Parents* is designed to inform parents about the role that adolescent brain development plays in substance use and addiction, and to offer practical tips for guiding children to make smart choices about tobacco, alcohol, and other drugs. I hope these tips help parents increase the likelihood that their children will grow up drug free. ♥

Excerpted from an essay by Joseph A. Califano, Jr. The full essay can be found at www.hms.harvard.edu/hmni/news.htm. *How to Raise a Drug Free Kid: The Straight Dope for Parents*, Fireside Books, August 2009, is available at www.amazon.com.

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

CORRESPONDENCE/CIRCULATION

Harvard Medical School
Gordon Hall
25 Shattuck Street, Room 001
Boston, MA 02115

NONPROFIT ORG.
US Postage Paid
Boston, MA
Permit No. 53825

For additional copies or changes to the *On The Brain* mailing list, please contact Ann Marie Menting at 617-432-7764 or by email at *ann_menting@hms.harvard.edu*

Alcohol and the Adolescent Brain
continued from page 6

frontal-lobe volume. They, too, are less able to hold back the wrong behavioral response, fueling a cycle of addiction.

A Window Within

Data from technologies such as fMRI, which can be used to measure year-to-year changes in the brain, provide solid evidence of the dangers of drinking at a young age, says Silveri. Using fMRI images to show kids how their brains change, as well as how early alcohol or drug use affects brain function, she adds, might influence their decisions to begin using alcohol or drugs while their brains are still rapidly changing.

"It would show them that drinking is bad for them. When the frontal lobes aren't fully developed, decision making becomes a challenge," says Silveri. And the results of poor decisions are clear and long lasting, even potentially catastrophic.

ON THE BRAIN

On The Brain is published three times a year through the Office of Communications and External Relations at Harvard Medical School, Gina Vild, Associate Dean and Chief Communications Officer.

Editor: Ann Marie Menting

Editorial Director: Karin Kiewra

Freelance Writer: Scott Edwards

Design: Gilbert Design Associates, Inc.

In collaboration with: Michael E. Greenberg, Nathan Pusey Professor of Neurobiology and Chair, Department of Neurobiology

Harvard Mahoney Neuroscience Institute
Harvard Medical School
Gordon Hall
25 Shattuck Street, Room 001
Boston, MA 02115

www.hms.harvard.edu/hmni
hmni@hms.harvard.edu