Hopkins BrainWise
THE NEWSLETTER OF THE JOHNS HOPKINS DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

JOHNS HOPKINS MEDICINE

FALL 2008

VOLUME 5, NUMBER 1

Deficit Schizophrenia: A First Daisy in the Chain

Of those who go through life pressed under the thumb of schizophrenia, a smaller group is nearly flattened by it. They're patients suffering deficit schizophrenia. It's an add-on, really, to the disease's usual disordered thinking, explains psychiatrist **Nicola Cascella**. People with "deficit" lack drive. Their emotional range is narrow; any sense of purpose that budded in their teens has withered. "Ask a patient what brings the greatest joy in life," Cascella says, "and 'I went for a walk this morning' is what I'll hear."

Psychiatry sees deficit—it affects some 20 percent of schizophrenia patients—mostly as a difference of degree within the disorder's spectrum of symptoms. But specialist Cascella thinks more might be at work. For one thing, a decade of his and others' study consistently turned up telltale differences from the more common illness. And now, work out this fall by a mostly Hopkins team including Cascella suggests that deficit may have its own biology.

Besides the distinct symptoms, the epidemiology stands out, he says: People with common schizophrenia are typically born in the spring, most in March. But deficit patients' birthdays fall in June or July. They tend to be medication-resistant. These patients are notorious for being hard to treat.

The reason may be tied to genetics. Four years ago, Cascella had his attention piqued by PCM1, a gene he'd come across during a Christmas holiday computer escape. Up popped a Hopkins study about an obscure genetic disorder, Bardet-Biedel syndrome, that linked the ailment to PCM1. Bardet-Biedel brings obesity and kidney damage. But, Cascella knew, patients also risk schizophrenia; it's twice as common as in healthy folk.

Nicola Cascella seriously believes biology's behind the deficit disease.

Curious, Cascella sought PCM1's particulars in an online database. The gene's address was on chromosome 8, at spot 22 on its short arm. More clicks brought up a 1998 mammoth Hopkins study that had linked a mystery gene at 8p22 to schizophrenia. Excited, Cascella confided in colleague **Akira Sawa**, who directs molecular psychiatry.

It took two years, but the two assembled a team that showed disrupting PCM1 in lab mice significantly flaws their brain development before birth (column, right); the flaws mimic those brought about by a known schizophrenia gene Sawa has long researched. The implication? There's a common mechanism for some forms of the disease.

PCM1, then, has the makings of a new schizophrenia gene. But was there proof in people? A tie to deficit schizophrenia?

Fortunately, Hopkins psychogeneticist **Ann Pulver** had preserved blood samples from her earlier mammoth schizophrenia gene hunt. "Ann saw the promise of our search," says Cascella, and soon they'd analyzed DNA from 32 volunteers with a strong family history of the disease. "When one family surfaced with a PCM1 mutation, and when we saw that only family members with schizophrenia had it, that finding was just fantastic," Cascella grins.

But there's one more wrinkle. Last year, a British group tied abnormal PCM1 to a loss of brain volume, specifically in the orbitofrontal cortex. "We're well aware of that area," Cascella says, "because people with lesions there get an apathy that looks a lot like deficit schizophrenia. We know it's speculation, but it's tantalizing to think that flawed PCM1 might be a deficit schizophrenia gene."

Of course repeat and expanded studies are in order. But the beauty of the work is that it sketches a possible outline for one sort of schizophrenia, from gene to cell to brain to person. That's just the sort of daisy chain that psychiatrists pray for, the sort that inspires therapy. ■

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TRANSLATIONS

Guilt By Centrosome

Centrosomes are a vague memory for most of us, a shaky freshman-biology recollection of cell parts having to do with mitosis and waving cilia, perhaps. Yet if that's the case, an update is in order: Not only do centrosomes ready a cell's internal scaffolding to carry out movement and transport, but now it seems they've a tie to psychiatric disease.

This fall, in lab mouse studies, a team led by Psychiatry's **Akira Sawa**, and including **Nicola Cascella** and colleague **Nicholas Katsanis** painstakingly clarified a key centrosomal pathway and showed its likely relation to one form of schizophrenia.

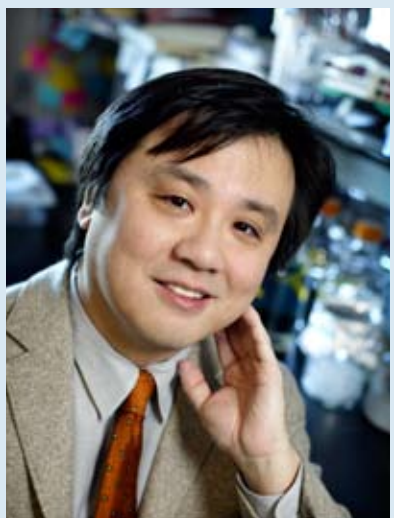
Normally, the new work suggests, proteins made by three centrosomal genes—abbreviated DISC1, BBS and PCM1—interact early in some as yet unknown way in embryonic cells. The cells then migrate properly to the developing cerebral cortex.

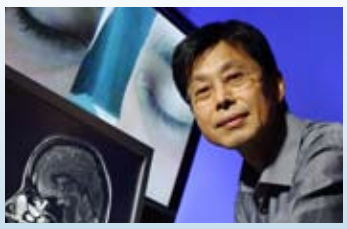
Mutations that warp the proteins, however, appear to cause a characteristic sort of havoc. And it's the team's additional achievement that they saw some of that havoc as an early stage of one type of schizophrenia.

One of the mutated genes, Disrupted In Schizophrenia (DISC1), was already linked with psychiatric disease in a Scottish family—hence the name. In 2006, Sawa's lab showed that developing mice whose brains are shortchanged of normal DISC1 mimic schizophrenia. (His group later proved DISC1 acts at the centrosome.)

The second mutant gene on its own causes Bardet-Biedl syndrome—a genetic eye and kidney disease that also can bring abnormal behavior, says Katsanis, who's published widely on its biology. And this new study led the researchers to believe that mutation in the third gene, PCM1, may be tied more subtly to schizophrenia (article, left, on deficit disease).

"Serendipity brought us together from the corners of the campus," says Katsanis, "and allowed us to see the links between these three proteins, centrosomes and schizophrenia." ■





A Psychosis Gene?

This subgroup of bipolar patients with psychosis may help us pinpoint the gene, says Goes.

Mr. B, who suffered from bipolar disorder (BP) for 30 years, had unusual thoughts and behaviors, but unusual in a typical way. When, for example, he'd stopped treatment and slipped into mania, Mr. B hallucinated that a neighbor wanted to harm him. Troubled by this, he attached an aluminum foil antenna to his radio to project the neighbor's voice and so warn his family.

Ms. C, who also had lived long with bipolar illness, had "incredible insight," she said, during a manic period that coincided with the start of the war in Iraq. She felt certain she could bring world peace because the baby she would soon deliver would mark the second coming of Christ. *

While both patients were no strangers to psychosis, there's a difference in the way their thinking goes amiss. In investigating that, psychiatrist **Fernando Goes** and colleagues have clarified the biology of psychosis. Also, they've gained insight on one form of bipolar disorder and are closer to confirm a gene for the risk of it—all steps toward better therapy.

Mr. B has mood-incongruent psychosis, meaning, Goes explains, "that the delusions suffered apparently lack ties to the person's abnormal mood." Mrs. C's mood-congruent thoughts, however, follow more reasonably from her overactive mood.

"Bipolar disorder is more complex than we'd thought," says Goes. "We now see it as more of a syndrome covering a number of diseases. And that complexity is probably why we've been stumped in mapping the genes." Today's approach, however, uses those differences. Researchers try to isolate subgroups of BP patients marked by some characteristic: Some, for example, have the classic euphoria of mania, while others have more irritable or "mixed" mania. Only around half of bipolar patients experience psychosis. And, to narrow it further, such psychosis is mood incongruent in only a third of them.

"Narrowing bipolar disorder clinically should let us narrow it down genetically," Goes explains.

In studying bipolar psychosis, the Hopkins team turned to their records of hundreds of study volunteers with the disorder—coded by number and not by name—who'd given detailed personal and family histories and blood samples. As part of a government project to get a large enough group to be trustworthy, those data from 708 families were analyzed and pooled with others from nine academic centers.

The results? Patients with mood-incongruent BD have a more severe illness. They're hospitalized, for example, or turn more often to addictive drugs. And the disorder clearly runs in families.

Even more interesting is the possibility that a gene underlies the disordered thinking—one on chromosome 13. Earlier Hopkins studies linked that site with both schizophrenia and psychotic bipolar disorder. "The fact that there's an overlap," Goes says, "tempts us to say there's a psychosis gene, one that brings a distinct character to illness, one we could target in therapy." ■

*We've altered both patient stories to protect identity.

For information: 443-287-6382

Mintzer's work adds to a national wave of study on how addiction clouds thinking.

Drug Dependency: A New Sort of Thinking Cap

Anesthesiologists know how useful a well-timed benzodiazepine can be: It chases away patients' presurgery fears and brings on a blessed amnesia for what goes on in the OR. And many psychiatrists trust a short course of the pills to dim memory enough after a traumatic event to keep acute anxiety from sliding into PTSD.

"But," says **Miriam Mintzer**, "that very effect—or other ways that drugs can alter thought processes—may get in the way of therapy for people who abuse them." So Mintzer, a cognitive neuroscientist, has joined a move to increase awareness of the scope of cognitive changes that drugs with abuse potential can bring, subtle as well as obvious.

Being impulsive, for example, is a common behavior tied to long-term drug abuse, Mintzer says, "and, presumably, it makes it more difficult to stop. The question is: Could we target it as part of treatment?"

Patients quickly learn what they need to do in the outside world to resist temptation, she explains, but they don't do it, especially in an environment booby-trapped with pill bottles or other cues. "Training them to recognize and inhibit their automatic response could make a difference," says Mintzer, who cites studies of successfully schooled impulsive children.

Support for such potential help, though, lies in the lab. While years of researching what makes people dependent on a substance are finally bearing fruit, knowing the fine cognitive effects—the changes in attention, memory, decision-making abilities—of opioids, marijuana, cocaine and amphetamines, for example, has lagged behind. Even work on otherwise well-studied alcohol and benzodiazepines lacks detail that might help fine-tune therapy.

Much of Mintzer's work has focused on the "benzos," teasing out cognitive effects of that drug family in healthy volunteers. Her research sparks interest in light of collected observations of chronic benzodiazepine abusers. Both have problems in encoding new information. "The drug's use doesn't impair your ability to retrieve memories of past events (episodic memory)," she says, "but to lay down new ones." Added clout has come from a PET scan study with Hopkins radiologist colleagues confirming that brain areas specific for memory-encoding are indeed sluggish.

What might that mean for patients who describe memories for events as "a fog" or "a blur?" Often-used tactics like cognitive behavioral therapy, which rely on remembering flawed ways of thinking and "encoding" better ones, may need adapting for drug abusers, Mintzer says.

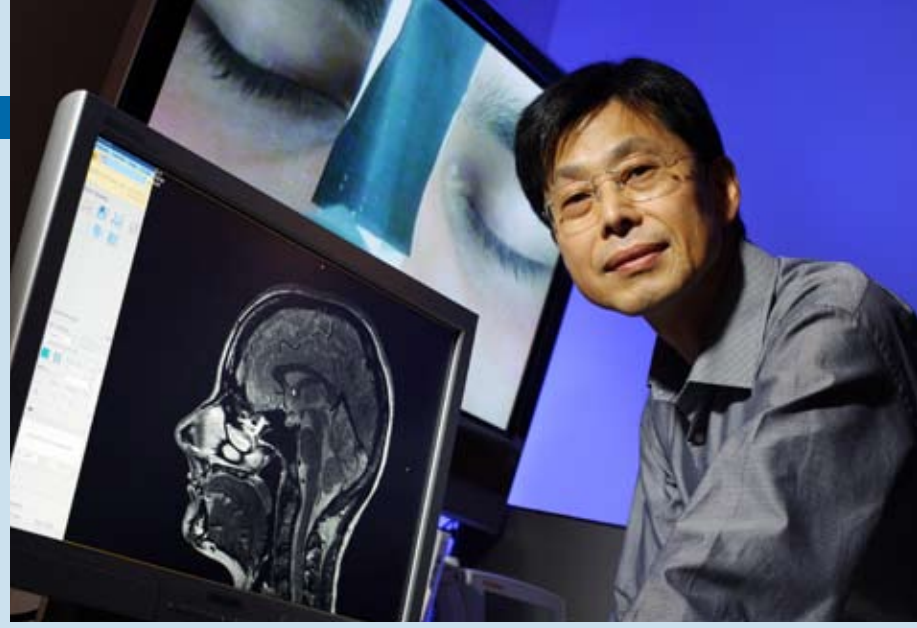
Recently, she's turned to cognitive science's newest baby, metacognition—an awareness of the state of one's own thinking. "It's a particular problem with the benzodiazepines," she says. "After just a single dose, people often have no idea how much their memory and performance is off." Again, Mintzer is laying a research base with studies on healthy volunteers.

Improved metacognition could literally save lives: "If you know you're impaired, you might not get in your car," she says. "Also, heightened metacognition is important generally in psychiatric disorders. It helps patients get well." ■

For more information, call: 410-550-0529.

To Sleep, Perchance to Diagnose

Team sees new friend to psychiatry in REM sleep.



Sleep studies could awaken a new field of psychiatric research, Hong says.

When Ebenezer Scrooge tried to explain away his ghostly visitors at night as "a bit of undigested cheese," his idea wasn't so far removed from one 20th century explanation of dreaming. Harvard's Hobson and McCarley held that the dreams we experience are a byproduct of biology—not of digestion, of course, but rather the result of twitchings of the brainstem that provoke an intriguing response from the brain's cortex as it tries to make sense of the random input.

But now, a new study by Psychiatry neuroscientist/psychiatrist **Charles Hong** and a mostly-Hopkins team offers evidence that may advance the field in what they and the earlier researchers think is a truer direction. The scientists are setting a platform for what may become a more purposeful biological rationale for dreams. The work suggests, for example, that the waking conscious mind and the dreaming one have far more in common than anyone suspected.

As exciting, says Hong, are the practical implications: "We believe our techniques could become a natural probe while people are asleep, a new way to simultaneously examine major brain systems—including those that go awry in psychiatric disease. This approach may clarify broadly what happens in patients with schizophrenia, depression or Alzheimer's disease," he explains, "or, one day, signal brain changes before symptoms appear."

Basically—and this understates the difficulty—Hong's team videotaped the rapid eye movements of healthy volunteers who spent the night asleep in an exquisitely sensitive functional MRI scanner. They then synchronized the results to get a real-time snapshot of active brain areas.

It wasn't a stretch to expect that regions for eye movement would light up. And because Hong and earlier colleagues had revealed that, in REM sleep, eyes apparently track what they "see" in dreams, the Hopkins team also anticipated activity in some cortical areas for sight. That was indeed the case.

Yet there was more. Unexpected brain sites for hearing, smell, touch and balance are turned on when rapid eye movements occur in sleep, they found, as well as motor areas that control body movements. They're likely the same areas active in awake, fully conscious people looking at and perceiving something.

"So, because so much is shared, we believe that consciousness in waking life and REM sleep dreaming are continuous," says colleague **James Harris** (Q&A below). It's just that the nature of consciousness differs somewhat in each: "During waking consciousness you're seeing things in the real world. In dream consciousness, you're also looking at images, but, it appears, they're created internally by your brain," Harris explains.

Now for the practical: Hong says many of the brain regions shown active under fMRI function poorly in psychiatric disease. Both language areas and the basal nucleus, for example, are profoundly affected in Alzheimer's disease—areas apparently active in eye-movement sleep. Other REM-active regions—for sensory processing, for example—go awry in schizophrenia.

Additionally, Hong's team found that a dense serotonin-secreting neural network has lowered activity in healthy dreaming subjects' brains. Having a window into the workings of serotonin, a molecule closely tied to mood and to mood disorder therapy, could be a great benefit, he says.

The plan, Hong explains, would be to compare healthy people at sleep with those touched by psychiatric disorders or even with their apparently healthy family members. "An advantage is that they're all asleep, all having rapid eye movements, probably scanning their dreams. So you can carry out accurate studies in uncooperative schizophrenia patients, in infants, or those with Parkinsonian tremors, which abate during sleep." Much work lies ahead, Harris adds, "but the potential has us excited."

The research team included scientists at Kennedy Krieger Institute's F.M. Kirby Research Center. An account is published online in November's *Human Brain Mapping*. ■

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All You've Got to Do Is Dream

A former head of Child Psychiatry at Hopkins, James C. Harris *holds deep interests in sleep, neuropsychiatry and emotional development. He co-founded a pediatric sleep disorders clinic in the early 1980s, for example, and is a specialist in autism and intellectual disability—once called mental retardation—championing whatever improves life for young patients dealt such a hand. His textbook,* Developmental Neuropsychiatry, *effectively established that specialty. And for some 30 years, he's taught Psychiatry's course that describes theories of how the human psyche comes to mature throughout a lifetime.*

Here we get Harris' perspective on the work (above) that ties the waking and sleeping brain in new ways.

You're really enthused about this new study, yes?
Absolutely! We think you'll be able to study the integrity of brain circuits while someone's asleep.

But, more, since I teach about Carl Jung's views, I'm pleased we've found evidence to support his thoughts on the continuity of consciousness in dreaming. The research suggests more strongly than before that what happens in sleep is important in emotional adaptation, in making us better able to carry out life's tasks.

How?
It's a lot like that Bergman film *Wild Strawberries* that I like to use to illustrate the human process. The main character dreams of his own death and, in the course of a day, is sharply reminded—by events and during dreams and daytime reveries—of the important phases of his life. He reflects on them, on their value to himself and by the movie's end, has become a more integrated person; he's found new meaning in relationships that he hadn't before. Why? Because throughout the film, he holds a dialogue between his dreams—his inner self—and his everyday waking consciousness. It's this back-and-forth that's important.

Elaborate, please.
There's a hypothesis that imagery from emotional events of the day surfaces in your REM sleep. When that's "matched" with something already present in your emotional memory banks and then re-experienced in REM sleep, the result is a biological modulating of your emotional life. It smooths the harsh edges, so to speak, helps you come to terms with your life. You're ready to adapt to a new day.

photo by Zuhair Kareem

And the study's exciting because...
It suggests that this process, where there is continuity between waking and REM sleep consciousness, is meaningful and real. We may be able to show, at some point, or begin to quantify how sleep's most valuable quality—restoring us by balancing our emotional life—works. Also, it may lead to early detection of depression, Alzheimer's disease or schizophrenia—all sleep-disrupting illnesses that affect our emotional life, memory and cognitive balance. And finally...

Yes?
This, to me, might begin to help us understand the neurophysiology that underlies psychotherapy. Is the alternation between narrating and reflecting that's so basic to psychotherapy mirrored in the continuity of waking and dreaming? That's what I'd like to find out. ■

When Trauma Is Trauma

Baghdad or Baltimore – kids show similar anxiety from life's daily blows.

It might be walking by the body of a dead friend on the way to school, day after day, that pushes an Iraqi child into posttraumatic stress disorder. (Fear of hidden bombs keeps officials from picking up bodies.) It could be knowing that terrorists kidnapped your brother and that after months, your parents can't raise the ransom. Or perhaps it's the constant atmosphere of fear that grinds at mental health as surely as the grit that now pervades war-torn Iraq.

Last summer, hearing what Iraqi children experience raised the consciousness of Hopkins community psychiatry clinicians involved in an unusual exchange. As part of a U.S.-Iraq program—one sponsored by our federal Substance Abuse and Mental Health Services Administration—Hopkins mentored Iraqi professionals who aim to reverse trauma's effects. "Thousands of children in that country don't meet normal developmental milestones because of what they've suffered psychologically," says psychiatrist **Anita Everett**.

Everett directs the Bayview campus' Community Psychiatry Program (CPP) and has been part of an international network of clinicians who, since 2005, have offered medical education and assistance in reviving Iraq's mental health system. Recently, she and colleagues held a Hopkins seminar about their experiences.

For three weeks, an Iraqi psychiatrist, two psychologists and a pediatrician studied community psychiatry in Baltimore and visited "marker" schools—both those where neighborhood violence or family indifference affects many students and those that stand as models of support. "We were the right choice for the visit because CPP has mental health care projects embedded in 14 Baltimore city schools," says **Kim Hauser**, the projects' manager.

"All of Iraq is hypervigilant."

Schools were a focal point because Iraq's efforts to help traumatized children are schools-based. The stigma of mental illness in that country is huge, Hauser and colleague **Paige Johnston** explained, but parents find no shame in visiting a child's school.

Traditionally, care for children with anxiety disorders has been the domain of grandmothers or other older women in the close-knit, stigma-wary families. For that and other reasons, "you'll find no child psychiatrists in Iraq," says Johnston. Also, medicines are less in use. Ritalin, for example, was banned after Saddam Hussein dosed soldiers with it to get them back to battle.

That's why, in a country where roughly half of the population is under the age of 18, officials in Iraq's health and education ministries see childhood trauma as an emergency. They embraced the idea of training teachers to recognize PTSD and to use basic therapeutic techniques. Perversely, many of the teachers suffer anxiety disorders as well. "The whole country is hypervigilant," the Iraqis told Johnston.

As for lessons learned? Seeing the differences in the Baltimore schools was likely useful. "Our teachers are at a different starting point," says Everett. "They've been educated to flag children at risk. Also, help for students here has two layers—the school counselors oriented toward learning-disabilities and CPP's added-on layer that helps kids who need treatment. In Iraq, teachers must do a little of both.

"It's hard to sort them out," Everett adds. "The kids who can't focus, who're distracted—do they have underlying ADHD or are they just reacting to trauma?"

Mentoring the team, however, wasn't all one-way. "The Iraqis did find negatives here," Hauser says, "specifically the lack of family involvement. They were appalled at one visit to a group home. Where was the family?" Both sides came to realize the common points of childhood trauma—whether it comes from war and dictators or from addicted parents and neighborhood violence—and that effective ways of treating it know no borders. ■

"It was such an honor to be with the Iraqis," says Paige Johnston, L.C.P.C., here with psychologist Fatima Hasim Asied.

Hailey Dart: She's increasing awareness of teenage mood disorders while fighting stigma.

Films Could Turn Night to Day

Roddy Dart had just celebrated his 22nd birthday early in 1997. A "much adored, strong-minded young man and great fun besides," his mother says, Dart was a gifted writer at his young age. He'd just begun to resume life as a college student after a hospitalization confirmed bipolar disorder and the idea of coping with the illness was sinking in.

A freak fall, however, ended Roddy's life. It also started a search by Hailey Dart, his mother, with backing from family and friends, to make a fitting memorial. Several projects caught her eye. But it was reading *An Unquiet Mind*—Kay Jamison's description of being on the cusp of life and wresting life from bipolar disorder—that helped Dart decide.

She contacted Jamison and others at Hopkins who, in turn, described the huge void in young adults' awareness of mood disorders. Could Dart perhaps fund a film that would get out the message? Something to show that these illnesses are both common and treatable?

In 1998, *Day for Night: Recognizing Teenage Depression* opened to quick praise. The documentary followed seven teenagers diagnosed with and successfully treated for mood disorders. It was accessible and, importantly, as color- and class-blind as the illnesses themselves, with the young patients racially varied and from diverse households. "It's been a wonderful film, fabulous, even, in what it's accomplished," says Sallie Mink, with the Adolescent Depression Awareness Program (ADAP), a Hopkins-based effort to educate that age group. Shown to more than 12,000 kids so far, as well as parents and teachers, it's still a mainstay.

But Dart, who runs the Rodwell Dart Memorial Foundation from its base in Aspen, Colo., has done more for the Hopkins cause. She's funded two more films—each needed to help ADAP extend its reach nationwide. One, a training film, shows ADAP director Karen Swartz in action with the program's students. And another is meant to educate their parents. "We want to be proactive," says Swartz. "We want to offer hope. And Hailey's commitment to sophisticated, much-needed media has been critical to our spreading this message." ■

Hopkins BrainWise

This issue of *Hopkins BrainWise* is published by Johns Hopkins Medicine Marketing and Communications for the Department of Psychiatry and Behavioral Sciences.

It is distributed to the scientific community, sponsors, friends and others interested in the department's research and activities.

Some of the research in this newsletter has corporate ties. For full disclosure information, call the Office of Policy Coordination at 410-223-1608.

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JOHNS HOPKINS MEDICINE

SAVE THE DATE!

This year's 23rd Annual Mood Disorders Symposium has ***Innovative Treatments*** as its focus. Renowned psycho-neurologist Helen S. Mayberg, whose work sparked the Deep Brain Stimulation now being eyed for depression is featured. Tuesday, April 28, 2009 at Hopkins' Turner Auditorium. Call 443-502-9634 for information.

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