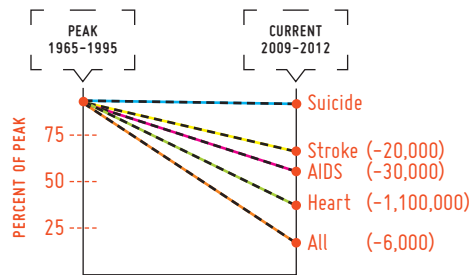


THE SCIENCE GUY

Director of
the National
Institute of
Mental Health
Thomas
Insel thinks
researchers
have neglected
a potential
wellspring
of solutions:
neuroscience

BY RICH
BARLOW

Mortality
from
medical causes



STARTING A SCIENTIFIC revolution in 2014 requires some powerful weaponry. So Thomas Insel, who at the moment is trying to persuade a roomful of mental health advocates that our treatments for diseased minds lack a foundation in, of all things, science, hauls out his biggest gun.

Insel screens slides depicting the plunging mortality rate from childhood leukemia (fatal in 95 percent of cases 30 years ago, today it's cured that often), heart disease (deaths have fallen 63 percent), AIDS ("essentially a death sentence" 15 years ago, today it's "considered a chronic disease"), and

strokes (20,000 fewer deaths annually than a few decades ago). "You know things are changing when Hallmark comes out with a centenary card," Insel says.

Then he shows them the suicide count.

Insel (CAS'72, MED'74) points to two trend lines since 1990: blue (suicide) and orange (homicide). The blue line flatlines near the top of the chart, virtually unchanged.

"Thirty-eight thousand suicides per year," Insel tells the 70 advocates gathered this April morning at the Bethesda, Md., campus of the National Institute of Mental Health (NIMH) for an annual conference. "It's more than twice the

number of homicides. It's more than the number of traffic fatalities. There are more deaths from suicide than there are from all forms of cancer except for lung, breast, and colon." And those numbers just count the dead. Mental illness also disables people early in life: 75 percent of those with the illness show symptoms by age 25, an onset that is "virtually unique in medicine."

All of this is unacceptable, says Insel, who has been methodically changing the direction of the NIMH since becoming director 12 years ago. He is convinced that researchers at the agency have been too easily satisfied with the

age-old practice of treating symptoms and have been insufficiently curious about the underlying architecture of mental illness. He wants to turn their attention, and much of his \$1.4 billion budget, to studying the biological mechanisms that make some brains malfunction. The big promise, he believes, lies in the mysteries of neuroscience.

Insel may have the mind of a revolutionary, but he has the soothing bedside manner of the psychiatrist that he has been all his professional life. At 63, his charcoal suit hugging his fit frame, his voice is easy and his metaphors catchy, even as he ponders the grim



"These are brain disorders. There is an organ that is involved."

"If depression is 10 different disorders requiring 10 different treatments, let's figure out what those are in the underlying neurobiology."



The first of five glimpses, with videos, of neuroscience research at BU.



suicide statistics: "What do we need to do to bend the curve here, at least 20 percent in 5 years and 40 percent over 10 years? You can do it for traffic fatalities; what would be the seat belt, what would be the air bag, that we can build in to reduce these numbers?"

"We don't even talk about cures the way we do for cancer and most other areas of medicine. We don't have vaccines. Prevalence hasn't gone down, and mortality hasn't gone down."

Conveniently, the facility working on Insel's version of the air bag happens to have opened just across campus the previous day. The John Edward Porter Neuroscience Research Center, begun in 2000, two years before Insel became NIMH director, is an angular steel-and-glass citadel housing almost four dozen principal investigators. Insel scoots from his meeting of nonscientist advocates to moderate a highly

technical research symposium celebrating the center's opening. The 15-minute hike through the 50-building NIMH campus is no problem for the doctor, who jogs mornings when time permits. He can't resist stopping and showing off the Porter building. "It is spectacular," he says with pride.

Still, it's just a building. Insel knows well that what goes on inside the center will make the difference. He starts with the obvious needs—more federal research dollars and better patient access to mental health services. "We doubled the budget at the National Institutes of Health [NIH] from 1998 to 2003," he says. "And we've just undoubled since," leaving NIMH, one of the 27 centers and institutes that make up the NIH, an inflation-adjusted budget equivalent to that of 1999. As for service delivery, he says, more than four-fifths of mental health providers lack training in treatments that have scientific evidence backing their effectiveness. "A patient would never accept this for cancer or heart disease," he says.

Insel has high hopes for President Barack Obama's BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, announced last year; \$40 million was spent on the initiative at the NIH in FY2014, and Obama has requested approximately \$200 million for the agency's work in FY2015. Insel also touts NIMH's Research Domain Criteria project, which seeks to rewrite existing diagnostic categories. "If depression is 10 different disorders requiring 10 different treatments," he says, "let's figure out what those distinct disorders and treatments are," by looking beyond symptoms to the underlying neurobiology of the disorders. At the same time, the institute is ending financial support for clinical trials of medications and psychotherapy targeting patients' symptoms only. To be funded these days, a trial must promise to reveal the malfunction behind mental disorders.

FUNDING SOURCES:

NIH, National Institute of Neurological Disorders and Stroke, Pew Foundation, Alfred P. Sloan Foundation, Michael J. Fox Foundation, Brain & Behavior Research Foundation, BU Peter Paul Award, BU Photonics Center

APPLICATION:

Parkinson's, Alzheimer's

CONTROLLING BRAIN CELLS WITH LIGHT

Xue Han, a College of Engineering assistant professor of biomedical engineering and a 2014 recipient of the Presidential Early Career Award for Scientists and Engineers, pioneered a technique called optogenetics, which uses pulses of light to turn brain cells off and on in an effort to learn how their malfunction influences psychiatric or neurological disorders. Han uses genetic methods to sensitize neurons to light, then studies the influence of those neurons on dopamine, which affects pathological oscillation in the brains of Parkinson's patients. Her research could lead to new drugs and other therapeutic approaches to a wide spectrum of ailments, including attention deficit disorders, depression, Parkinson's disease, and Alzheimer's disease. ART JAHNKE

**FUNDING SOURCES:**

National Institute of Environmental Health Sciences, Alzheimer's Association, Massachusetts Neuroscience Consortium, BrightFocus Foundation, Cure Alzheimer's Foundation, CurePSP, American Parkinson's Disease Association

APPLICATION: ALS, Alzheimer's

BREAKING UP PROTEIN BLOCKS

Ben Wolozin, a School of Medicine professor of pharmacology, studies the mechanisms that cause Parkinson's disease, amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, and

Alzheimer's disease. In all three cases, Wolozin believes, the culprit is the aggregation of particular proteins, called RNA binding proteins. These aggregations, known as "stress granules," occur

naturally when the body is stressed, and they usually disperse, as they are programmed to do. If they fail to disperse, neurons misfire and the body's messaging system goes haywire. Wolozin is

developing compounds that have the potential to reverse the persistent aggregation of stress granules, and that reversal may be useful in treating ALS and Alzheimer's disease. *AJ*

The goal is to understand "not just whether a therapy is working statistically," Insel says, "but is it really getting at something that's core to the disorder."

Another project, Recovery after Initial Schizophrenia Episode (RAISE), is developing therapies that can be deployed early, before the devastating illness derails lives. This would address what Insel calls a damning defect, the failure to catch many mental disorders early. Similarly, symptoms in conditions such as Alzheimer's typically don't appear until well after the onset of the disease, when "you're already in the ninth inning," he says. "You want to be there in the first or second inning.

"Symptom-based diagnoses just aren't where we need to be," he says. With an obsessive look-out for symptoms, it's no wonder that so many treatments for brain disorders focus on relieving those symptoms rather than addressing their causes. Elsewhere in medicine, he says, "we don't just try to bring the fever down, we try to treat the infection."

THE INQUISITIVE EAGLE SCOUT

The son of an eye surgeon and a social worker, Insel was an "Eagle Scout who collected insects and snakes and filled the basement with aquariums," in the words of a *New York Times* profile. His three older brothers attended medical school, and at 15, before the age when some kids get their learner's permits, he entered BU's six-year bachelor's/MD program. Two years later, contrary to his father's wishes, he left. "I began to think, maybe I don't want to do what everyone else had done," he says. "I wanted to explore."

He worked at a tuberculosis clinic in Hong Kong "just as a kind of gofer," and then at a remote hospital in India, and he loved both experiences. "I got really fired up about what, at that time, was called tropical medicine. Today it's called global health."

Returning to complete his BU education, Insel became interested in brain science after

learning about strange syndromes that damaged very particular connections in the brain, leaving people with such afflictions as the inability to recognize faces and names. "I was just absolutely fascinated by that," he says.

After graduating in 1974 and completing a residency in psychiatry, Insel moved on to a job as an NIMH researcher, studying obsessive-compulsive disorder (OCD). While there, he shared an office with Ben Wolozin, now a BU School of Medicine professor of pharmacology and head of the University's Laboratory of Neurodegeneration (*see sidebar above*). "Tom has always had a straightforward, down-to-earth way of thinking," says Wolozin. "He was a great scientist, but he also was a psychiatrist, and he really gets it with patients."

He also commends Insel's communication skills. "NIMH has to be able to communicate with the scientists doing mechanistic work and with different people on different levels. Insights come not just from a brain researcher, but from a cancer researcher, or maybe a researcher on aging. Tom has to be able to communicate with the people working with the behavioral component, and he has to be a cogent spokesperson for mental health, because he is the face of NIMH, and I can't think of a better face. He can talk to Story Landis [director of the National Institute of Neurological Disorders and Stroke] and Anthony Fauci [director of the National Institute of Allergy and Infectious Diseases] at their level, and he can talk to activists and parents. He is exactly the person you want in that role."

During his initial stint at NIMH, Insel co-authored research showing the superiority of treatment of OCD with an antidepressant drug over the psychotherapeutic approach beloved by the field's then-dominant Freudians. The OCD treatment evolved into the widely accepted practice of combining medicines and short-term behavioral treatment that endures to this day.

Insel's gaze next fell on voles—appealing subjects for a brain-fascinated scientist. The

WEB EXTRA

Watch videos about neuroscience research at Boston University at bu.edu/bostonia.



FUNDING SOURCES:

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NINDS

APPLICATION:

Down syndrome

FINDING THE GENES BEHIND DOWN SYNDROME

Tarik Haydar, a School of Medicine associate professor of anatomy and neurobiology, believes that the keys to developmental brain disorders, such as Down syndrome, lie in study of the earliest moments of brain development. In Down syndrome, he says, genetic changes impact brain development and function starting from before birth and continuing throughout one's entire life. Haydar uses genetic mouse models to study brain growth from the fetal to adult stages of life, focusing primarily on cellular and molecular changes in the living brain. His lab has identified several genes that change cellular processes in the Down syndrome brain. Working with collaborators at Tufts Medical School, Haydar and his team are testing whether prenatal treatments can offset or prevent these changes. *AJ*

bonding behaviors of two particular species vary greatly; depending on the species, males can be monogamous or playboys, for example, and Insel wondered if neural factors explained the difference. He and colleagues confirmed that hypothesis by altering a protein level in the creatures' brains—and changed their behavior. He pursued his animal research as head of Emory University's renowned Yerkes National Primate Research Center for eight years before coming home to the NIMH in 2002.

"I get bored very easily," Insel confesses, although his current run in the NIMH directorship suggests he has found enough stimulation there to warrant staying put. "Part of why I've been doing this so long is I keep thinking I really can bend the curve. If we can bring the right science to bear, we can really save lives."

FACING CRITICISM

Advocating the best science to battle, say, climate change or cancer doesn't usually bend noses out of joint, but some corners of the mental health world have bridled at Insel's critique.

Arthur Caplan, director of medical ethics at New York University's Langone Medical Center, erupted at Insel's assertion that psychiatry's scripture, the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, "lacked validity." "The view that the only medical classifications that are valuable are those grounded in molecular biology can be dismissed out of hand," Caplan wrote in *Time* magazine, adding that scientific exercises, from weather forecasting to predicting earthquakes, "do not have coherent explanations in atomic physics for their categories or for their causes. But their categories are accepted because they work."

Others condemn Insel's broader efforts to reorient the NIMH. "Instead of being an institute of mental health, he has made it almost exclusively a brain research institute," Allen Frances, the psychiatrist who oversaw an earlier revision of the *DSM*, complained in the *New York Times*. "NIMH is betting the house on the long shot that neuroscience will come up with answers to help people with serious mental illness. It does little or no psychosocial health services research that might relieve the current suffering of patients."

Dig deeper, however, and it becomes clear that a larger consensus of the psychiatric community supports Insel. Caplan himself agreed that the *DSM* needed to consider new findings from neurology and genetics, and the president of the manual's publisher admitted it could be better. Both said the *DSM* is the best guidance currently available, a point Insel does not dispute.

"Our treatments are undoubtedly lacking,"



FUNDING SOURCES:

National Institute on Deafness and Other Communication Disorders, NICHD

APPLICATION:

Autism

STRENGTHENING BRAIN CONNECTIONS

Helen Tager-Flusberg, a College of Arts & Sciences professor of psychology and director of the Center for Autism Research Excellence, focuses on cracking the code of silence in the brains of minimally verbal children. She believes the key problem may be

"connectivity differences" between the brain regions used for comprehending speech and the motor areas needed to articulate it. Tager-Flusberg and her center colleagues will compare brain scans of minimally verbal children with neural models of how healthy brains create

speech, created by Barbara Shinn-Cunningham, a College of Engineering professor of biomedical engineering, and Frank Guenther, a Sargent College professor of speech, language, and hearing sciences. They will also test a novel therapy called auditory motor mapping

training, which combines singing and drumming to help strengthen the connections between the brain's cognitive and motor regions. Tager-Flusberg believes the center's research could give minimally verbal children back their own voices. CHRIS BERDIK



FUNDING SOURCES:
NIMH, NIH, Office
of Naval Research

APPLICATION:
Alzheimer's

TRACKING TIME AND SPACE

Michael Hasselmo, a College of Arts & Sciences professor of psychology and director of Boston University's Center for Systems Neuroscience (see sidebar below), is studying grid cells, neurons in the brains of rats and other animals whose firings

help the brain record both location and time, which also play a central role in episodic memory. Working with Howard Eichenbaum, a CAS professor of psychology and director of the Center for Memory & Brain, and Chantal Stern, a CAS professor of psychology

and director of the Cognitive Neuroimaging Laboratory, Hasselmo is examining the influence of the neuromodulator acetylcholine on cell firing. Acetylcholine, which is heavily implicated in Alzheimer's disease, regulates the excitability of cells,

making them more easily excited and at the same time diminishing how much that activity will spread. His research reveals the mechanisms of episodic memory, which may help us understand the memory impairments in a range of disorders. AJ

says Sherry Glied, dean of New York University's Robert F. Wagner Graduate School of Public Service, who keynoted the advocates' meeting in Bethesda. "But we know that many people are still not receiving treatments that we already do have on hand and that could help them. At the same time, research aimed at cures is unlikely to pay off for some extended period of time"—17 years is the best guess, she says. "That makes this balance complicated."

David Barlow, a College of Arts & Sciences psychology professor and founder of Boston University's Center for Anxiety & Related Disorders, has known Insel for more than 30 years. "Unlike many of my colleagues, I applaud many

of Tom's initiatives," says Barlow. "The focus of the institute seems radically different recently to many investigators, but is actually meant to encompass a healthy integration of behavioral and neurobiological mechanisms" in treatments. Improved drug treatments for mental disorders have stalled in recent years, according to Barlow, and Insel is seeking to "light a fire in the field to develop some new paradigm.

"Whether these initiatives will succeed or not, of course, remains to be seen," he adds. Meanwhile, bold rhetoric demanding change, such as Insel uses, "can be a tonic to facilitate creativity."

Wolozin, the BU professor and long-ago office mate, believes that since Insel assumed leadership of NIMH, "our understanding of genetic factors and biological factors that impact mental illness has increased manyfold. This is not a field where there is one gene and you get the illness," says Wolozin. "It's more like diabetes, where there are many little factors, and it also depends on how you were brought up and what you eat. Under Tom, our understanding of all the factors contributing to mental illness has coalesced."

To the charge that he's focused the NIMH almost single-mindedly on brain science, Insel pleads simply, "Yes. Because these are brain disorders....They have an organ that's involved. It's an organ that we're learning an awful lot about right now, and we should use the revolution in neuroscience to help us come up with better diagnostics and better treatments."

Indeed, for all the new research avenues that he has led the institute down, Insel says, "probably the thing that I'm most proud of" is that an increasing number of MDs and PhDs with training in neuroscience are entering psychiatry. That's a result, he says, of "convincing them that this is the most exciting place to be." ■

BU LAUNCHES CENTER FOR SYSTEMS NEUROSCIENCE



As brain science takes a prominent position on the nation's research agenda, Boston University has launched an interdisciplinary research center to explore the roots of psychiatric diseases and neurological impairments. The Center for Systems Neuroscience, which studies how nerve cells in different brain regions interact to guide functions such as learning, memory, speech, perception, and attention, is led by Michael Hasselmo, a College of Arts & Sciences professor of psychology. BU, which last year invested \$55 million from various

sources in neuroscience research, already does significant research in this area, but the new center, which opened in July, will enhance collaboration among scientists at CAS, the College of Engineering, Sargent College, and the School of Medicine. The center's administrative offices and some staff, drawn from faculty at the Medical and Charles River Campuses, will eventually be located in the Center for Integrated Life Sciences & Engineering at 610 Commonwealth Avenue. That building, now in the design phase, is scheduled to open in three and a half years. RB